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***Optimising The Maturation Rate Of Arteriovenous Fistula
(AVF) In Patients With End Stage Renal Disease (ESRD)***

A thesis submitted to the

National University of Ireland, Galway

For the degree of *Doctor of Philosophy*

By

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2016

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CONTENTS

| | |
|--|--------------|
| <i>ACKNOWLEDGEMENTS:</i> | <i>I</i> |
| <i>CONTENTS</i> | <i>II</i> |
| <i>DECLARATION:</i> | <i>X</i> |
| <i>Communications originating from this work</i> | <i>XI</i> |
| Peer Reviewed Published Manuscripts: | <i>XI</i> |
| Presentations to Learned Societies: | <i>XIII</i> |
| <i>SUMMARY</i> | <i>XIV</i> |
| <i>List of Figures</i> | <i>XVI</i> |
| <i>List of Tables</i> | <i>XVIII</i> |
| <i>List of Appendices</i> | <i>XIX</i> |
| <i>List of Abbreviations:</i> | <i>XXI</i> |
| <i>INTRODUCTION</i> | <i>1</i> |
| <i>I Chapter One: Introduction</i> | <i>2</i> |
| 1.1 Characteristics of arteriovenous fistulae | <i>3</i> |
| 1.2 Intimal Hyperplasia: | <i>5</i> |
| 1.3 Inflammatory Markers:..... | <i>7</i> |
| 1.4 Haemodynamic Changes:..... | <i>9</i> |
| 1.5 Remote Ischaemic Preconditioning:..... | <i>12</i> |
| 1.6 Preoperative Ultrasound Mapping | <i>13</i> |
| 1.6.1 Current Practice..... | <i>13</i> |
| 1.6.2 Evidence for routine ultrasonography..... | <i>14</i> |
| 1.6.3 Ultrasonographic criteria..... | <i>15</i> |
| <i>METHODS</i> | <i>18</i> |
| <i>II Chapter Two: Methods</i> | <i>19</i> |

Contents

| | | |
|-------|--|----|
| 2.1 | Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease | 20 |
| 2.1.1 | Patients: | 20 |
| 2.1.2 | Inclusion and exclusion criteria: | 20 |
| 2.1.3 | Data collection:..... | 21 |
| 2.1.4 | Study's primary and secondary endpoints: | 21 |
| 2.1.5 | Statistical analysis: | 22 |
| 2.2 | The role of venous diameter in predicting arteriovenous fistula maturation..... | 23 |
| 2.2.1 | Three-part question:..... | 23 |
| 2.2.2 | Search strategy:..... | 23 |
| 2.3 | End-To-Side versus Side-To-Side Anastomosis Techniques in Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis | 24 |
| 2.3.1 | Eligibility Criteria: | 24 |
| 2.3.2 | Search strategy:..... | 24 |
| 2.3.3 | Endpoints and definitions: | 25 |
| 2.3.4 | Data Collection: | 25 |
| 2.3.5 | Quality assessment for risk of bias: | 26 |
| 2.3.6 | Data analysis: | 26 |
| 2.4 | The utility of a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests in predicting Arteriovenous Fistula Maturation.. | 27 |
| 2.4.1 | Materials and Methods:..... | 27 |
| 2.4.2 | Study objectives and definitions:..... | 27 |
| 2.4.3 | Statistical analysis: | 28 |
| 2.5 | One-Stage Vs Two-Stage Brachio-Basilic Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis..... | 29 |
| 2.5.1 | Eligibility Criteria: | 29 |
| 2.5.2 | Search strategy:..... | 29 |

Contents

| | | |
|---------|---|-----------|
| 2.5.3 | Outcomes assessed:..... | 30 |
| 2.5.4 | Data Collection: | 30 |
| 2.6 | Role of Far Infra-Red therapy in dialysis Arterio-venous Fistula maturation and survival: Systematic review and meta-analysis..... | 31 |
| 2.6.1 | Eligibility Criteria | 31 |
| 2.6.2 | Search strategy | 31 |
| 2.6.3 | Outcomes assessed..... | 32 |
| 2.6.4 | Data Collection | 32 |
| 2.6.5 | Quality assessment for risk of bias | 32 |
| 2.6.6 | Data analysis | 33 |
| | <i>RESULTS</i> | <i>34</i> |
| | <i>III Chapter Three: Predictive Parameters of Arteriovenous Fistula Functional Maturation in a Population of Patients with End-Stage Renal Disease</i> | <i>35</i> |
| 3.1 | Introduction: | 36 |
| 3.2 | Methods: | 39 |
| 3.2.1 | Patients: | 39 |
| 3.2.2 | Inclusion and exclusion criteria: | 39 |
| 3.2.3 | Data collection:..... | 39 |
| 3.2.4 | Study's primary and secondary endpoints: | 40 |
| 3.2.5 | Statistical analysis: | 41 |
| 3.3 | Results: | 42 |
| 3.3.1 | Patients' characteristics: | 48 |
| 3.3.1.1 | Preoperative blood tests: | 52 |
| 3.4 | Discussion: | 56 |
| 3.5 | Conclusion:..... | 60 |
| | <i>IV Chapter Four: The role of venous diameter in predicting arteriovenous fistula maturation</i> | <i>61</i> |
| 4.1 | Introduction: | 62 |

Contents

| | | |
|---|--|-----|
| 4.2 | Clinical Scenario: | 62 |
| 4.3 | Three-part question: | 62 |
| 4.4 | Search strategy:..... | 63 |
| 4.5 | Search outcome:..... | 63 |
| 4.6 | Results: | 65 |
| 4.7 | Discussion: | 70 |
| 4.8 | Clinical bottom line: | 73 |
| <i>V Chapter Five: End-To-Side Versus Side-To-Side Anastomosis Techniques In Arteriovenous Fistula For Dialysis Access: A Systematic Review And A Meta-Analysis</i> | | |
| 5.1 | Introduction: | 75 |
| 5.2 | Methods:..... | 76 |
| 5.2.1 | Eligibility Criteria: | 76 |
| 5.2.2 | Search strategy:..... | 76 |
| 5.2.3 | Data Collection: | 77 |
| 5.2.4 | Quality assessment for risk of bias: | 81 |
| 5.2.5 | Data analysis: | 85 |
| 5.3 | Results: | 86 |
| 5.3.1 | Study selection:..... | 86 |
| 5.3.2 | Participants:..... | 88 |
| 5.3.3 | Patency rate after 3 months:..... | 91 |
| 5.3.4 | Patency rate after 6 months:..... | 93 |
| 5.3.5 | Patency rate after 12 months:..... | 96 |
| 5.3.6 | Patency rate after 24 months:..... | 98 |
| 5.3.7 | Postoperative wound haematoma: | 100 |
| 5.3.8 | Arterial steal syndrome: | 103 |
| 5.4 | Discussion: | 106 |
| 5.5 | Conclusion:..... | 110 |

Contents

VI Chapter Six: The Utility of a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests in predicting Arteriovenous Fistula Maturation 111

| | | |
|-------|--|-----|
| 6.1 | Introduction: | 112 |
| 6.2 | Materials and Methods: | 114 |
| 6.2.1 | Study objectives and definitions:..... | 114 |
| 6.2.2 | Statistical analysis: | 115 |
| 6.3 | Results: | 116 |
| 6.3.1 | Predictive value of the NLR: | 124 |
| 6.4 | Discussion: | 129 |
| 6.5 | Conclusion:..... | 133 |

VII Chapter Seven: One-Stage Vs Two-Stage Brachio-Basilic Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis..... 134

| | | |
|---------|--|-----|
| 7.1 | Introduction: | 135 |
| 7.2 | Methods: | 138 |
| 7.3 | Eligibility Criteria: | 138 |
| 7.4 | Search strategy: | 138 |
| 7.5 | Data Collection: | 140 |
| 7.5.1 | Quality assessment for risk of bias: | 146 |
| 7.5.2 | Data analysis: | 152 |
| 7.6 | Results: | 153 |
| 7.6.1 | Study selection: | 153 |
| 7.6.2 | Participants:..... | 154 |
| 7.6.3 | Successful Maturation rate: | 159 |
| 7.6.4 | Postoperative complications:..... | 164 |
| 7.6.4.1 | Haematoma: | 164 |
| 7.6.4.2 | Wound infection:..... | 167 |
| 7.6.4.3 | Steal Syndrome: | 170 |

Contents

| | | |
|--|--|-----|
| 7.7 | Systematic review: | 173 |
| 7.8 | Discussion: | 178 |
| 7.9 | Conclusion:..... | 182 |
| <i>VIII Chapter Eight: Role of Far Infra-Red therapy in dialysis Arterio-venous Fistula maturation and survival: A Systematic review and meta-analysis 183</i> | | |
| 8.1 | Introduction: | 184 |
| 8.2 | Methods: | 186 |
| 8.2.1 | Eligibility Criteria | 186 |
| 8.2.2 | Search strategy | 186 |
| 8.2.3 | Data Collection | 187 |
| 8.2.4 | Quality assessment for risk of bias | 187 |
| 8.2.5 | Data analysis | 191 |
| 8.3 | Results: | 192 |
| 8.3.1 | Study Selection..... | 192 |
| 8.3.2 | Characteristics of included studies | 194 |
| 8.3.2.1 | Far Infrared (FIR) technique | 194 |
| 8.3.3 | Participants..... | 194 |
| 8.3.4 | Primary - unassisted - patency rates at 1 year: | 200 |
| 8.3.5 | Secondary - assisted - patency rates: | 205 |
| 8.3.6 | Intervention: | 207 |
| 8.4 | Discussion: | 209 |
| 8.5 | Conclusion:..... | 213 |
| <i>DISCUSSION..... 214</i> | | |
| <i>IX Chapter Nine: Discussion 215</i> | | |
| 9.1 | Introduction: | 216 |
| 9.2 | Patient characteristics: Sex, age and diabetes mellitus..... | 217 |
| 9.3 | Pathophysiology of AVF non-maturation:..... | 219 |

Contents

| | | |
|---|--|-----|
| 9.4 | Timing of initial cannulation and previous access: | 220 |
| 9.5 | Surgical Technique, site and ultrasound mapping: | 221 |
| 9.6 | Vein Diameter:..... | 222 |
| 9.7 | Anatomic lesions within vessels:..... | 223 |
| 9.8 | Far-Infra Red therapy: | 224 |
| 9.9 | Brachio-Basilic AVFs: | 225 |
| 9.10 | Pharmacological manipulation:..... | 226 |
| 9.11 | Future Work:..... | 227 |
| 9.11.1 | Immunological manipulation: | 227 |
| 9.11.2 | Markers of maturation: | 227 |
| <i>REFERENCES</i> | | 229 |
| <i>APPENDICES</i> | | 256 |
| Appendix 1: Ethics Approval Form (Galway University Hospitals):..... | | 257 |
| Appendix 2: Ethics Approval Form (University Hospitals Limerick): | | 258 |
| Appendix 3: Publication from the thesis “Pre-operative ultrasonography and arteriovenous fistulae maturation”:..... | | 259 |
| Appendix 4: Publication from the thesis “Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease”: | | 263 |
| Appendix 5: Publication from the thesis “The role of venous diameter in predicting arteriovenous fistula maturation: when not to expect an AVF to mature according to pre-operative vein diameter measurements? A best evidence topic”: | | 278 |
| Appendix 6: Publication from the thesis “Can a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests predict Arteriovenous Fistula Maturation?” | | 282 |
| Appendix 7: Publication from the thesis “One-stage vs. two-stage brachio-basilic arteriovenous fistula for dialysis access: a systematic review and a meta-analysis”: | | 289 |

Contents

| | |
|---|-----|
| Appendix 8: Publication from the thesis “Role of far infra-red therapy in dialysis arterio-venous fistula maturation and survival: systematic review and meta-analysis”: | 314 |
| Appendix 9: Publication from the thesis “Arteriovenous Fistula in dialysis patients: Factors implicated in early and late AVF maturation failure”: | 325 |
| Appendix 10: Work submitted for publication “End-To-Side Versus Side-To-Side Anastomosis In Upper Limb Arteriovenous Fistula For Dialysis Access: A Systematic Review And A Meta-Analysis”: | 332 |
| Appendix 11: Work submitted for publication “Arterio-Venous Fistula (AVF) in dialysis patients: Understanding the Pathophysiology behind arteriovenous fistulae non-maturation”: | 333 |
| Appendix 12: Publication arising from data collected during the research period “ <i>The Role of Shear Stress in Arteriovenous Fistula Maturation and Failure: A Systematic Review</i> ”: | 334 |
| Appendix 13: Publication arising from data collected during the research period “In vivo validation of the in silico predicted pressure drop across an arteriovenous fistula”: | 335 |

DECLARATION:

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is being submitted concurrently in candidature for any degree or other award.

This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD in Surgery.

This thesis is the result of my own independent work/investigation, except where otherwise stated. Other sources are acknowledged by explicit references. The views expressed in this thesis are my own.

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Communications originating from this work

Peer Reviewed Published Manuscripts:

Bashar K, Zafar A, Elsheikh S, Healy DA, Clarke-Moloney M, Casserly L, Burke PE, Kavanagh EG, Walsh SR.: *Predictive Parameters of Arteriovenous Fistula Functional Maturation in a Population of Patients with End-Stage Renal Disease*. PLoS One. 2015 Mar 13;10(3):e0119958. doi: 10.1371/journal.pone.0119958. eCollection 2015. PMID: 25768440.

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Presentations to Learned Societies:

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Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease: *Presented at the 5th Global Nephrologists Annual Meeting in Valencia, Spain, 31 March 2016.*

SUMMARY

A well-functioning Arteriovenous Fistula (AVF) has been shown to be the best modality for access in patients with end-stage kidney disease going for dialysis. Maturation of AVF is complex and depends on various biomechanical forces induced into the vascular system following creation of AVF. The focus of this thesis was to study factors that can lead to optimising fistula maturation in patients with End Stage Renal Disease (ESRD).

The author looked into various factors related to patients' demographics and clinical characteristics that are associated with the maturation process. The thesis also examined the evidence behind several debatable practices in formation of new AVFs. The optimal size of the vein diameter used in creating the anastomosis was evaluated. Comparisons between the end-to-side anastomosis technique and the side-to-side technique were assessed in a systematic fashion. Similarly, the differences between the one-stage versus the two-stage techniques in formation of brachiobasilic AVFs (BB-AVFs) were examined. In addition, the utility of using a neutrophil-lymphocyte ratio (NLR) as a fast blood test was evaluated. A third systematic review was conducted to examine the effect of post-conditioning on fistula maturation by means of far infrared (FIR) technology was conducted.

There seems to be a lack of effective clinical, demographic and biological markers to reliably predict the outcome of a newly formed AVF. Vein diameter is a hugely important factor, arguably, the single most important predictor of maturation as fistulae created using veins of < 2 mm diameter are more likely to fail. Other factors such as female gender, diabetes mellitus, age, arterial diameter, surgical technique, and timing of the fistula formation in relation to starting HD sessions, can all be considered as additional predictors of AVF maturation. Side-to-side anastomosis has comparable maturation rates to end-to-side anastomosis. Similarly, two-stage BB-AVFs have similar maturation rates to those created using one-stage techniques. FIR has shown promising results in promoting fistula maturation; however, further studies are needed to evaluate its efficacy. Similarly, new emerging treatments - such as molecular biological manipulation - need further assessment.

OLLSCOIL NA hÉIREANN, GAILLIMH
NATIONAL UNIVERSITY OF IRELAND, GALWAY

THE PhD / MD DEGREE
APPROVAL FOR EXAMINATION

To: The Registrar & Deputy President, the National University of Ireland, Galway

Please tick (✓) as appropriate: **PhD** ✓

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Submitted by Candidate (please write in caps or type)

KHALID BASHAR

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List of Figures

| | |
|---|------------|
| <i>Figure 3.1: Age distribution among male patients.....</i> | <i>43</i> |
| <i>Figure 3.2: Age distribution among female patients</i> | <i>44</i> |
| <i>Figure 3.3: Variation in age between groups according to gender</i> | <i>45</i> |
| <i>Figure 3.4: Variation in age between mature and non-mature AVF groups.....</i> | <i>49</i> |
| <i>Figure 3.5: Variation in haemoglobin count between mature and non-mature AVF groups</i> | <i>53</i> |
| <i>Figure 4.1: A diagram summarising search results</i> | <i>64</i> |
| <i>Figure 5.1: PRISMA flow diagram</i> | <i>87</i> |
| <i>Figure 5.2: A Forest's Plot for patency rate in 3 months (random effects):</i> | <i>92</i> |
| <i>Figure 5.3: A Forest's Plot for patency rate in 6 months (random effects):</i> | <i>94</i> |
| <i>Figure 5.4: A Forest's Plot for patency rate in 6 months (a sensitivity test with fixed effects model):.....</i> | <i>95</i> |
| <i>Figure 5.5: A Forest's Plot for patency rate after 12 months (random effects):.....</i> | <i>97</i> |
| <i>Figure 5.6: A Forest's Plot for patency rate after 24 months (random effects):.....</i> | <i>99</i> |
| <i>Figure 5.7: A Forest's Plot for postoperative wound haematoma (random effects): ..</i> | <i>101</i> |
| <i>Figure 5.8: A Forest's Plot for postoperative wound haematoma (a sensitivity test with fixed effects model):.....</i> | <i>102</i> |
| <i>Figure 5.9: A Forest's Plot for development of postoperative arterial steal (random effects):</i> | <i>104</i> |
| <i>Figure 5.10: A Forest's Plot for development of postoperative arterial steal (a sensitivity test with fixed effects model):.....</i> | <i>105</i> |
| <i>Figure 6.1: A box Plot showing age distribution per gender:.....</i> | <i>117</i> |
| <i>Figure 6.2: A box Plot showing age distribution per functional maturation.....</i> | <i>121</i> |
| <i>Figure 6.3: A box Plot showing NLR distribution per Maturation</i> | <i>125</i> |
| <i>Figure 6.4: Q-Q Plots showing NLR distribution per mature/non-mature:.....</i> | <i>126</i> |
| <i>Figure 6.5: ROC Curve (area under the curve = 0.63):.....</i> | <i>128</i> |

| | |
|--|-----|
| <i>Figure 7.1: PRISMA flow diagram</i> | 139 |
| <i>Figure 7.2: A Forest's Plot for successful maturation rate (random effects):</i> | 162 |
| <i>Figure 7.3: A Forest's Plot for successful maturation rate (A sensitivity test using fixed effects):</i> | 163 |
| <i>Figure 7.4: A Forest's Plot for postoperative haematoma (random effects):</i> | 165 |
| <i>Figure 7.5: A Forest's Plot for postoperative haematoma (a sensitivity test using fixed effects):</i> | 166 |
| <i>Figure 7.6: A Forest's Plot for postoperative wound infection (random effects):</i> | 168 |
| <i>Figure 7.7: A Forest's Plot for postoperative wound infection (a sensitivity test using fixed effects):</i> | 169 |
| <i>Figure 7.8: A Forest's Plot for the development of steal syndrome (random effects):</i> | 171 |
| <i>Figure 7.9: A Forest's Plot for the development of steal syndrome (a sensitivity test using fixed effects):</i> | 172 |
| <i>Figure 8.1: PRISMA flow diagram</i> | 193 |
| <i>Figure 8.2: A Forest Plot showing Primary AVFs patency at 12 months (random effects):</i> | 201 |
| <i>Figure 8.3: Funnel plot for Primary AVFs patency at 12 months:</i> | 202 |
| <i>Figure 8.4: A Forest Plot showing Primary AVFs patency at 12 months, Lin et al RCT on new AVFs excluded (random effects):</i> | 204 |
| <i>Figure 8.5: A Forest plot showing assisted patency rates at 12months (random effects):</i> | 206 |
| <i>Figure 8.6: A Forest plot showing surgical intervention for AVF malfunction (random effects):</i> | 208 |
| <i>Figure 8.7: A Forest Plot showing Primary AVFs patency at 12 months (Study with maturation rate measured in 3 months added as a sensitivity test (random effects):</i> | 210 |

List of Tables

| | |
|---|------------|
| <i>Table 3.1: Characteristics of patients in study:</i> | <i>46</i> |
| <i>Table 3.2: Characteristics of continuous variables:</i> | <i>47</i> |
| <i>Table 3.3: Categorical variables association with functional maturation</i> | <i>51</i> |
| <i>Table 3.4: Continuous variables (age and blood investigations) association with functional maturation:</i> | <i>54</i> |
| <i>Table 4.1: Summary of included studies</i> | <i>66</i> |
| <i>Table 5.1: characteristics of individual studies.....</i> | <i>78</i> |
| <i>Table 5.2: Results of the study quality assessment</i> | <i>82</i> |
| <i>Table 5.3: Main outcomes from included studies.....</i> | <i>89</i> |
| <i>Table 6.1: Characteristics of patients in study:</i> | <i>118</i> |
| <i>Table 6.2: Characteristics of continuous variables:.....</i> | <i>119</i> |
| <i>Table 6.3: Categorical variables association with functional maturation</i> | <i>122</i> |
| <i>Table 7.1: characteristics of individual studies.....</i> | <i>141</i> |
| <i>Table 7.2: Results of the study quality assessment</i> | <i>147</i> |
| <i>Table 7.3: Main outcomes from included studies.....</i> | <i>155</i> |
| <i>Table 7.4: Maturation outcomes.....</i> | <i>160</i> |
| <i>Table 8.1: Results of the quality assessment of the studies.....</i> | <i>188</i> |
| <i>Table 8.2: Inclusion & exclusion criteria and definition of AVF malfunction for included studies</i> | <i>195</i> |
| <i>Table 8.3: Patients' Characteristics across included studies:.....</i> | <i>198</i> |

List of Appendices

Appendix 1: Ethics Approval Form (Galway University Hospitals)

Appendix 2: Ethics Approval Form (University Hospitals Limerick)

Appendix 3: Publication from the thesis “Pre-operative ultrasonography and arteriovenous fistulae maturation”

Appendix 4: Publication from the thesis “Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease”

Appendix 5: Publication from the thesis “The role of venous diameter in predicting arteriovenous fistula maturation: when not to expect an AVF to mature according to pre-operative vein diameter measurements? A best evidence topic”

Appendix 6: Publication from the thesis “Can a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests predict Arteriovenous Fistula Maturation?”

Appendix 7: Publication from the thesis “One-stage vs. two-stage brachio-basilic arteriovenous fistula for dialysis access: a systematic review and a meta-analysis”

Appendix 8: Publication from the thesis “Role of far infra-red therapy in dialysis arterio-venous fistula maturation and survival: systematic review and meta-analysis”

Appendix 9: Publication from the thesis “Arteriovenous Fistula in dialysis patients: Factors implicated in early and late AVF maturation failure”

List of Appendices

Appendix 10: Work submitted for publication “End-To-Side Versus Side-To-Side Anastomosis In Upper Limb Arteriovenous Fistula For Dialysis Access: A Systematic Review And A Meta-Analysis”

Appendix 11: Work submitted for publication “Arterio-Venous Fistula (AVF) in dialysis patients: Understanding the Pathophysiology behind arteriovenous fistulae non-maturation”

Appendix 12: Publication arising from data collected during the research period “*The Role of Shear Stress in Arteriovenous Fistula Maturation and Failure: A Systematic Review*”

Appendix 13: Publication arising from data collected during the research period “In vivo validation of the in silico predicted pressure drop across an arteriovenous fistula”

List of Abbreviations:

AF: Atrial Fibrillation
AUC: Area Under Curve
AVF: Arteriovenous Fistula
AVG: Arteriovenous Graft
BBAVF | BB-AVF: Brachiobasilic Arteriovenous Fistula
BCAVF | BC-AVF: Brachiocephalic Arteriovenous Fistula
BET: Best Evidence Topic
BMI – body mass index
BVT-AVF: Basilic Vein Transposition Arteriovenous Fistula
BVT: Basilic Vein Transposition
CAD: Coronary Vascular Disease
CKD: Chronic Kidney Disease
cm: Centimetre
COX: Cyclooxygenase
CVC: Central Venous Catheter
DM: Diabetes Mellitus
DOPPS: Dialysis Outcomes and Practice Patterns Study
DVT: Deep Vein Thrombosis
ECM: Extracellular Matrix
ELISA: Enzyme-Linked Immunosorbent Assay
eNOS: endothelial Nitric Oxide Synthase
ESRD: End-Stage Renal Disease
ETS: End-To-Side
g/l: gram per Litre
HD: Haemodialysis
HMWA: High-Molecular Weight Adiponectin
HO-1: Haeme Oxygenase-1
HR: Hazards Ratio
hsCRP: High-Sensitivity C-Reactive Protein
HSE: Health Service Executive
IBM: International Business Machines
IH: Intimal Hyperplasia

K-DOQI: Kidney Disease Outcomes Quality Initiative
l: Litre
mg/dL: Milligram per Decilitre
Min: Minute
mL/min: Millilitre per Minute
mm: Millimetre
MMP: Matrix Metalloproteinases
NKF-KDOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NLR: Neutrophil-Lymphocyte Ratio
NO: Nitric Oxide
NOS: Nitric Oxide Synthase
OR: Odds Ratio
PDGF: Platelet-Derived Growth Factor
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PVD: Peripheral Vascular Disease
Q-Q: Quantile-Quantile
Qa: Access Flow
RCT: Randomised Controlled Trial
RIPC: Remote Ischaemic Preconditioning
ROC: Receiver Operator Curve
RR: Risk Ratio | Relative Risk
SD: Standard Deviation
SOD: Super-Oxide Dismutase
SPSS: Statistical Package for the Social Sciences
STS: Side-To-Side
SVS: Society for Vascular Surgery
TGF- β 1: Transforming Growth Factor Beta-1
TIMP: Tissue Inhibitor Metalloproteinases
Type-II DM: Type Two Diabetes Mellitus
UHL: University Hospital Limerick
VAPR: Derived Static Venous Pressure
VEGF: Vascular Endothelial Growth Factor
WMD: Weighted Mean Difference
WSS: Wall Shear Stress
X²: Chi-Square

Abbreviations

μm : Micrometre

$\mu\text{mol/L}$: Micromole per Litre

INTRODUCTION

I Chapter One: Introduction

Chapter 1: Introduction

1.1 Characteristics of arteriovenous fistulae

A well-functioning arteriovenous fistula (AVF) has been shown to be the best modality for vascular access in patients with end-stage renal disease (ESRD) undergoing haemodialysis (HD) [1-5]. A mature AVF has lower incidence of thrombosis and stenosis compared to the other two modalities - Arteriovenous Graft (AVG) and Central Venous Catheter (CVC), resulting in prolonged patency rates and lower risk for infection. With the exclusion of fistulae that fail to mature primarily, the cumulative patency from formation to permanent failure is superior to grafts, and fewer interventions are required (angioplasty, stenting or thrombectomy) to maintain patency [6-10]. In addition, fistulae are associated with fewer complications compared to grafts and CVCs, such as infection, death, vascular access salvage procedures and hospitalisations [9, 10].

However, around 20% - 50% of fistulae fail to mature into a useable access for haemodialysis [11-14]. The widely used definition for AVF maturation is the one published in the updated Kidney Disease Outcomes Quality Initiative (K-DOQI) guidelines that define mature fistulae as those placed within 6 millimetres from the skin surface, at least 6 millimetres in diameter and finally allow for flow rate of ≥ 600 ml/minute.

AVF has been proven the preferred type of vascular access for haemodialysis patients because of their significantly lower rate of complications when compared to AVGs and CVCs. Grafts are inferior to fistulae in terms of cumulative access survival, cost effectiveness and the need of salvage procedures. On the other hand, CVCs are high risk for sepsis and result in significant morbidity and mortality. The use of CVCs for HD should be discouraged based on the significantly higher risk of complications. Nonetheless, it is estimated according to the DOPPS II study that 46% of European and 66% of American patients start haemodialysis via a CVC (61). Reasons for this include late diagnosis with ESRD, late referral to

nephrologists, lack of time to wait for AVFs to mature, vascular disease, diabetic disease, and the preference of nephrologists and nursing staff in dialysis centres (5). Educating primary physicians and general practitioners in making early diagnosis of patients with Chronic Kidney Disease (CKD) coupled with prompt referral to nephrologists was shown to improve the number of patients starting haemodialysis with mature fistulae (62-64).

However, AVF maturation remains a major concern with as many as one third of first time created fistulae expected to fail. Maturation of AVFs is a complex active process with many variables involved. The haemodynamics of blood flow through the circuit of the AVF seems to be the single most contributing factor in the process of vascular remodelling associated with newly created fistulae. Altered biomechanical forces induces a cascade of reactions induced by the vascular endothelial layer in response to wall shear stress and changes in Haemodynamics. The endothelial response triggers pathways mostly mediated by the release of nitric oxide that can result in increased intimal hyperplasia, in particular in the venous end of the fistula, as well as increased vascular medial thickening and fibrosis. Arterial dilatation is mediated by increased production of nitric oxide; however, matrix metalloproteinases play an important role in the further arterial dilatation required to normalize WSS.

The use of inflammatory markers can prove useful in the prediction of fistula maturation outcomes, as the process seems to be closely mediated and influenced by inflammatory pathways that either are in existence at the time of fistula formation or are induced by the creation of the new AVF. In addition, pharmacological agents that can alter responses to the inflammatory mediators associated with access failure - once fully understood - can lead to increased numbers of mature AVFs.

While it is important to place a new fistula as distal as possible to preserve venous real estate, however, this needs to be weighed against other factors, such as the age of the patient and the size and quality of the vessels distally. In some situations, placing the new fistula more proximally should be acceptable, as it would reduce unnecessary morbidity for little or no gain.

1.2 Intimal Hyperplasia:

Intimal hyperplasia (IH) was first described by Noble Prize winning surgeon Alexis Carrel in 1906 when he noticed that few days following vascular bypass procedure, the stitches placed to make the anastomosis were covered with a “glistening substance similar in appearance to the normal endothelium” [15]. However, it was not until 1971 when Grondin et al published a paper on “Progressive and late obstruction of an aorto-coronary venous bypass graft” that the link was established between intimal hyperplasia and graft restenosis [16].

Intimal Hyperplasia is the process of cellular proliferation within the inner most layer of the blood vessel. It is defined as the abnormal migration and proliferation of vascular smooth muscle cells provoked by injury, inflammation or stretch with the associated deposition of extracellular matrix in the intimal layer of the vein [17-19].

Maturation of AVF depends on variable biomechanical forces induced into the vascular system following creation of the AVF. The remodelling process of the arterial limb of the fistula results in dilatation and outward hypertrophic changes of the intimal layer. Remodelling at the venous end can be accompanied by aggressive thickening of the intimal layer resulting in inward hypertrophic remodelling, which ultimately can lead to stenosis and failure of the AVF to mature. Marked increase in the flow rate and the accompanying abnormal distribution in wall shear stress (WSS) are believed to contribute significantly to intimal hyperplasia and ultimately AVF non-maturation [20-22]. In the absence of significant injury, wall stretch can lead to a less remarkable smooth muscle cells proliferation [18, 23].

The surgical technique used should take into consideration the effects of the newly created haemodynamic forces on the maturation process of arteriovenous fistulae. Fistulae should be constructed in a way that will minimise the negative effects of those changes that can ultimately result in excessive development of intimal hyperplasia that will lead to non-maturation. The newly created access should not be placed under tension,

and the blood vessels - in particular the vein - should be handled with respect to minimise the risk of endothelial damage. In addition, the size of the anastomosis should be adequate to allow for good flow into the conduit, however, big anastomosis - particularly at the elbow - may result in a higher incidence of arterial steal syndrome. Small details like the size of the suture material, and the placement of the suture along the anastomosis line can make the difference in the maturation of the new fistula. Complicated fistulas, such as those formed in patients with small vessels or those with multiple previous failed attempts should be left to the most senior vascular surgeon to give those AVFs the best chance to mature successfully.

1.3 Inflammatory Markers:

It is believed that ESRD patients are predisposed to increased inflammatory changes within the vascular endothelial layer even before the formation of the HD access [24-26]. Wali et reported wall thickening and IH with loss of internal lamina layer in 45% of AVFs created for HD access in ESRD patients, loss of endothelial cell layer in 30%, inflammatory cell infiltration in 25%, mural calcifications in 3 patients (15%) and telangiectasia in 10% of their patients [24]. Liang et al induced chronic kidney disease (CKD) into a group of mice, and then they anastomosed the common carotid artery to the internal jugular vein. Their results showed that mice with CKD had 45% more neointima formation than controls. Also CKD mice had more inflammatory cells, and showed increased endothelial barrier dysfunction [26].

Wasse et al suggested that IH pre-exist in patients with CKD prior to the creation of the fistula. They also observed that inflammation and oxidation markers were present within the veins at least one year before commencement of haemodialysis [27]. Conversely, Allon et al in a series of 50 patients with CKD undergoing AVF formation found that intimal hyperplasia was not present at baseline, but rather developed later in non-maturing fistulae. They also found that medial fibrosis and micro calcifications are common in arteries used for AVFs [28].

Recent studies have shown that matrix metalloproteinases (MMPs) are important in the process of AVF maturation [29-31]. MMPs belong to a group of zinc-dependent proteases capable of degrading extracellular matrix (ECM) proteins [32, 33]. In particular, MMP-2 is expressed by a variety of cell types and is activated by the membrane-bound type-1 MMP (MT1- MMP) and is inhibited by tissue inhibitor metalloproteinases type 2 (TIMP-2). MMP-9 is also expressed by a variety of cell types and is inhibited by TIMP type 4 (TIMP-4) [34]. Because increased expression of MMP-2 and MMP-9 has been found in the tissue of the outflow-vein after AVF construction [30, 35], MMP expression in the patient serum at the time of the initial surgery may serve as an important biomarker of intimal hyperplasia and can possibly predict the maturation outcomes of the newly created fistulae [31].

Owens et al, in a prospective study of lower extremity bypass surgery using autogenous vein, used enzyme-linked immunosorbent assay (ELISA) to measure High-sensitivity C-reactive protein (hsCRP) and the adipokines resistin and high-molecular weight adiponectin (HMWA). They concluded that serum biomarkers of insulin resistance and inflammation might be predictive of clinical outcomes following lower extremity bypasses [36].

Tsapenko et al in 2012 examined the relationship between increased anion production and AVF stenosis in a rat model. They concluded that the increased production of superoxide anion could be due to decreased levels of scavenging promoted by Super-Oxide Dismutase (SOD), combined at the same time with increased generation of superoxide anions by uncoupled Nitric Oxide Synthase. This increase in superoxide anion production promotes juxta-anastomotic stenosis of AVFs and ultimately result in non-maturation [37]. Recently, short term oxygen supplementation following creation of AVFs has been shown to reduce both intimal hyperplasia and smooth muscle cell proliferation in a group of rabbits which were subjected to short term 30% oxygen therapy for forty two days [38].

1.4 Haemodynamic Changes:

AVF maturation is an active process of vascular remodelling that occurs in response to the altered biomechanical forces induced in the vascular system by the creation of the fistula. In order for an AVF to mature into a functioning fistula, sufficient blood flow needs to be obtained through the AVF circuit to insure successful HD repeatedly. This depends on the pressure gradient and the total resistance of the circuit. Mean arterial blood flow needs to be increased several folds to sustain sufficient blood flow - typically around 500 ml/min. This leads to increase in the cardiac output to maintain blood pressure and prevent loss of perfusion to other vascular beds, as well as dilatation of the artery to insure adequate perfusion distal to the fistula and reduce the risk of steal syndrome [39]. However, several factors should be considered when measuring expected arterial dilatation; distal arterial flow occurs in about 75% of forearm fistulae and contributes an average of 25% of venous flow of the AVF [40]. Moreover, blood flow is pulsatile rather than steady, and the average pressure gradient increases following creation of AVF, as well as the decrease in blood viscosity with increasing flow rate limiting wall shear stress (WSS). All of that will limit the expected arterial dilatation to maintain required blood flow through the circuit as per Poiseuille's law [39, 41, 42].

Arterial remodelling is a response to pressure and flow changes, and is controlled by the endothelium, sensing wall shear stress (WSS) changes. The changes are caused by creating opposing forces within the vessel wall as a result of the deformation that occurs in three directions; longitudinal, circumferential and radial creating both normal tensile stress and shear stress resulting in nine static forces (three static deformation and six static stresses) that can affect vascular dilatation and remodelling [39]. The flow-mediated remodelling affects both the artery and the vein of the AVF. Arterial dilatation has been shown to lower WSS to baseline levels [21, 43]. Fashioning a new AVF in a way that will result in decreased WSS over time is thought to positively impact on maturation [21]. Venous response to WSS is variable, as some studies have shown venous dilatation, while others reported reduction in luminal area with similar levels of WSS [21, 29, 44-46]. Dobrin et al examined mechanical and histological changes in femoral vein applied as a

graft to bypass a ligated femoral artery in dog models. They found that intimal hyperplasia correlated with low WSS, while medial thickening correlated with circumferential deformation, and concluded that intimal hyperplasia and medial thickening are different responses to different stimuli influencing vascular dilatation and remodelling [47]. Ben Driss et al examined the effects of chronic increase in blood flow on arterial wall remodelling in Aortocaval Fistulae in rats. They found that shear stress promotes expansive remodelling in relation to flow dependant vasodilatation, whereas medial thickening was related to increase in the tensile stress [48].

Since the remodelling process is mediated by endothelial response to flow and pressure, the loss of endothelial cells impairs remodelling and prevent WSS from dropping to baseline levels following creation of AVF [39]. The physiology of vascular remodelling and reconstruction mediated by the endothelial cell response to stress is not fully understood [22, 39]. It is believed that an increase in shear stress results in increased production of Nitric Oxide (NO) among other endothelial derived vasodilators in an attempt to normalise WSS following fistula formation [49, 50]. Miller VM. et al in 1992 showed that chronic increase in blood flow may induce endothelial cells to either inhibit production of endothelin or promote its depletion, and at the same time enhances the smooth muscle cells response to its contractile effects [49]. However, further arterial dilatation is required to lower WSS than the endothelial-mediated response in the acute phase by generation of NO. This fragmentation of vascular elastic lamina is mediated by MMPs, which is also induced by changes in blood flow and pressure. The activation of MMPs can be inhibited by Doxycycline treatment that inhibits Nitric Oxide Synthase production; hence, MMPs are likely controlled by levels of Nitric Oxide [51]. Castier et al examined the effect of homozygous targeted deletion of endothelial nitric oxide synthase (NOS) on MMPs in mice. They found that both the increase in MMPs activity and the arterial dilatation were lost. Their findings further underline the role of NOS in regulating MMPs activity and flow induced vascular remodelling [52].

Several studies showed the association between the anatomical configuration of fistulas and WSS, and consequently the pattern of luminal stenosis because of intimal hyperplasia, and media thickening and fibrosis. Using computer

modelling to alter anatomic configuration has been suggested to reduce WSS deformation and hence improve fistula successful maturation rates [20, 21, 53, 54].

1.5 Remote Ischaemic Preconditioning:

To date, no randomised controlled studies have looked into the effect of remote ischaemic preconditioning (RIPC) on the maturation of AVF in patients with end stage renal disease. Remote Ischaemic Preconditioning (RIPC) is a phenomenon that occurs in mammals whereby brief periods of ischaemia in a remote distant tissue, followed by reperfusion causes subsequent resistance in different organs to a much prolonged periods of ischaemia. It has been so far mostly applied to the heart. C. E. Murry in 1986 showed that brief periods of ischaemia slowed the rate of ATP depletion during subsequent ischaemic episodes, and proposed that multiple brief ischemic episodes might actually protect the heart from a subsequent sustained ischemic insult. Ischemia limited infarct size to 25% of that seen in the control group ($p < \text{than } .001$) [55]. RIPC is expected to lower inflammatory markers that are associated with higher risk of intimal hyperplasia and subsequently, graft failure. Owens CD et al in 2010 reported a prospective longitudinal study of lower extremity bypass surgery using autogenous vein. They used enzyme-linked immunosorbent assay (ELISA) to measure High-sensitivity C-reactive protein (hsCRP) and the adipokines resistin and high-molecular weight adiponectin (HMWA). Their main outcome measure was primary patency. Endpoints were screened against biomarkers and patient characteristics for univariate associations. They concluded that serum biomarkers of insulin resistance and inflammation might be predictive of clinical outcomes following lower extremity bypass [36].

Recent studies showed promising results of RIPC when applied to patients undergoing a number of vascular procedures such as elective abdominal aortic aneurysm repair, angioplasty, coronary artery bypass graft surgery, carotid endarterectomy and as a conservative treatment option to improve claudication symptoms in patients with peripheral vascular diseases [56-62].

1.6 Preoperative Ultrasound Mapping

Arteriovenous fistulas (AVFs) are the preferred mode of vascular access for dialysis. AVF formation is an operative vascular procedure, involving considerable resource utilisation in terms of staff and theatre time. A considerable proportion of surgically- created AVFs fail to mature into usable dialysis access, with failure rates as high as 53% reported [63, 64]. AVF maturation is a complex process. Formation of an AVF alters the biomechanical forces within the local vascular system, as flow is diverted from the artery and the venous limb is exposed to increased pressure. Maturation into a usable AVF depends upon obtaining sufficient flow within the AVF circuit.

Flow is a function of the pressure gradient across the circuit and also the resistance within the circuit [39]. Inadequate baseline flow in the arterial limb may thus impede fistula maturation due to an inadequate pressure gradient. Narrow diameter segments, stenoses and occlusions in the venous limb will result in increased resistance within the circuit, also impeding AVF maturation. Duplex ultrasonography is a non-invasive and safe method of evaluating morphologic and functional vessel characteristics such as diameter, the presence of stenosis, occlusions, or low arterial flow that could identify proposed AVF circuits that are unlikely to mature successfully. Duplex is intuitively attractive for this role with several current guidelines recommending routine duplex mapping in advance of AVF formation [65], although robust level 1 evidence to support this is lacking.

1.6.1 Current Practice

Although recommended as routine practice in some guidelines, there is no clear consensus regarding the role of pre-AVF duplex mapping. Traditionally, suitability for AVF formation was evaluated by clinical examination alone. Factors such as obesity and compromised vessels e.g. previous cannulation or multiple previous access attempts may render physical examination findings unreliable. Various imaging modalities have been evaluated as adjuncts to

physical examination alone, with units developing selective imaging protocols for AVF candidates.

Patel et al initially screened patients by physical examination [66]. If the examination findings did not identify any suitable vessels for haemodialysis access, the patients underwent duplex ultrasonography. If no suitable vessels were identified by ultrasound, or only a basilica vein was suitable, the patients underwent venography. They found that autogenous AVF formation in first-procedure patients increased from 66% to 83% using this protocol. Ultrasound was performed in two-thirds of the patients, while 32% underwent venography. The frequency with which imaging was used in this selective protocol underlines the limitations of clinical examination.

The reliability of clinical examination for AVF planning was evaluated in a recent prospective study [67]. Patients attending a 'one-stop' AVF formation clinic were examined by a surgeon and a plan agreed for AVF formation. Each patient then underwent ultrasound examination by the surgeon using portable ultrasound equipment in the clinic. In total, the surgical plan was revised in 30% of patients following the ultrasound, with 10% of patients receiving a more distal AVF and 20% a more proximal one. Cumulative patency of 86% was achieved at 3 months post-procedure, although the study cohort was small (n=39 patients). Another small series (n=52 patients) also reported that ultrasound altered the surgical plan in 32% of patients planned based on clinical examination alone [68]. These findings further highlight the limitations of clinical examination alone and support the argument for routine imaging.

1.6.2 Evidence for routine ultrasonography

The effect of routine pre-AVF duplex mapping on subsequent AVF maturation rates was evaluated in a recent systematic review [69]. The review included randomised trials of patients undergoing primary AVF formation who were assigned to either pre-operative clinical examination plus ultrasound or

clinical examination alone. Pubmed and the Cochrane library were searched for relevant trials whilst conference proceedings from a number of relevant surgical conferences were manually searched for otherwise unpublished trials. The outcome for the review was successful use of the formed fistula for dialysis.

The systematic review identified three eligible trials, containing 402 patients [70-72]. Of those, 214 patients that were randomised to ultrasound underwent surgery, of whom 174 successfully used their fistula for dialysis. Of the 188 patients assessed by clinical examination alone, 130 subsequently used their fistula for dialysis. Two trials reported that duplex improved successful AVF formation [70, 71] while the remaining trial reported no benefit [72]. When the data were pooled for meta-analysis, there was no clear benefit for routine duplex (pooled odds ratio 1.96; 95% confidence interval 0.85 to 4.50; $p=0.12$) [69].

The review has a number of limitations. Random sequence generation and allocation concealment were clearly reported in only one of the included trials [70], introducing a possibility of selection bias. It was also not possible to establish clearly that all outcome data had been collected and reported in most of the trials, leading to risks of attrition bias and reporting bias [69]. The ultrasonographic criteria used to determine suitability for AVF formation differed between the trials, with a variety of arterial and venous criteria utilised [69]. None of the trials included an economic analysis.

1.6.3 Ultrasonographic criteria

The variability in ultrasound criteria found between the trials reflects clinical practice, with no clear consensus regarding minimal acceptable arterial or venous characteristics. The optimal cut-off for arterial diameter with respect to AVF maturation and adequacy for dialysis is unknown and difficult to establish given the confounding influence of arterial disease elsewhere in the arterial tree. Using an arterial lumen diameter of at least 2mm on ultrasound resulted in 92% of radiocephalic AVFs maturing [73]. Several studies suggest using a lower radial arterial diameter cut-off. Early failure has been reported

in all AVFs formed using radial arteries less than 1.6mm diameter [74, 75]. Malovrh reported the results from 35 patients who underwent duplex mapping prior to AVF formation. Among patients with an internal arterial diameter < 1.5mm, immediate patency of the AVF was present in 45% (5/11) compared to 92% (22/24) for those with an internal diameter > 1.5mm [76]. By 12 weeks, the AVF remained patent in only 36% of those with an initial arterial diameter <1.5mm. Another study of 21 patients reported that 45% of those with an arterial diameter below 1.5mm immediately thrombosed while all patients with an initial diameter >1.5mm had patent AVFs at 12 weeks [77]. Other ultrasonographic criteria have been investigated e.g. intimal medial thickness [78] and reactive hyperaemia [79] but are not routinely available in many centres.

No agreed consensus exists regarding the minimum venous diameter values that predict radiocephalic AVF maturation. Silva et al reported good outcomes using a cut-off of 2.5mm with a tourniquet, reporting 83% functional primary patency at 1 year [73]. Wong et al reported that all AVF failed if the venous diameter was less than 1.6mm. These investigators reported no difference in the average venous diameter at the wrist between failed and successful fistulae, although the sample size was small [75].

Mendes et al evaluated 44 patients undergoing wrist AVF formation. In this cohort, only 16% of patients with a maximum venous diameter less than 2mm developed a successful AVF compared to 76% among the remaining patients [80]. Day-to-day variation in vein diameters combined with examination conditions (ambient temperature, patient position) render it essential that veins be evaluated under optimal conditions with distensibility testing for apparently small veins [81]. These factors complicate efforts to identify an optimal vein diameter to predict success.

Contrast venography was once considered the gold standard in investigating the suitability of veins for the creation of an AVF. However, due to relatively high cost, risk of allergic reactions and the invasive nature of the test, it has been replaced with duplex scans [82, 83]. Venography is still a valuable test when investigating certain patients prior to access formation, such as those

with suspected central venous stenosis based on history of previous placements of ipsilateral CVCs for haemodialysis. Duplex scans will be of limited value in assessing the central veins due to their anatomic positions behind bony structures limiting the penetration of ultrasound waves.

Accurate prediction of success is essential to optimise the use of scarce haemodialysis access resources. Clinical examination alone is not sufficiently reliable to allow accurate AVF planning and some form of adjunctive imaging is needed. Duplex ultrasonography is widely available and non-invasive, although operator-dependent. Current data are insufficient to justify a policy of routine duplex ultrasound for all AVF candidates although a selective policy appears justified. Consensus regarding ultrasonographic vessel criteria for AVF formation is needed.

METHODS

II Chapter Two: Methods

Chapter 2: Methods

2.1 Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease

The objective of this study was to test the hypothesis that certain patients' characteristics (age, gender and medical co-morbidities - diabetes in particular) affect the maturation of AVF. The author of this thesis also aimed to test the association between specific inflammatory markers (white cell count and neutrophils) and preoperative haemoglobin's level with AVF maturation.

2.1.1 Patients:

The author of this thesis performed a retrospective chart review of all patients with ESRD who were referred to the vascular service in the University Hospital of Limerick for creation of vascular access for HD. Three surgeons performed the procedures. The data-analysis was performed according to a predefined set of outcomes based on extensive search of the literature.

2.1.2 Inclusion and exclusion criteria:

All patients aged 18 years or older who underwent formation of AVF in the upper limb between 2006 and 2013 were included. Patients with multiple episodes, each episode was considered separately and data from the corresponding episode was recorded on our data sheet. It needs to be highlighted that patients with history of a failed fistula in the past are more likely to have poor outcomes from a new fistula, as they are more likely to have factors that predispose to non-maturation, such as small vessels or poor quality vessels. Patients that underwent salvage procedures to improve maturation, i.e. secondary maturation, were excluded as the author analysed

data related to primary functional maturation rates only. All patients who had prosthetic graft and/or tunnelled catheters as the only means for HD were excluded.

2.1.3 Data collection:

After obtaining an ethical approval for the study from the research ethics committee and the risk management department of the regional Health Service Executive (HSE West), data for all included patients were extracted from their medical records. Patients were not asked to provide consents (written/oral), as all records were anonymised and data were de-identified prior to analysis and reporting of findings. It should be highlighted that seeking at least a verbal consent would be the normal practice in many other institutes as we have used data collected from patients for a different purpose in our study than the originally intended purpose behind the data collection, however, we have not used any identifiers in our study, and that satisfied our ethics committee. Baseline demographic information, site and type of the AV fistula were retrieved from the medical records, whereas results of blood investigations were obtained from electronic records. Functional maturation was recorded from dialysis records.

2.1.4 Study's primary and secondary endpoints:

The author aimed to evaluate patients' characteristics that have been reported to be associated with AVF non-maturation in the literature following an extensive review of published evidence. A functional maturation definition was used in this study, which was defined as the successful use of the arteriovenous fistula for six consecutive sessions of HD, and this was obtained from dialysis records. The use of functional maturation defined as sustained HD sessions ≥ 6 for the evaluation of AVF maturation has been validated in the literature in several previous studies [84-86]. This method is acceptable, particularly in retrospective studies assessing AVF maturation before the regular use of preoperative venous mapping and postoperative US scans – as the case with this study as most of our patients did not have postoperative US scans. However, the author should point to its inferiority compared to the

definition recommended in the updated National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines, famously known as the rule of (6s) (flow of approximately 600 mL/min, less than 0.6 cm below the skin surface and a minimal diameter of 0.6 cm) [1]. In addition, in the absence of postoperative imaging scans, it will be difficult if not entirely impossible to differentiate between non-maturation and mis-cannulation by less experienced staff in dialysis units. At our hospital, new fistulas are looked after by senior dialysis nurses who are well experienced in cannulation of arteriovenous fistulas.

The author examined the relationship between age, gender, diabetes, smoking, hypertension, hyperlipidaemia, history of steroids use, history of Calcium channel blockers at the time of access formation and the history of previous dialysis access (AVF, AVG or CVC). Secondary endpoints were perioperative blood investigations (Haemoglobin, White cells count and Neutrophils count). In addition, the aetiology behind ESRD was recorded whenever available from medical records.

2.1.5 Statistical analysis:

Data were extracted and recorded on spread sheet using IBM SPSS version 22.0 [87]. Categorical data are expressed in true value and as percentages and were compared using the Pearson Chi-Square (X^2) test, whereas continuous data were reported as mean \pm SD and compared using the independent sample t-test for normally distributed data, and the Mann-Whitney U when indicated by normality tests. Levene's test for equality of variances was used to determine the p value in t-test regression analysis for continuous data [88]. Data distribution of the various predictor variables were assessed by means of histograms, Q-Q plots and box plots. Finally, a prediction model was calculated by logistic regression analysis using data from variables that have been suggested to correlate to fistula in the literature, as well as variables from our study with a *p* value of < 0.1 in univariate analysis with functional maturation being the dependent (outcome) measure of analysis. In addition, an overall logistic regression test was performed with all of the included variables in our study without restrictions in terms of the *p* value.

2.2 The role of venous diameter in predicting arteriovenous fistula maturation

The objective of this study was to determine the adequate diameter of the vein used in creating an AVF that is likely to mature successfully.

2.2.1 Three-part question:

In patients with [ESRD waiting to be started on HD], who are being [referred for AVF formation] with a preoperative venous mapping, what is [the minimum vein diameter] predictive of successful maturation?

2.2.2 Search strategy:

The Medline database and the Cochrane Central Register of Controlled Trials (up to June 2014) were searched using the terms (([vein diameter] AND [arteriovenous fistula] AND ([maturation] OR [successful] OR [patent]) AND ([haemodialysis] OR [haemodialysis]) AND ([preoperative] OR [US] OR [Ultra Sound])). The search was restricted to English language and humans. No time restriction was applied. Studies that cross-matched preoperative vein diameter used to create AVF to successful maturation were included. Studies that did not correlate the diameter of vein to maturation were excluded.

2.3 End-To-Side versus Side-To-Side Anastomosis Techniques in Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis

This systematic review was designed to examine the differences between the two configurations (ETS vs STS) by assessing maturation, primary and secondary patency rates, as well as postoperative complications associated with both anastomosis techniques.

2.3.1 Eligibility Criteria:

All randomised controlled trials (RCTs) and observational studies that compared the outcomes of interest from using an end-to-side (ETS) technique to a side-to-side (STS) technique in creating an arteriovenous fistula (AVF) for haemodialysis access were included in this systematic review. Case series and review articles were excluded. Only studies published in English language were included in this systematic review. This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89]. The author accepts that pooling results from RCTs and observational studies together to perform a meta-analysis can result in significant heterogeneity because of the distinctively different methodological approaches intrinsic to each study type. One recognised method of dealing with this limitation when it results in significant heterogeneity is to perform a sensitivity test by pooling data from RCTs and observational studies in separate tests and compare the difference in statistical significance.

2.3.2 Search strategy:

An extensive search of the literature was performed in November 2015 looking for relevant studies conducted using the following terms: ([“Arteriovenous Fistula” OR “Fistula” OR “AVF” OR “Access” OR “Haemodialysis” OR “Hemodialysis”] AND [“End to Side” OR “End-to-Side”] AND [“Side to Side” OR “Side-to-Side”]). The authors searched the following databases: Medline, CINAHL, EMBASE, SCOPUS, the Cochrane library and Google Scholar. No

restrictions were applied in terms of publication date or status. Studies were limited to English language and trials reporting on human subjects. In addition, the author searched the bibliographies of included studies for any additional citations.

Following the initial search, the first author (KB) and the second author (MM) evaluated all obtained abstracts for eligibility as per the agreed protocol. When the first two authors could not resolve ambiguity from the abstract, the full article was examined in full. Any remaining discrepancies regarding eligibility of potential studies was then settled by consulting with the senior author (SRW). The complete manuscripts of all abstracts that were deemed eligible were subsequently obtained.

2.3.3 Endpoints and definitions:

The main endpoint of this review was primary patency as reported in included studies. Secondary endpoints were the development of postoperative complications, namely wound haematoma, wound infection and steal syndrome. The authors used the definitions provided in individual studies for “maturation”, “primary patency” and “secondary patency”. Similarly, individual definitions were used for postoperative complications.

2.3.4 Data Collection:

Two authors independently extracted the relevant data from included studies (KB, MM) which were then entered in Microsoft® Excel spreadsheet. Ambiguity in data collection and disagreements that remained following discussions between the first authors (KB, MM) were then resolved by the senior author (SRW). All included studies were examined for the following: age, sex, comorbid conditions, history of smoking, primary patency rate, secondary patency rate, cumulative access survival (overall maturation by the end of the study follow-up period) and postoperative complications (arterial steal syndrome, venous hypertension, wound haematoma and wound infection). The primary patency rate was defined as the unassisted patency rate without the help of salvage procedures (endovascular and open). The

secondary patency rate was defined as the assisted patency rate of all fistulas including the ones that required salvage procedures to improve access flow rates. Patency rates were pooled together for comparison whenever those rates were reported at similar interval from the time of AVF formation. No restrictions were applied based on the length of postoperative follow-up.

2.3.5 Quality assessment for risk of bias:

The Downs and Black tool was used to assess the quality of included studies [90]. This tool consists of 27 questions that examine the quality of both randomised and non-randomised studies. The tool evaluated the quality, external validity, bias and confounding from individual studies. In this modified tool, sample size calculation is considered in one question only, as opposed to five in the original tool that has 32 questions. Therefore, the maximum score for an individual study is 27, with a lower score indicating poor quality.

2.3.6 Data analysis:

The statistical tool Review Manager version 5.3 was used to perform the tests included in the meta-analysis section of the review [91]. The random effects model of DerSimonian and Laird was used to compare categorical outcome measures pooled as risk ratios [92]. Statistical heterogeneity among studies was assessed by the Cochran's Q-test. Statistically significant differences were reported if the p-value was less than 5%. In addition, publication bias was evaluated by comparing between the fixed and random effects models for outcomes in a sensitivity test to determine the impact of small-study effects [93].

2.4 The utility of a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests in predicting Arteriovenous Fistula Maturation

The author of this thesis hypothesised that inflammatory markers at the time of access formation are associated with the process of fistula maturation through increased production of haematological factors associated with increased levels of Intimal hyperplasia. The author examined if calculating the Neutrophil-Lymphocyte Ratio (NLR) obtained at the time of AVF creation would predict the maturation outcome.

2.4.1 Materials and Methods:

Patients who were referred to the vascular unit in the University Hospital Limerick (UHL) for formation of an upper limb AVF between 2009 and 2013 with a known fistula maturation outcome measured functionally in the haemodialysis unit were included in this study. Three surgeons performed the procedures. Patients with a minimum age of 18 years were included. In those with multiple episodes of a new AVF formation, the author of this thesis considered each episode separately. All fistulae were created in the wrist or forearm.

Ethical approval for the study was obtained from the research ethics committee and the risk management department of the regional Health Service Executive (HSE West). The author extracted all relevant data from the patients' medical records including electronic records for discharge notes and laboratory blood tests; all records were anonymised and data de-identified prior to processing.

2.4.2 Study objectives and definitions:

The author aimed to test the hypothesis that a Neutrophil-Lymphocyte Ratio (NLR) – defined as the absolute neutrophils count divided by the absolute lymphocytes count – can predict fistula maturation. The NLR was calculated

from blood tests obtained routinely on the morning of the fistula operation on all patients with the exception of in-patients who would have their routine blood tests done the evening prior to the procedure. A functional maturation rate was assessed in this study, which was defined as the successful use of the arteriovenous fistula for six consecutive sessions of HD, and this was obtained from dialysis records. This method has been validated and extensively used in published literature (20-23).

In addition, the author aimed to evaluate the association between certain demographics (age, gender, diabetes, smoking, hypertension, hyperlipidaemia, history of steroids use, history of Calcium channel blockers at the time of the access formation and the history of previous dialysis access) and functional AVF maturation as secondary endpoints. The aetiology behind ESRD was also recorded whenever possible.

2.4.3 Statistical analysis:

Data were collected and recorded on spreadsheet; IBM SPSS version 22.0 was used for statistical analysis (24). Categorical data are expressed in true value and as percentages and were compared using the Pearson Chi-Square (X^2) test. The independent sample t-test was used to compare normally distributed continuous data that were reported as mean \pm SD; for abnormally distributed continuous data (reported as median and range), the author used the Mann-Whitney U test. Levene's test for equality of variances was used to determine the p value in the t-test regression analysis for continuous data (25). Distribution of data was assessed by histograms, Q-Q plots and box-plots. The 5% level with a confidence interval of 95% was considered significant.

2.5 One-Stage Vs Two-Stage Brachio-Basilic Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis

This systematic review was designed to assess the differences between the one-stage and the two-stage brachiobasilic AVF (BB-AVF) procedures in terms of access maturation and survival, as well as complications and interventions required to maintain patency for haemodialysis.

2.5.1 Eligibility Criteria:

Randomised controlled trials (RCTs) and observational studies that compared the one-stage technique with the two-stage technique for creating a brachiobasilic arteriovenous fistula (BB-AVF) for haemodialysis access were searched online. Case series and review articles were excluded from this review. Only studies published in English language were included in this systematic review. This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89]. The author accepts that pooling results from RCTs and observational studies together to perform a meta-analysis can result in significant heterogeneity because of the distinctively different methodological approaches intrinsic to each study type. One recognised method of dealing with this limitation when it results in significant heterogeneity is to perform a sensitivity test by pooling data from RCTs and observational studies in separate tests and compare the difference in statistical significance.

2.5.2 Search strategy:

A search of the literature for relevant studies was conducted in August 2014 using the following terms: [“Basilic Vein” OR “Basilic”] AND [“Fistula” OR “Arteriovenous” OR “Access”] AND “dialysis”). A search of the following online databases was conducted: Medline, CINAHL, EMBASE, the Cochrane library and Google Scholar. The search was not restricted by publication date or status, however, only studies published in English language and those conducted on humans were included. In addition, the author searched the

bibliographies of included trials for additional studies. Studies were not restricted based on the duration of follow-up. Eligibility for inclusion was determined by two researchers separately (KB, DH) by going through the abstracts of the relevant citations. Differences were settled by examining the full article by both authors, and then any remaining uncertainties regarding eligibility of studies were settled following a discussion with a third author (SRW).

2.5.3 Outcomes assessed:

The main outcome measures for this review were successful maturation and development of postoperative complications, namely wound haematoma, wound infection and steal syndrome. Secondary outcomes were primary and secondary patency rates. Definitions for “maturation”, “primary patency” and “secondary patency” were those specified in individual studies.

2.5.4 Data Collection:

KB and DH independently extracted the data from included studies on a Microsoft Excel spreadsheet. Any differences in recording the outcomes of interest were discussed between two authors (KB, DH), and if remained unsettled, a third author was consulted to resolve the issue (SRW). The following characteristics regarding participants were recorded: age, sex, presence of co-morbidities, primary patency rate, secondary patency rate, maturation rate and postoperative complications (Haematoma, wound infection and steal syndrome). Usability of fistula for Haemodialysis, time to first use for HD and interventions needed to maintain patency were recorded when possible. Data extracted in compliance with the Society for Vascular Surgery (SVS) recommended standards for reports dealing with arteriovenous haemodialysis accesses [29]. To this end, the author assessed whether studies provided SVS standard-based grading of factors that affect outcomes and whether studies provided SVS standard-based grading of severity of arteriovenous access complications.

2.6 Role of Far Infra-Red therapy in dialysis Arterio-venous Fistula maturation and survival: Systematic review and meta-analysis

This systematic review was designed to examine the effect of post-conditioning by means of using Far-Infrared technology on AVF maturation using primary and secondary patency rates as the main outcomes of interest.

2.6.1 Eligibility Criteria

Included studies were observational studies or randomised controlled trials (RCTs) that examined FIR therapy in patients with AVFs and ESRD. Eligible studies reported on AVF patency rates in FIR and non-FIR groups at one year or more following initiation of FIR therapy. Case series and case reports were excluded. There was no restriction with regard to publication status or language. This systematic review only included RCTs, as there were no observational studies found. Therefore, heterogeneity from pooling data from papers with different research methodologies was not an issue. This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89].

2.6.2 Search strategy

A search of the literature for relevant studies was conducted in March 2014. The author searched Medline without date restriction using the free text “far infra-red”. Additionally the author used the strategy ([“far infra-red” OR “far infrared” OR “post conditioning”] AND [“arteriovenous fistula” “dialysis” OR “end stage renal disease” OR “dialysis access” OR “access survival” OR “primary patency” OR “secondary patency” OR “fistula maturation”]) to search CINAHL, EMBASE, the Cochrane library and Google Scholar. Bibliographies of included studies were searched for additional studies.

Abstracts of the relevant titles were subsequently obtained and evaluated for eligibility (KB, DH). Any remaining uncertainty was resolved by examination of

the full article (KB, DH). Discussion with a third author (SRW) resolved discrepancies in cases of disagreement regarding eligibility.

2.6.3 Outcomes assessed

The relevant outcomes for this review were primary patency – defined as unassisted AVF patency rates after at least 12 months of follow up - and secondary patency – defined as assisted patency rates after at least 12 months of follow up. The incidence of salvage procedures (endoluminal procedures or surgical procedures) for dysfunctional fistulas during follow up was a secondary outcome.

2.6.4 Data Collection

Data were extracted and checked for accuracy by two reviewers (KB, DH) independently and recorded on a Microsoft® Excel spreadsheet. Any disagreements in extracting data were discussed between two reviewers (KB, DH), and if not settled this was resolved by consulting with a third reviewer (SRW). The following information regarding participant characteristics were recorded: age, sex, , presence of co-morbidities, start of HD, primary and secondary patency rates, AVF salvage procedures, underlying cause of ESRD, definition of first AVF malfunction and overall access survival. The trials' inclusion and exclusion criteria were also recorded.

2.6.5 Quality assessment for risk of bias

The risk of bias for each study was assessed according to the criteria outlined in the in the Cochrane Handbook for Systematic Reviews of Interventions [94]. For each included study, the methods used to perform random sequence generation, allocation concealment and blinding were described. The study was then scrutinised for incomplete data outcomes, selective reporting and other potential sources of bias. Where possible, study protocols were obtained from trial registries to ascertain whether there was selective reporting within studies.

2.6.6 Data analysis

Statistical analyses were performed using Review Manager version 5.2.8 [91]. Pooled risk ratios were calculated using the random effects model of DerSimonian and Laird [92]. For continuous outcome variables, the weighted mean difference (WMD) was calculated. The presence of statistical heterogeneity between studies was evaluated using the Cochran's Q statistic. P-values less than 5% were considered as statistically significant. Publication bias was assessed visually using a funnel plot, and additionally by comparing fixed and random effects modelling in a sensitivity analysis – this is a recognised method that can detect the influence of small-study effects [93].

RESULTS

III Chapter Three: Predictive Parameters
of Arteriovenous Fistula Functional
Maturation in a Population of Patients
with End-Stage Renal Disease

3.1 Introduction:

The number of patients with end stage renal disease (ESRD) has been increasing steadily, a trend that is expected to continue; as a result, more patients are expected to require vascular access placement for haemodialysis (HD) [95, 96]. A mature and functional arteriovenous fistula (AVF) is considered the best modality for HD access when compared to arteriovenous grafts (AVG) and central venous catheters (CVC) [97-99], however it is expected that approximately one third (20% - 50%) of AVFs will fail to mature into useful access [7, 100, 101]. Although the chances for AVFs to fail are relatively high, they should still be considered first in all patients planned to start HD sessions, and for those who have already started HD, an attempt to form an AVF should always be considered when feasible. Mortality rate has been shown to be significantly higher in those who dialyse first by means of tunnelled catheters, and at the same time, they are at increased risk of failure of a subsequent AVF [100, 102, 103]. Arteriovenous grafts tend to have better primary patency rates compared to AVF [7, 104, 105], however AVFs last longer, and with the exception of those fistulas that fail to mature primarily; the cumulative patency (from formation to permanent failure) is superior to grafts. Moreover, AVFs - once they fully mature - are less likely to require secondary procedures for vascular access salvage to maintain patency, including angioplasty, stenting or thrombectomy [6-10]. The 2006 updated NKF-KDOQI Guidelines recommend AVF prevalence of $\geq 65\%$ for patients undergoing HD [1]. Currently, the prevalence of AVF in those patients is around 80% in Europe and around 60% in the United States [100, 103, 106].

Certain patients' characteristics have been associated historically with poor AVF maturation rates, in particular female gender, age and diabetes. Conte MS et al published study of 31 patients who had AVFs created as part of their V-HEALTH trial. They found that diabetic patients had significantly lower patency rates in the 24 weeks of the follow-up period [107]. Similarly, Salmela et al reported that diabetes, female sex and thrombophilia were all associated with decreased primary fistula patency rates [108]. Conversely, Sedlacek et al in study of 195 patients reported that diabetes was not associated with AVF maturation as 67% matured in the diabetic group compared to 62% in the non-diabetic group. In addition, diabetes did not influence the prevalence of AVF

creation as 66% in the diabetic group underwent fistula placement compared to 60% in the non-diabetic group [109]. More recently, Allon et al found that both age and diabetes were not associated with increased non-maturation rates, although they were both significantly linked to increased medial fibrosis [28].

Another factor thought to be associated with AVF maturation is age. Elderly patients are traditionally thought to have worse patency rates and more likely to suffer from AVF non-maturation [110, 111]. However, this has been disputed by other authors [101, 112].

Concerning the association between gender variation, and AVF non-maturation, there have been conflicting results reported in published literature. Several studies suggested a significant correlation between female gender and decreased patency rates in AVFs, as well as prolonged maturation time before the fistula can be successfully cannulated for HD sessions [108, 110, 113]. A combination of female gender and increased age (> 65) has been shown to be significantly associated with non-maturation when compared to men of the same age group [28, 111]. However, several other studies found no significant association between female gender and high risk of AVF non-maturation [28, 112, 114].

Certain haematological findings have been implicated in the maturation process of AVF. Khavanin Zadeh et al in a prospective study of HD patients who were referred for first time AVF formation reported higher risk of AVF failure in those with haemoglobin level < 8 g/dl (RR=1.41; p=0.01) [115]. More recently, Yilmaz et al looked into the relationship between late AVF stenosis and neutrophil-lymphocyte-ratio (NLR) based on blood results obtained from chronic haemodialysis patients. They hypothesised that increased level of inflammatory markers will lead to increased number of stenosed AVFs. They suggested that the mechanisms responsible for AVF stenosis might be similar to those involved in atherosclerosis disease [116].

The objective of this paper was to report our own findings from the last 7 years in a regional hospital - situated in the Mid-Western area of Ireland - in relation to patients' characteristics and comorbidities that might affect the process of AVF maturation according to predefined outcomes. This study was aimed to test the hypothesis that certain characteristics (age, gender and medical comorbidities - diabetes in particular) affect the maturation of AVF. The author also aimed to test the association between specific inflammatory markers (white cell count and neutrophils) and haemoglobin's level preoperatively with AVF maturation.

3.2 Methods:

3.2.1 Patients:

The author performed a retrospective chart review of all patients with ESRD who were referred to the vascular service in the University Hospital of Limerick for creation of vascular access for HD. Three surgeons performed the procedures. The data-analysis was performed according to a predefined set of outcomes based on extensive search of the literature.

3.2.2 Inclusion and exclusion criteria:

All patients aged 18 years or older who underwent formation of new AVFs in the upper limb between 2006 and 2013 were included. Patients with multiple episodes, each episode was considered separately and data from the corresponding episode was recorded on our data sheet. It needs to be highlighted that patients with history of a failed fistula in the past are more likely to have poor outcomes from a new fistula, as they are more likely to have factors that predispose to non-maturation, such as small vessels or poor quality vessels. Patients that underwent salvage procedures to improve maturation, i.e. secondary maturation were excluded from the study, as the author analysed data related to primary functional maturation rates only. All patients who had prosthetic graft and/or tunnelled catheters as the only means for HD were excluded.

3.2.3 Data collection:

After obtaining an ethical approval for the study from the research ethics committee and the risk management department of the regional Health Service Executive (HSE West), data for all included patients were extracted from their medical records. Patients were not asked to provide consents (written/oral), as all records were anonymised and data were de-identified prior to analysis and reporting of findings. It should be highlighted that seeking at least a verbal consent would be the normal practice in many other institutes as we have used data collected from patients for a different purpose

in our study than the originally intended purpose behind the data collection, however, we have not used any identifiers in our study, and that satisfied our ethics committee. Baseline demographic information, site and type of the AV fistula were retrieved from the medical records, whereas results of blood investigations were obtained from electronic records. Functional maturation was recorded from dialysis records.

3.2.4 Study's primary and secondary endpoints:

The author aimed to evaluate patients' characteristics that have been reported to be associated with AVF non-maturation in the literature following an extensive review of published evidence. A functional maturation rate was used in this study, which was defined as successful use of the arteriovenous fistula for six consecutive sessions of HD, and this was obtained from dialysis records. The use of functional maturation defined as sustained HD sessions ≥ 6 for the evaluation of AVF maturation has been validated in the literature in several previous studies [84-86]. This method is methodologically acceptable, particularly in retrospective studies assessing AVF maturation before the regular use of preoperative venous mapping and postoperative US scans – as the case with this study as most of our patients did not have postoperative US scans. However, the author of this thesis should point to its inferiority compared to the definition recommended in the updated NKF-KDOQI guidelines, famously known as the rule of (6s) (flow of approximately 600 mL/min, less than 0.6 cm below the skin surface and a minimal diameter of 0.6 cm) [1]. In addition, in the absence of postoperative imaging scans, it will be difficult if not entirely impossible to differentiate between non-maturation and mis-cannulation due to less experienced staff. At our hospital, new fistulas are looked after by senior dialysis nurses who are well experienced in cannulation of those fistulas, however, it should be emphasised that the US based definition for AVF maturation adopted by the NKF-DOQI is superior to the one used.

The author examined the relationship between age, gender, diabetes, smoking, hypertension, hyperlipidaemia, history of steroids use, history of Calcium channel blockers at the time of access formation and the history of previous dialysis access (AVF, AVG or CVC). Secondary endpoints were

perioperative blood investigations (Haemoglobin, White cells count and Neutrophils count). In addition, the aetiology behind ESRD was recorded whenever available from medical records.

3.2.5 Statistical analysis:

Data were extracted and recorded on spread sheet using IBM SPSS version 22.0 [87]. Categorical data are expressed in true value and as percentages and were compared using the Pearson Chi-Square (X^2) test, whereas continuous data were reported as mean \pm SD and compared using the independent sample t-test for normally distributed data, and the Mann-Whitney U when indicated by normality tests. Levene's test for equality of variances was used to determine the p value in t-test regression analysis for continuous data [88]. Data distribution of the various predictor variables were assessed by means of histograms, Q-Q plots and box plots. Finally, the author calculated two prediction models by logistic regression analysis. The first model was based on variables that have been suggested to correlate to fistula maturation in the literature, and had p values of < 0.1 in our study in univariate analysis with functional maturation being the dependent (outcome) measure of analysis. The second prediction model was an overall logistic regression test with all of the included variables in our study without restrictions in terms of the p value.

3.3 Results:

The study included a total of 86 patients (all diagnosed with ESRD by their attending consultant nephrologists and referred to the vascular department for access creation) with 97 arteriovenous fistulas formed to serve as vascular access for HD sessions. The most common cause leading to ESRD was diabetes ($n = 37/97$; 38.1%) followed by congenital renal agenesis ($8/97$; 8.2%), hypertension ($7/97$; 7.2%) and ischaemic injury ($6/97$; 6.2%). Other diagnosis included vasculitis, hypercalcaemia and a number of autoimmune diseases. From the 97 AVFs included in the study, 68 (70.1%) were constructed in men while 29 (29.9%) were constructed in female patients. Age did not follow a normal distribution with regards to gender variation in our patients [Figures 3.1 and 3.2]. Age of all included patients was (mean \pm SD) 60.9 ± 16.9 ; men aged 63.7 ± 14.8 with a median of 67 (22 – 86) while women aged 54.5 ± 19.6 with a median of 55 (21 – 81); this difference was statistically significant ($P = 0.012$) [Figure 3.3]. Demographic data of included patients along with comorbidities and drug therapy at the time of fistula formation are summarised in [Table 3.1], and summary of the continuous variables in our study can be found in [Table 3.2].

Figure 3.1: Age distribution among male patients

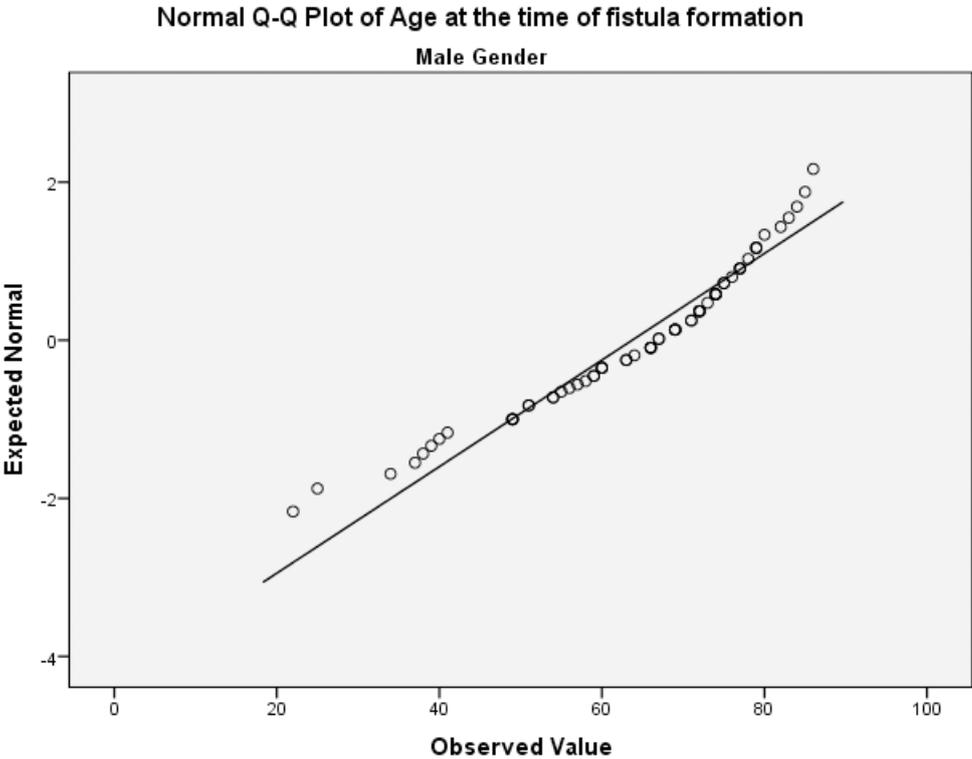


Figure 3.2: Age distribution among female patients

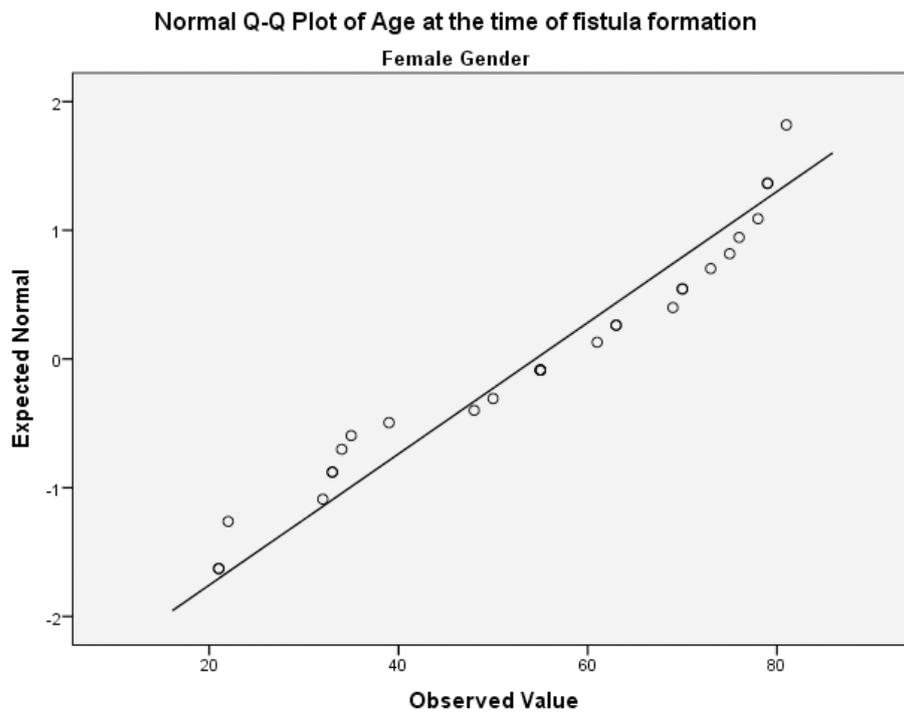


Figure 3.3: Variation in age between groups according to gender

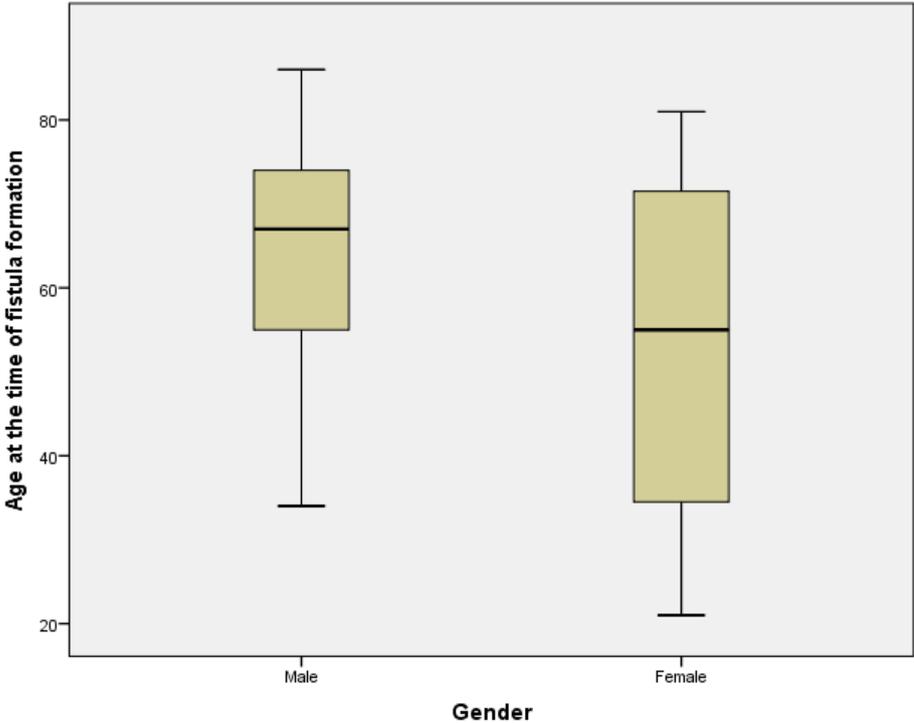


Table 3.1: Characteristics of patients in study:

| Baseline characteristic | Frequency and percentage of the positive (yes) values | |
|-----------------------------------|---|-------------------|
| | Frequency (Observed %) | Valid % N = 97 |
| Functional maturation | 52 (53.6) | 57.6 |
| Female gender | 29(29.9) | 29.9 |
| Male gender | 68 (70.1) | 70.1 |
| Diabetes | 40 (41.2) | 41.2 |
| Smoking | 30 (30.9) | 32.3 |
| Hypertension | 81 (83.5) | 85.3 |
| Hyperlipidaemia | 71 (73.2) | 74.7 |
| Coronary artery disease | 35 (36.1) | 36.8 |
| Atrial fibrillation | 15 (15.5) | 15.8 |
| Warfarin | 16 (15.5) | 15.8 |
| Congestive cardiac failure | 24 (24.7) | 25.3 |
| Insulin | 17 (17.5) | 18.1 |
| Calcium channel blockers | 30 (30.9) | 32.3 |
| Previous history of haemodialysis | 69 (71.4) | 73.4 |
| Dialysis through Venous Catheter | 64 (66) | 70.3 |
| Previous kidney transplant | 9 (9.3) | 10.1 |
| Previous Arteriovenous fistula | 21 (21.6) | 32.8 |
| Site of AVF: Wrist | 45 (46.4) | 50 |
| Site of AVF: Forearm | 45 (46.4) | 50 |

Table 3.2: Characteristics of continuous variables:

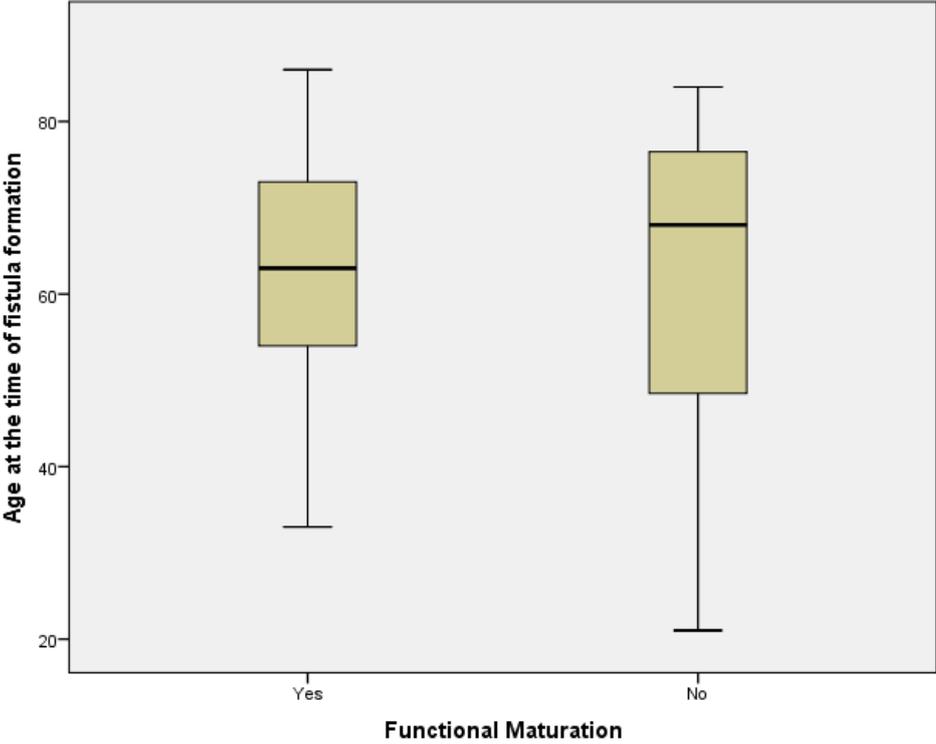
| | Age at creation of fistula | Urea (mg/dL) | Creatinine ($\mu\text{mol/L}$) | Haemoglobin (g/dl) | Platelets ($10^9/\text{L}$) | White Cells Count ($10^9/\text{L}$) | Neutrophils Count ($10^9/\text{L}$) |
|-------------------|----------------------------------|--------------|-------------------------------------|-----------------------|----------------------------------|--|--|
| Mean | 60.92 | 17.915 | 528.42 | 11.049 | 252.73 | 7.6639 | 5.3045 |
| Std. Deviation | 16.858 | 8.8747 | 260.563 | 1.6074 | 111.809 | 2.08253 | 1.82589 |
| Median | 66.00 | 16.800 | 448.00 | 11.000 | 234.00 | 7.2900 | 4.9400 |
| Minimum | 21 | 1.8 | 214 | 7.2 | 110 | 3.58 | 2.20 |
| Maximum | 86 | 45.4 | 1506 | 14.5 | 1007 | 14.04 | 12.11 |

3.3.1 Patients' characteristics:

The overall AVF functional maturation rate in our study was 53.6% (52/97). When nine patients that did not have sufficient information to establish the outcomes of their AVFs confidently from their medical records were excluded from the final analysis, the functional maturation rate was 57.6%.

The author examined the relationship between different characteristics, comorbidities and drug therapy, and functional maturation in our patients using the appropriate statistical tests as outlined above. In our study; 40/59 (67.8%) fistulas matured in men while 9/26 (34.6%) matured in female patients; this difference was statistically significant ($P = 0.004$) suggesting female gender is associated with poor functional maturation. Age was not distributed equally among patients with a documented maturation outcome; however it was not found to be statistically associated with functional maturation as those who were found to have a functional access aged (62.4 ± 13.9) compared to (60 ± 20) in patients who could not dialyse from their AVFs ($P = 0.926$; Mann-Whitney U test) [Figure 3.4]. Hypertension was diagnosed in 72 cases, 44 (61.1%) of those matured, whereas of the 13 cases who did not suffer from hypertension five (38.5%) fistulas matured ($P = 0.128$). Of the 34 fistulas with a positive diagnosis of diabetes, 18 fistulas of those matured, whereas 16 did not mature, compared to 31 and 20 respectively of the 51 patients who had a documented different aetiology for ESRD. The difference between the two groups of patients was not significant ($P = 0.473$). The use of Insulin for the treatment of diabetes also did not correlate significantly to functional maturation ($P = 0.839$).

Figure 3.4: Variation in age between mature and non-mature AVF groups



Being on a calcium channel blocker at the time of fistula formation was significantly associated with a more favourable outcome as 21/25 patients on those medications had mature fistulas compared to 27/59 of patients who were not on calcium channel blockers ($P = 0.001$). There was no statistically significant difference in functional maturation if the patient was on Aspirin and/or Clopidogrel, or neither of the two drugs ($P = 0.617$). Previous history of HD was not found to be statistically related to functional maturation, as 37/60 functional AVFs were created successfully in patients with previous access (AVF, AVG or CVC) whereas 12/25 non-mature fistulas were created in patients with previous access ($P = 0.245$). Results remained unchanged even when a separate analysis was performed on those who only dialysed via tunnelled catheters, i.e. excluding AVF and AVG, the result remained insignificant ($P = 0.407$). Also, those who underwent a new fistula formation for a failed previous AVF did not do any worse or better in terms of functional maturation ($P = 0.530$). However, history of a previous kidney transplant surgery was found to be associated with better functional maturation ($P = 0.036$).

The site of the newly created AVF was not found to statistically influence the outcome of functional maturation in our study; of the 43 fistulas created around the wrist, 23 (53.5%) matured and 20 (46.5%) failed, compared to 26 (61.9%) and 18 (38.1%) of those placed in the forearm respectively ($P = 0.432$). The association between functional maturation and other categorical variables are shown in [Table 3.3].

Table 3.3: Categorical variables association with functional maturation

| Variable | Functional maturation | N | % | P value |
|-----------------------------|-----------------------|----|------|--------------|
| Female gender | Yes | 9 | 34.6 | 0.004 |
| | No | 17 | 65.4 | |
| Male gender | Yes | 40 | 67.8 | |
| | No | 19 | 32.2 | |
| Diabetes | Yes | 18 | 52.9 | 0.473 |
| | No | 16 | 47.1 | |
| Smoking | Yes | 13 | 48.7 | 0.193 |
| | No | 14 | 51.9 | |
| Hypertension | Yes | 44 | 61.1 | 0.128 |
| | No | 28 | 38.9 | |
| Hyperlipidaemia | Yes | 38 | 57.6 | 0.980 |
| | No | 28 | 42.4 | |
| Coronary Artery Disease | Yes | 17 | 54.8 | 0.691 |
| | No | 14 | 45.2 | |
| Atrial fibrillation | Yes | 8 | 66.7 | 0.495 |
| | No | 4 | 33.3 | |
| Peripheral vascular disease | Yes | 10 | 58.8 | 0.913 |
| | No | 7 | 41.2 | |
| HD history | Yes | 37 | 61.7 | 0.245 |
| | No | 23 | 38.3 | |
| HD by central catheter | Yes | 35 | 61.4 | 0.407 |
| | No | 22 | 38.6 | |
| Previous AVF | Yes | 11 | 55 | 0.530 |
| | No | 9 | 45 | |
| Site of AVF: Wrist | Yes | 23 | 61.9 | 0.432 |
| | No | 20 | 38.1 | |
| Site of AVF: Forearm | Yes | 26 | 65.4 | |
| | No | 16 | 34.6 | |
| Renal transplant history | Yes | 8 | 88.9 | 0.036 |
| | No | 1 | 11.1 | |
| Calcium channel blocker | Yes | 21 | 84 | 0.001 |
| | No | 4 | 16 | |
| Warfarin | Yes | 8 | 61.5 | 0.758 |
| | No | 5 | 38.5 | |
| Insulin | Yes | 9 | 60 | 0.839 |
| | No | 6 | 40 | |

3.3.1.1 Preoperative blood tests:

The author also examined the relationship between functional maturation and a number of blood based investigations obtained within 24 hours prior to the time of access placement. The (mean \pm SD) was used to report and compare our findings. Patients with fistulas which were used successfully for HD had a haemoglobin level of (10.6 \pm 1.5 g/dl), platelets count (252.2 \pm 136.1 10⁹/L), white cells count (7.6 \pm 2.2 10⁹/L) and neutrophils count of (5.4 \pm 1.9 10⁹/L) compared to (11.5 \pm 1.7 g/dl), (263 \pm 82.4 10⁹/L), (8 \pm 2 10⁹/L) and (5.5 \pm 1.8 10⁹/L) in patients with non-mature fistulas respectively [Table 2].

Independent sample t-test analysis were performed to assess the relationship between each of the above blood investigations and AVF functional maturation in our study. The author found that the most statistically significant predictor of functional maturation of the laboratory variables was haemoglobin (P = 0.01) [Figure 3.5], with variances in both tests proven to be equally distributed in a Levene's test for equality of variances. Other blood investigations obtained preoperatively were not found to be independently associated with functional maturation [Table 3.4].

Figure 3.5: Variation in haemoglobin count between mature and non-mature AVF groups

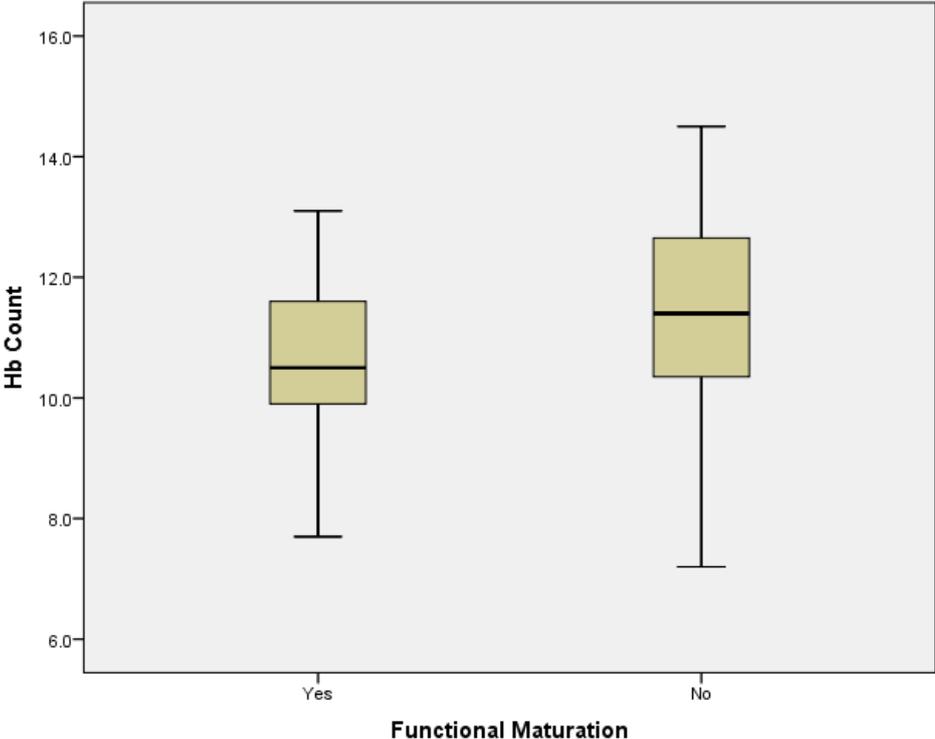


Table 3.4: Continuous variables (age and blood investigations) association with functional maturation:

| | Functional Maturation | N | Mean | Std. Deviation | P value |
|----------------------------|-----------------------|----|--------|----------------|--------------|
| Age at creation of fistula | Yes | 49 | 62.37 | 13.869 | 0.926 |
| | No | 36 | 59.97 | 20.029 | |
| Urea | Yes | 49 | 19.122 | 9.5929 | 0.243 |
| | No | 36 | 16.764 | 8.4825 | |
| Creatinine | Yes | 49 | 574.00 | 265.916 | 0.033 |
| | No | 36 | 458.31 | 209.047 | |
| Haemoglobin | Yes | 49 | 10.635 | 1.4720 | 0.010 |
| | No | 36 | 11.547 | 1.7039 | |
| Platelets | Yes | 49 | 252.24 | 136.058 | 0.676 |
| | No | 36 | 262.97 | 82.417 | |
| White cells count | Yes | 49 | 7.6110 | 2.21715 | 0.378 |
| | No | 36 | 8.0219 | 1.95970 | |
| Neutrophils | Yes | 49 | 5.3404 | 1.93037 | 0.899 |
| | No | 36 | 5.4625 | 1.80142 | |

The author performed two logistic regression analysis tests for study. The first test included all the variables in our study with a P value of < 0.1 ; this included gender, history of renal transplant prior to fistula construction, haemoglobin and a medical history of being on calcium channel blockers. The Omnibus test for model coefficients had a significant p value of < 0.001 , the overall prediction accuracy of the model was 77.8% with the independent predictors for non-maturation being female gender ($P = 0.04$) and history of calcium channel blockers ($P = 0.034$).

A second multiple regression test was performed and included other variables that have been reported in the literature to be associated with fistula maturation, in addition to the variables from the first regression analysis model mentioned in the above paragraph. The new variables in this second test were age, history of diabetes, smoking, hypertension, hyperlipidaemia, warfarin, congestive cardiac failure, history of starting HD prior to AVF placement, history of dialysing through CVC, and history of a previous failed AVF. Omnibus test for model coefficients had a significant p value of 0.016, the overall prediction accuracy of the model was 71.7%, and as in the first model, the only independent predictor for functional non-maturation was a female gender ($P = 0.011$).

3.4 Discussion:

It has been established that a functional AVF access is the least likely to be associated with thrombosis, infection, hospital admissions, secondary interventions to maintain patency and death [9, 10]. However, the process of AVF maturation is complex and remains poorly understood despite numerous studies looking into the pathophysiology of the process and the biomechanical factors associated with maturation. Intimal hyperplasia (IH) has been identified as the main reason behind non-maturation in the newly formed arteriovenous conduit, it is the process of cellular proliferation within the inner most layer of the vessel resulting in remodelling of both the arterial and venous ends of the new fistula [17-19]; however factors influencing this process are yet to be fully elucidated.

Our study included a total of 86 who had a combined total of 97 fistulas. Functional maturation was achieved in 52/97 fistulas (53.6%), however the author was unable to determine functional maturation from dialysis records in 9 patients, and as such, the observed maturation rate in our study was 57.6%. Both percentages are in agreement with maturation rates reported in other studies [7, 100, 101]. Age did not follow a normal distribution in our study when explored against both gender and functional maturation using various normality tests provided by SPSS; however, a Mann-Whitney U did not suggest an association between age and functional non-maturation. The functional maturation process in our study was statistically influenced by a female gender ($P = 0.004$), previous history of a kidney transplant ($P = 0.036$), patient on a calcium channel blocker at the time of AVF formation ($P = 0.001$) and haemoglobin levels. Out of those factors, functional non-maturation was associated with female gender and increased average of haemoglobin, while successful functional maturation was associated with a previous history of renal transplant and the use of calcium channel blockers.

A logistic regression analysis test that included all the variables in our study with a P value of < 0.1 ; (female gender, history of renal transplant, haemoglobin and being on a calcium channel blocker), showed that the only independent predictors of functional non-maturation were female gender ($P = 0.04$) and a history of calcium channel blockers ($P = 0.034$). The overall

prediction accuracy of the model was 77.8%. Another model with the addition of other variables that have been reported elsewhere in the literature to be significantly associated with fistula functional maturation was performed. The overall prediction of this second model was 71.7%, with female gender being the only independent predictor for functional non-maturation ($P = 0.011$).

Although old age (> 65) was shown to be significantly associated with non-maturation in previous studies [110, 111], this however is by no means a consistent finding. Indeed many other authors found no association between age and maturation, including Renaud et al who reported similar maturation rates across all age groups in their study of 280 primary AVFs. In their study, only female gender and a tunnelled catheter were significantly associated with non-maturation [84], the author report similar findings concerning age and gender, however, in our study a history of tunnelled catheters was not associated with functional non-maturation. In addition, Lok et al reported a comparable five years cumulative patency using 65 years as a cut-off point (64.7% in the ≥ 65 group and 71.4% in the < 65 group). They argued that age should not be a limiting factor when deciding which patients should have which vascular access procedure [101]. Those differences can be related to a different population, or confounding from other factors that might have influenced the maturation process.

It is important to highlight that a patient with a previous renal transplant tend to be healthier and in better medical conditions in order to be considered for a transplant operation. This fact could have confounded our results in terms of successful maturation being associated with a history of renal transplant, as those patients probably had better vessels, better reserves and fewer medical comorbidities. In addition, most of them would have undergone venography or angiography with corrections of the vascular issues identified on those scans.

The significant association between calcium channel blockers and successful functional maturation is possibly mediated through the vasodilation effect commonly caused by most of those therapeutic agents. However, the

association between successful maturation and the use of calcium channel blockers might be a reflection of the fact that those patients have higher blood pressure than the rest, and that resulted in higher flow rates within the fistula conduit favouring higher maturation rates. This can be explored further in the future either by a randomised study comparing patients on those agents to patients on other antihypertensive medications, or by stratifying the results by both blood pressure values and medical treatment for hypertension. However, our sample size was too small for statistical stratification of our findings.

The author found that a lower haemoglobin level was associated with better functional maturation rates. The author of this thesis hypothesises that this might be explained by the up-regulation of endothelial Nitric Oxide Synthase (eNOS) in the newly formed conduit, leading to increased production of Nitric Oxide (NO) and Haeme Oxygenase-1 (HO-1) as a result of the relative hypoxia status caused by lower haemoglobin levels in the blood. NO is associated with vasodilation and decreased cellular proliferation [49], whereas HO-1 has been shown to inhibit proliferation of vascular smooth muscle cells, platelet aggregation, and vasospasm [97]. However, those are mere speculations and further studies aimed to specifically test the association of those markers and fistula maturation are needed. In addition, the difference in haemoglobin levels between mature fistulae and those that failed to mature was probably not clinically significant, even though it was statistically significant. Moreover, this finding can also be a result of the play of chance from testing multiple variables, which could have confounded our results. In addition, Erythropoietin and blood transfusion could have been the reasons behind the higher haemoglobin levels in some patients, and it is conceivable that their known prothrombotic effects have resulted in increased thrombosis within the newly constructed fistulae in those patients.

Our findings contradict some of those reported by other authors. Non-maturation in study by Feldman et al of 348 HD patients was associated with a history of stroke, transient ischaemic attack, increasing age and dependence on dialysis at the time of fistula formation [117]. However, in a study by Lee et al that evaluated factors affecting cumulative access survival of AVF, they reported that age, race, diabetes, gender and peripheral vascular disease did not show significant association with access survival [112]. In this study, the

only predictor of poor outcome being the number of salvage procedures, as the higher number of secondary interventions required to maintain patency, the less likely for the fistula to last for a long period [112]. The findings about the demographics of patients reported in the latter study – with the exception of gender – were mirrored in our study.

Limitations of this work were the retrospective nature of data collection, and data missing from medical records. In addition, certain continuous variables like age lacked a normal distribution pattern. It is important to mention that some of those fistulas deemed non-mature according to the criteria used in this study – functional maturation – would have been patent on duplex scans and fistulograms, and certainly, the variation in expertise among dialysis staff should be expected to have influenced our maturation rate. Another limitation of this study is the fact that it assessed several independent risk factors for AVF non-maturation, which could have confounded our results, and as such, the author accepts that the estimated associations calculated in our study could have been because of the play of chance rather than true effects. In addition, since those patients were referred to the vascular service by the nephrology consultants in our hospital, certain types of bias should be considered. Referral bias by referring only those that the nephrologists considered more likely to have successful mature AVFs cannot be safely excluded. Similarly, selection bias should be taken into account, as our sample might not have been representative of the whole population of interest concerning patients with ESRD that require fistulas for HD.

3.5 Conclusion:

While a retrospective study will inevitably suffer from inherent weaknesses in the methodology preventing it from sufficiently answering all questions concerning the associations between demographic data and haematological factors with AVF maturation, this paper would serve as a guide for future studies, as well as an up-to-date review of published evidence. Arteriovenous fistula maturation is a complex process with multiple factors involved (demographic, haematological and biomechanical). A female gender has been found to be associated with functional non-maturation, while a history of kidney transplant, calcium-channel blocker agents and low haemoglobin levels were all associated with successful functional maturation. Logistic regression analysis showed that the only independent predictor of functional non-maturation was a female gender. In view of the conflicting evidence in the literature, large multi-centre registry-based studies with well-defined outcomes are required; however, other biomechanical factors that influence intimal hyperplasia should be considered as playing a leading role in AVF maturation.

IV Chapter Four: The role of venous diameter in predicting arteriovenous fistula maturation.

4.1 Introduction:

This best evidence topic was generated according to the structure outlined in the International Journal of Surgery [118].

4.2 Clinical Scenario:

In a regional hospital multidisciplinary team meeting, a patient with end stage renal disease (ESRD) is referred to the vascular service for formation of an arteriovenous fistula (AVF) before starting haemodialysis (HD). A preoperative venous mapping of the patient's left upper limb showed good measurements of the arteries; however, the cephalic vein at the wrist is 2.5 mm, whereas it is 3 mm in the forearm. The operating surgeon feels an AVF at the wrist has a reasonable chance to mature, while another one argues a vein diameter < 3 mm is highly predictive of maturation failure. You decide to review the literature for evidence.

4.3 Three-part question:

In patients with [ESRD waiting to be started on HD], who are being [referred for AVF formation] with a preoperative venous mapping, what is [the minimum vein diameter] predictive of successful maturation?

4.4 Search strategy:

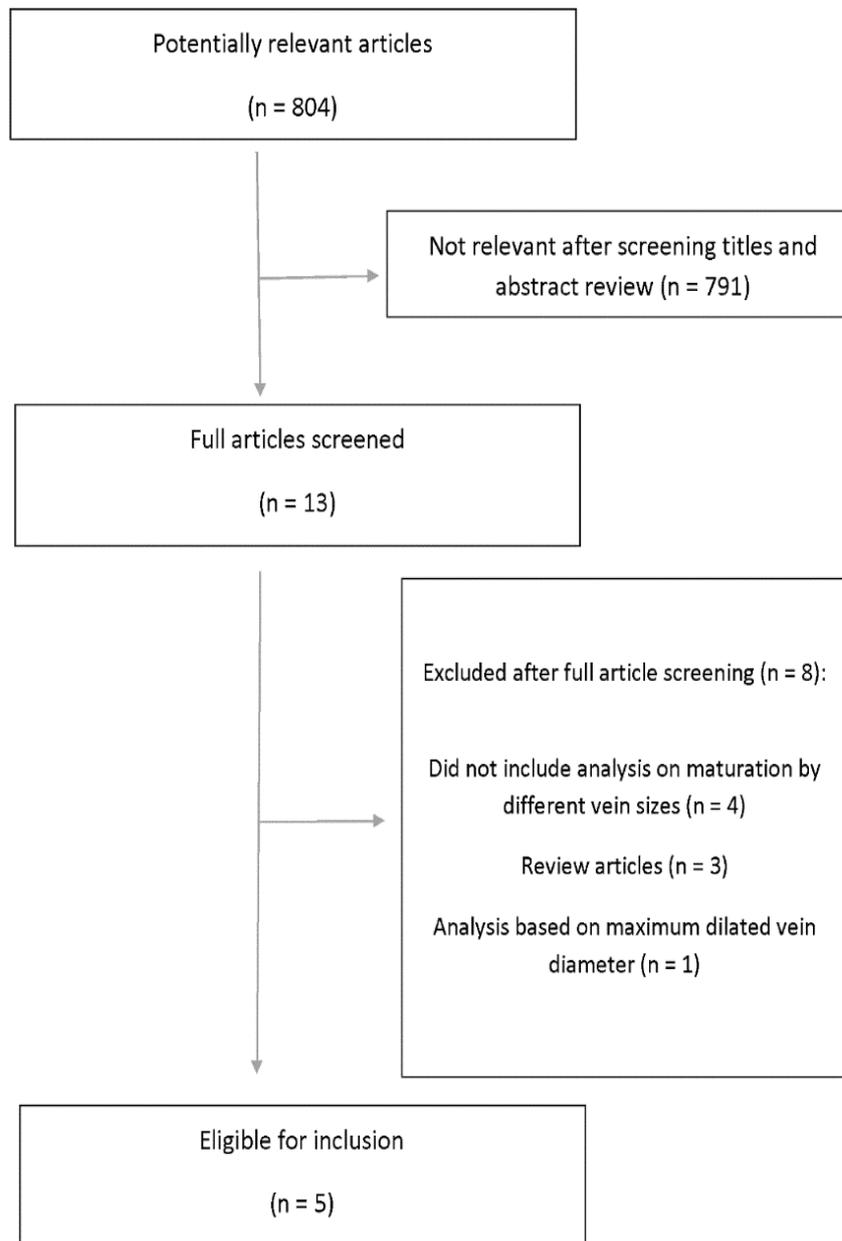
The Medline database and the Cochrane Central Register of Controlled Trials (up to June 2014) were searched using the terms (([vein diameter] AND [arteriovenous fistula] AND ([maturation] OR [successful] OR [patent]) AND ([haemodialysis] OR [haemodialysis]) AND ([preoperative] OR [US] OR [Ultra Sound])). The search was restricted to English language and humans. No time restriction was applied. Studies that cross-matched preoperative vein diameter used to create AVF to successful maturation were included. Studies that did not correlate the diameter of vein to maturation were excluded.

4.5 Search outcome:

Initial search produced 804 citations from Medline, and 11 trials from the Cochrane Central Register of Controlled Trials. Five studies provided the best evidence to answer the question [Figure 1].

Figure 4.1: A diagram summarising search results

Figure 1: A diagram summarising search results



4.6 Results:

Three retrospective observational studies, one non-randomised controlled follow-up study and one prospective multicentre cohort study were included in this BET article as shown in [Table 4.1].

Table 4.1: Summary of included studies

| Author, date and country of research | Patient group | Study type and level of evidence | Outcomes | Key results | comments |
|--|--|---|--|---|---|
| Luavao et al [119] 2009 United States J Vasc Surg | Patients undergoing dialysis access formation between 2003 and 2007 (n=158): PRCAVF=24 WRCAVF=72 BCAVF=62 Only patients with first time AVF were included. Preoperative venous mapping performed in 88 patients Patients with temporary dialysis catheter were not excluded | Retrospective, observational study, level IV evidence | Primary endpoints: - Fistula clinical maturation: adequate blood flow, ability of vein to dilate > 6 mm, for a length of > 10 cm and being < 6 mm deep from surface - Fistula functional maturation: successful cannulation with ability to deliver 350-400 ml/min for 4 hours session of HD | Vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis (p=0.002). This did not change when using mean, smallest or largest vein size for each region, although was more significant with largest (>4 mm) as follows: o PRCAVF = 2/2 patients o WRCAVF = 15/18 o BCAVF = 28/28 Age, gender, diabetes and BMI had no significant effect on maturation Fistula type (p=0.032) and vein size on DUS (p=0.002) significantly predicted maturation in univariate analysis. BCAVFs showed better maturation rates. Similarly, AVFs constructed with bigger veins matured more successfully. Patients with preoperative venous mapping had similar maturation rates to those who did not (71% vs 69%) | Maturation in some cases was determined clinically by physical examination only; however, 91% of clinically mature AVF achieved functional maturation. Of the 9 that did not, 5 were never used due to death, transplant or renal preservation. Vein diameter was recorded using mean, smallest and largest for each anatomical region |
| Mendes et al [80] 2002 United States J Vasc Surg | Consecutive Patients undergoing formation of a wrist AVF between 1999 and 2001 (n=44/48). Local or regional block Vein diameter obtained preoperatively using US. Patients were removed from study for: Inadequate US mapping (n=1) Died within 6 weeks of study (n=1) Lost to follow-up (n=2) | Prospective cohort study, level III evidence | Primary outcome was fistula maturation defined as successful HD at 3 months from access formation Patients who were lost to follow-up or died within 3 months were excluded Smallest diameter of vein from the wrist to proximal upper arm was used as preoperative predictor for maturation | Successful maturation in 22 (50%) procedures Cephalic vein ≤ 2 mm used in 19 patients, with 3 (16%) showing functional maturation Cephalic vein > 2 mm used in 25 patients with 19 (76%) showing successful maturation The difference between the 2 groups was significant (P = 0.0002, X ² test) 3 AVFs with veins ≤ 2mm matured (minimal vein diameter of 1.2 mm, 1.8 mm and 2.0 mm) 6 AVFs with minimal diameter > 2 mm failed to mature (vein diameter 2.1 mm to 3.2 mm) | Small sample size First cannulation attempted by experienced dialysis nurse High failure rate for AVF maturation in this study Statistical analysis for possible confounding factors such as age, gender and diabetes were not included with the results. Cumulative patency rates following possible salvage procedures were not mentioned |

| | | | | | |
|---|--|--|---|---|--|
| <p>Feldman et al [117] 2003 United states Am J Kidney Dis</p> | <p>Patients undergoing dialysis access formation between 1994 and 1998 (n=348)</p> <p>Inclusion criteria: Age ≥ 18 with ESRD who underwent AVF formation. Only the first fistula was included</p> <p>Vein diameter obtained preoperatively using US or ruler after the vein has been collapsed</p> | <p>Prospective, multi-centre, cohort study, level III evidence</p> | <p>The main outcome was successful maturation defined as AVF used at least 6 successive times for HD.</p> <p>Patients followed for 3 months</p> <p>Did not differentiate between non-maturation and thrombotic occlusion</p> | <p>228/348 had at least one use of their AVFs, and 193 patients met the definition for AVF maturation of the study</p> <p>Using a large vein diameter was associated with maturation (P < 0.001)</p> <p>Results by vein diameter (upstream) :</p> <p>< 3 mm resulted in 45% matured AVF</p> <p>3-4 mm resulted in 56% matured AVF</p> <p>4-5 mm resulted in 58% matured AVF</p> <p>> 5 mm resulted in 65% matured AVF</p> <p>Thrill distance associated with maturation: distance < 4 cm associated with 51% or less odds of maturation</p> <p>Higher doses of heparin associated with higher rates of successful maturation</p> <p>Mean arterial pressure < 85% associated with 48% reduction in odds of maturation</p> | <p>Did not differentiate between non-maturation and thrombotic occlusion</p> <p>Logistic regression analysis add to the rigour of this study as known confounding factors were considered</p> |
| <p>Lockhart et al [120] 2006 United states J Ultrasound Med</p> | <p>Patients undergoing wrist RCAVF (n=73), between 2003 and 2005</p> <p>Group (A), (n=28) : patients with pre-tourniquet vein diameter ≥ 0.25 cm</p> <p>Group (B), (n=45) : patients with pre-tourniquet vein diameter < 0.25 cm that increased to ≥ 0.25 cm after tourniquet</p> | <p>Retrospective, observational study, level IV evidence</p> | <p>Primary outcome was fistula maturation: cannulated with 2 needles and allowed flow of ≥ 350 ml/min in at least 6 sessions in 1 month.</p> <p>Primary failure: early thrombosis if clotted within 12 weeks</p> <p>Failure to mature: patent, but not adequate for HD after 6 months</p> | <p>26/73 (36%) AVFs were adequate for HD</p> <p>47/73 (64%) could not be used for HD:</p> <p>Technical failure (n=6)</p> <p>Early thrombosis (n=23)</p> <p>Failure to mature (n=18)</p> <p>15/45 (33%) fistulas in group (B) [patients with pre-tourniquet vein diameter < 0.25 cm that increased to ≥ 0.25 cm after tourniquet] used successfully for HD compared to 11/28 (39%) in group (A) [patients with pre-tourniquet vein diameter ≥ 0.25 cm] .</p> <p>Difference between groups was not significant (P = 0.624), however, use of tourniquet resulted in more fistulas being created</p> | <p>Excluded 24 patients from the initial 97 patients from final analysis for not having a clear fistula outcome, which is a significant number and a concern for possible reporting and information bias</p> <p>Only 36% of AVFs were deemed adequate for HD. This rate is lower than most studies.</p> <p>AVFs that were not adequate for HD were not analysed based on vein diameter measurements</p> <p>Assisted maturation rates for early thrombosis were not reported in the study</p> |

| | | | | | |
|--|--|---|--|---|--|
| | | | | Men had higher overall fistula adequacy (50%) compared to women (19%), (P = 0.015) | |
| | | | | Arterial diameters were larger in those with adequate AVFs | |
| Maya et al [121] 2009 United States Clin J Am Soc Nephrol | <p>Patients who had Upper arm dialysis access (n=678):</p> <p>BC-AVF (n=322)</p> <p>BB-AVF (n=67)</p> <p>Grafts (n=289)</p> <p>Minimal vein diameter was ≥ 2.5 mm following application of tourniquet</p> <p>Fistulas cannulated after 6-8 weeks</p> <p>Immature fistulas underwent US assessment and appropriate salvage procedure</p> <p>Thrombectomy only attempted following successful cannulation for HD</p> | Retrospective, observational study, level IV evidence | <p>Primary outcome was fistula maturation defined as repeated successful cannulation with 2 needles for 1 month with blood flow ≥ 300 ml/min</p> <p>Primary failure was defined as inability to use the fistula for dialysis due to early thrombosis or failure to mature</p> <p>Cumulative access survival calculated from access placement to complete failure</p> | <p>Primary access failure: 15% to 18% in grafts and transposed BB-AVF, whereas 38% in BB-AVF</p> <p>Multiple variable logistic regression analysis in patients with BCAVF showed only arterial and venous diameters predicted failure (P < 0.001)</p> <p>Mean venous diameter for BCAVF was (3.9 \pm 1.0 mm) vs (4.6 \pm 1.5 mm) for BB-AVF</p> <p>Mean arterial diameter for BCAVF was (4.0 \pm 0.9 mm) vs (5.1 \pm 1.2 mm) for BB-AVF</p> <p>The only predictors for primary failure in multiple variable logistic regression analysis were gender [Higher in females (HR 0.54; 95% CI, 0.38 to 0.78, P = 0.001)] and access type [higher for BCAVF vs BB-AVF (HR 2.76; 95% CI, 1.41 to 5.38, P < 0.003)]</p> <p>BB-AVFs had similar primary failure rates to grafts (HR 0.78; 95% CI 0.38 to 1.57, P = 0.48)</p> <p>Median cumulative access survival – including primary failures – was 1 year for grafts and BCAVF, and 2.7 years for BB-AVF</p> <p>Excluding primary failures, cumulative survival was similar for BCAVF and BBAV (3.4 and 4.1 years respectively), and 1.6 years for grafts.</p> <p>Gender and prior access were the only predictors for cumulative access failure when primary failures were included (P = 0.01), when primary failures were excluded, access type was the only predictor (P = 0.001)</p> <p>Access interventions among 3 groups:</p> <p>Angioplasty occurred at similar rates</p> | <p>Large number of patients</p> <p>Detailed logistic regression analysis</p> <p>Association between venous diameter and fistula maturation was provided as mean \pm SD, but not broken into sub-groups according to different venous measurements (receiver operating characteristic analysis).</p> |

Thrombectomy similar
between BCAVF and BB-AVF,
and much higher for grafts

Surgical revisions were less
common in BB-AVF than
BCAVF

Annual rates of infection was <
1% for BCAVF and BB-AVF, and
10% for grafts.

4.7 Discussion:

Arteriovenous fistula (AVF) has been established as the best modality for haemodialysis (HD) in patients with end stage renal disease (ESRD) [1, 2, 4, 5, 122]. AVFs has superior cumulative patency rates than arteriovenous grafts (AVGs) and lower incidence of thrombosis, stenosis, infection and hospital re-admissions compared to (AVGs) and central venous catheters (CVCs) [11-14]. However, primary maturation failure remains the main disadvantage of AVF. The maturation of the new AVF depends on several biomechanical factors that result in the formation of a low resistance conduit capable of dilation to accommodate the increased blood flow required for successful HD sessions. One of the main predictors for maturation has been shown to be the diameter of the vein used in creation of the AVF.

Luavao et al [119] assessed AVF maturation and functional maturation in 158 patients undergoing dialysis access formation. Only patients with first time fistulas were included, of those 88 patients had preoperative venous mapping assessing diameter, compressibility, depth and continuity. In total, 111/158 fistulas matured (70%), with 71% maturation rate for those with preoperative US compared to 69% for those without preoperative US. In their univariate analysis, they found that fistula type and vein size significantly affected maturation ($P = 0.032$ and $P = 0.002$, respectively). In addition, vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis ($p=0.002$), a finding that was not affected when using the smallest or largest vein size for each anatomical region, however it was more significant with largest vein diameter (>4 mm). In their study, age, race, gender, body-mass index (BMI), diabetes, hypertension, smoking, time to referral, and dialysis through prior catheter placement had no effect on fistula maturation by univariate or multivariate analysis. The main limitation of this study is the fact that maturation in some cases was determined clinically by physical examination alone; however, 91% of clinically mature AVF achieved functional maturation.

Mendes et al [80] performed a nonrandomised controlled follow-up study ($n=44$) in patients undergoing formation of a wrist AVF who had preoperative venous mapping. They carried US venous assessment for diameter,

compressibility, stenosis, anatomic variation, thickness and depth. They used the smallest cephalic vein diameter from the wrist to the proximal upper arm as a preoperative predictor of fistula maturation. They reported a successful maturation in 22 patients (50%). Of those with a cephalic vein ≤ 2 mm (n=19), only three (16%) showed functional maturation, whereas a cephalic vein > 2 mm used in 25 patients with 19 (76%) showing successful maturation (P = 0.0002). It is worth noting while three AVFs with veins ≤ 2 mm matured successfully, six AVFs had minimal vein measures of more than 2 mm failed to mature. The results did not include statistical tests for confounding factors such as age, gender, diabetes and obesity, therefore limiting their findings.

Feldman et al [117] carried a prospective, multi-centre, cohort study in patients undergoing dialysis access formation (n=348). They included adults (≥ 18) diagnosed with ESRD who were referred for having a first time AVF. Diameters of vessels at the anastomotic site was obtained by using a ruler after the vein had been collapsed or by US. Fistulas were performed by surgeons from the 12 participating hospitals, and only the first AVF was considered for analysis. Of their patients, 228/348 had at least one use of their AVFs, and 193 patients met the definition for AVF maturation used in the study. Maturation was associated with the use of a large vein diameter (P < 0.001) in creating the fistulas. Of note, thrill distance was significantly associated with maturation in the study (distance < 4 cm associated with 51% or less odds of maturation), and higher doses of heparin associated with higher rates of successful maturation. Also, Mean arterial pressure < 85% was associated with 48% reduction in the odds of maturation. Main limitations of the study are having more than one surgeon performing procedures with expected variations in technique, equipment and experience. In addition, they did not differentiate between non-maturation and thrombotic occlusion.

Lockhart et al [120] retrospectively assessed access maturation in patients undergoing wrist RCAVF (n=73) following recommendations by preoperative US. They had 2 groups in the study, Group (A), (n=28) consisted of patients with pre-tourniquet vein diameter ≥ 0.25 cm, and Group (B), (n=45) of patients with pre-tourniquet vein diameter < 0.25 cm that increased to ≥ 0.25 cm after application of tourniquet. Of the 73 patients who had known fistula outcome,

26/73 (36%) AVFs were adequate for HD, while 47/73 (64%) could not be used for HD. Analysis showed there was no statistical difference in the number of AVFs used successfully for HD between the two groups ($P = 0.624$). However, the use of tourniquet resulted in more fistulas being created, as those patients would have been denied the opportunity of AVF formation based on venous measurements without tourniquet. They also noted that men had higher overall fistula adequacy (50%) compared to women (19%), ($P = 0.015$), and arterial diameters in preoperative US scans were larger in those with adequate AVFs for HD. The study excluded 24 patients of the initial 97 from final analysis raising concerns regarding selection bias. Additionally, a separate analysis by vein size on the subgroup of AVFs that were not adequate for HD was lacking.

Maya et al [121] retrospectively looked at patients who had Upper arm dialysis access ($n=678$). Those included were brachiocephalic-AVF (BCAVF) ($n=322$), brachiobasilic-AVF (BB-AVF) ($n=67$), and Grafts ($n=289$). Minimal inclusion criteria for AVFs were arterial diameter ≥ 2 mm and venous diameter ≥ 2.5 mm with absence of stenosis or thrombosis in the draining vein. Fistulas were performed by one of five surgeons or by a trainee under supervision by staff surgeon. Brachiocephalic approach was considered first, if not suitable according to preoperative US, then a transposed brachiobasilic fistula was considered if suitable, otherwise, a graft. Multiple variable logistic regression analysis in patients with BCAVF showed that only arterial and venous diameters predicted AVF failure ($P < 0.001$). The mean venous diameter for BCAVF was (3.9 ± 1.0 mm) vs (4.6 ± 1.5 mm) for BB-AVF. In addition, the only predictors for primary failure in multiple variable logistic regression analysis were gender [Higher in females (HR 0.54; 95% CI, 0.38 to 0.78, $P = 0.001$)] and access type [higher for BCAVF vs BB-AVF (HR 2.76; 95% CI, 1.41 to 5.38, $P < 0.003$)]. The only predictors for cumulative access failure when primary failures were included in their study were gender and prior access ($P = 0.01$). When primary failures were excluded, access type was the only predictor ($P = 0.001$). This was a rigorously designed study; however, it lacked a more detailed analysis, such as a receiver-operating characteristic on the association between vein size and AVF maturation, a test that was lacking in the rest of the included studies as well.

4.8 Clinical bottom line:

Improving the maturation rate of AVFs remains a challenging task due to the complex nature of the process and the multiple factors contributing to the maturation of those fistulas. However, the diameter of the vein used to create an AVF has been shown to be a consistent and reliable predictor for successful maturation. Nonetheless, there is still no agreement on the exact size of minimal venous diameter to predict the outcome of fistula maturation confidently, however, the evidence suggests it is between 2.5 mm to 4 mm. In addition, routine use of tourniquet makes it possible to form AVFs in patients who otherwise would have been rejected. A large multicentre randomised clinical trial assessing the use of different vein sizes both with and without tourniquet application using proper statistical tools - such as receiver-operating characteristic - is required to make a final recommendation. Until then, a vein diameter of < 2.5 mm should be considered inadequate for formation of an AVF, particularly if those measurements remain unchanged following the use of tourniquet, i.e. lack of venous distensibility.

V Chapter Five: End-To-Side Versus
Side-To-Side Anastomosis Techniques In
Arteriovenous Fistula For Dialysis Access:
A Systematic Review And A Meta-Analysis

5.1 Introduction:

The prevalence of end stage renal disease (ESRD) is rising, and with it, is the requirement for haemodialysis access [99]. Arteriovenous fistula (AVF) is the preferred method of access for long-term haemodialysis worldwide.

Autogenous AVFs have been shown to have better patency rates and are associated with less morbidity than other types of vascular access [8, 123-126]. However, the main disadvantage to AVFs is the significant rate of primary failure that prevents many fistulae (20% to 50%) from maturing into a useful vascular access capable of sustaining haemodialysis (HD) requirements [7, 100, 101]. Many factors have been implicated in the maturation and cumulative patency of AVFs with conflicting evidence in many cases [127-130].

There is consensus regarding the location of primary AVF formation [131, 132]; however, there is paucity in the evidence supporting the use of side-to-side (STS) versus end-to-side (ETS) anastomosis. In the early 1980's, Wedgwood et al suggested that the ETS configuration is "the one of choice" in creation of AVF [133]. Since then, there has been conflicting evidence regarding the superiority of one anastomosis over the other. There is data suggesting improved outcomes with the STS configuration in terms of early maturation and cumulative patency rates [134, 135]. On the other hand, data to support ETS configuration showing improved patency and reduced complication rates also exist [136]. Considering the complexity of the maturation process of a newly formed AVF, the anastomosis should be constructed in a fashion that will positively influence the haemodynamic changes associated with access formation to support favourable maturation outcomes, while at the same time reduce the risk of postoperative complications and arterial steal syndrome.

This review was designed to examine the difference between the two configurations, assessing maturation, primary and secondary patency rates, as well as complications.

5.2 Methods:

A systematic review and a meta-analysis were both conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89]. The review followed an agreed protocol, which was not published online.

5.2.1 Eligibility Criteria:

All randomised controlled trials (RCTs) and observational studies that compared the outcomes of interest from using an end-to-side (ETS) technique to a side-to-side (STS) technique in creating an arteriovenous fistula (AVF) for haemodialysis access were included in this review. Case series and review articles were excluded. Only studies published in English language were included in this systematic review. The author accepts that pooling results from RCTs and observational studies together to perform a meta-analysis can result in significant heterogeneity because of the distinctively different methodological approaches intrinsic to each study type. One recognised method of dealing with this limitation when it results in significant heterogeneity is to perform a sensitivity test by pooling data from RCTs and observational studies in separate tests and compare the difference in statistical significance.

5.2.2 Search strategy:

An extensive search of the literature was performed in November 2015 looking for relevant studies using the following terms: ([“Arteriovenous Fistula” OR “Fistula” OR “AVF” OR “Access” OR “Haemodialysis” OR “Hemodialysis”] AND [“End to Side” OR “End-to-Side”] AND [“Side to Side” OR “Side-to-Side”]). The authors searched the following databases: Medline, CINAHL, EMBASE, SCOPUS, the Cochrane library and Google Scholar. No restrictions were applied in terms of publication date or status. Studies were limited to English language and trials reporting on human subjects. In addition, the author searched the bibliographies of included studies for any additional citations.

Following the initial search, the first author (KB) and the second author (MM) evaluated all obtained abstracts for eligibility as per the agreed protocol. When the first two authors could not resolve ambiguity from reading the abstract, the full article was examined in details. Any remaining discrepancies regarding eligibility of potential studies was then settled by consulting with the senior author (SRW). The complete manuscripts of all abstracts that were deemed eligible were subsequently obtained.

The main endpoint of this review was primary patency as reported in included studies. Secondary endpoints were the development of postoperative complications, namely wound haematoma, wound infection and steal syndrome. The authors used the definitions provided in individual studies for “maturation”, “primary patency” and “secondary patency”. Similarly, individual definitions were used for postoperative complications.

5.2.3 Data Collection:

Two authors independently extracted the relevant data from included studies (KB, MM) which were then entered in Microsoft® Excel spreadsheet. Ambiguity in data collection and disagreements that remained following discussions between the first authors (KB, MM) were then resolved by the senior author (SRW). All included studies were examined for the following: age, sex, comorbid conditions, history of smoking, primary patency rate, secondary patency rate, cumulative access survival (overall maturation by the end of the study follow-up period) and postoperative complications (arterial steal syndrome, venous hypertension, wound haematoma and wound infection). The primary patency rate was defined as the unassisted patency rate without the help of salvage procedures (endovascular and open). The secondary patency rate was defined as the assisted patency rate of all fistulas including the ones that required salvage procedures to improve access flow rates. Patency rates were pooled together for comparison whenever those rates were reported at similar interval from the time of AVF formation. No restrictions were applied based on the length of postoperative follow-up. Inclusion and exclusion criteria were recorded [Table 5.I].

Table 5.1: characteristics of individual studies

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Technique of the End-to-Side anastomosis | Technique of the Side-to-Side anastomosis | Number: End-to-Side | Characteristics: End-to-Side | Number: Side-to-Side | Characteristics: Side-to-Side | Outcomes assessed | Main findings |
|-----------------------|----------------|---|-------------------------------------|--------------|--|--|---------------------|---|----------------------|--|--|--|
| Khan [137] | 2015 | Randomised controlled study conducted over a 6-month period (July/2012 to January/2013). Authors used non-probability techniques in collecting the sample. | Undetermined | Undetermined | Undetermined | Undetermined | 168 patients | Undetermined | 168 patients | Undetermined | Haematoma in 24 hours and at 1 month. Overall patency at 6 months | ETS technique was associated with fewer incidents of postoperative haematoma both in 24 hours and at 4 weeks. Patency rates were similar between both groups. |
| O'Banion [135] | 2014 | Retrospective observational study assessing data from fistulae from Jan.2012 to Dec/2013 in a single centre. Similar preoperative assessment and postoperative follow-up. No limitations in vein size in the STS group. Patency was defined as audible bruit or palpable thrill on clinical examination | All cases of radiocephalic fistulae | Undetermined | End vein to side artery in an interrupted suture fashion | Mobilisation of both the vein and artery. Direct side-to-side anastomosis in a continuous fashion. Anastomosis measured 1.3 to 1.5 cm. Veins were ligated distally | 29 patients | Age was 55 ± 14.6. 19/29 were male and 10/29 were female. 8/29 were smokers. 28/29 suffered from hypertension. 23/29 were diabetics | 32 patients | Age was 58 ± 12.5. 25/32 were male and 7/32 were female. 18/32 were smokers. 28/29 suffered from hypertension. 25/32 were diabetics. | Primary and secondary patency at 6 months. Early thrombosis, conversion to graft, minor revision, and cannulation rate at 3-month and 6-month. | STS anastomosis was significantly associated with less early thrombosis ($P < 0.05$), and superior 3-month cannulation rate ($P < 0.03$), and better primary patency ($P = 0.03$). A |

| | | | | | | | | | | | | |
|-----------------------|------|---|--|---|--|---|--------------|--|--------------|---|---|---|
| Mozaffar [138] | 2013 | Randomised controlled study conducted between 2010 and 2012. Patients had pre and postoperative duplex scans. Veins measured between 2-3 mm, and arteries were ≥ 2 mm. Absence of a thrill immediately postoperatively resulted in exclusion of that access from the study | Patients with End stage renal disease referred for dialysis access | Injection or blood sampling within 2 weeks before the procedure | End vein to side artery | Longitudinal arteriotomy and venotomy. Anastomosis 10 mm in length. Veins were ligated distally | 30 patients | 9/30 were diabetics. 21/30 had hypertension. 18/30 had a previous central line for haemodialysis | 30 patients | 10/30 were diabetics. 21/30 had hypertension. 16/30 had a previous central line for haemodialysis | Patency in 6 months | Maturation rate was similar in both groups after 6 months of follow-up |
| Ganie [139] | 2013 | Retrospective and prospective study for 4 years on all patients referred to a single centre for access formation. Site of AVF was based on clinical assessment. Venous puncture avoided for 1 week prior to procedures, and phlebitis treated with antibiotics and anti-inflammatory for 2-3 weeks. | All cases of upper limb AVFs | Undetermined | Continuous suturing technique. Anastomosis measured 1 to 1.8 on the radial artery. | Continuous suturing technique. Anastomosis measured 1 to 1.8 on the radial artery. | 26 patients | Undetermined | 131 patients | Undetermined | Patency in 12 and 24 months | Patency rates after 12 months were 77% for STS and 80 for ETS. Patency rates in 2 years were 50% and 55% respectively |
| Galic [136] | 2008 | Retrospective study of patients who underwent haemodialysis treatment through an upper limb AVF. Primary patency measured at 6 months. Secondary patency measured at 2 years. A third group of patients with end-to-end anastomosis were not included in this review. | All cases of upper limb AVFs in patients undergoing haemodialysis. | Undetermined | Undetermined | Undetermined | 130 patients | Undetermined | 90 patients | Undetermined | Primary patency in 6 months. Secondary patency in 2 years. Rates of postoperative infections, steal syndrome aneurysms, haemorrhage and monomelic neuropathy. | The ETS technique was associated with better patency rates and fewer postoperative vascular complications. |

| | | | | | | | | | | | | |
|-----------------------|------|---|--|--------------|--|---|-------------|--------------------------------|-------------|-------------------------------|---|---|
| Dunlop [140] | 1986 | Retrospective of brachiocephalic fistulae. Of the 41 ETS fistulae, 26 were actually created by STS anastomosis, however ligation the vein distally lead authors to classify those as ETS fistulae. | Fistulae created for haemodialysis in patients with chronic renal failure. | Undetermined | Continuous suturing technique. Anastomosis measured 4-5 mm. Only 15 were actually constructed as ETS fistulae | Continuous suturing technique. Anastomosis measured 4-5 mm. | 41 fistulae | Undetermined | 40 fistulae | Undetermined | Cumulative patency at 6, 12, 18, and 24 months. Excess fistulous flow, arterial steal syndrome, venous hypertension, aneurysms, stenosis and haemorrhage. | STS anastomosis is associated with a higher incidence of flow complications. Cumulative fistulae survival was similar in ETS and STS. |
| Wedgwood [133] | 1984 | Randomised controlled study from 1981 to 1983. If STS anastomosis was not possible, patients were allocated in the ETS group. Primary failure defined as inability to sustain dialysis for 1 month. | All patients referred for primary vascular access for haemodialysis | Undetermined | Continuous suturing technique was used in adults and interrupted in children. Anastomotic length (9.8±1.2 mm). | Continuous suturing technique was used in adults and interrupted in children. Anastomotic length (10.4±2.1 mm). | 39 patients | Venous diameter (3.8±0.73 mm). | 32 patients | Venous diameter (3.4±1.43 mm) | Patency at 3 and 9 months. Fistula flow rates. Venous pressure distal to the AVF. Correlation between fistula flow and vein diameter. | Similar patency rates in the two groups after 9 months. Hyperaemia of the hand was only observed in the STS group (7/32 fistulae). |

5.2.4 Quality assessment for risk of bias:

The Downs and Black tool was used to assess the quality of included studies [90]. This tool consists of 27 questions that examine the quality of both randomised and non-randomised studies. The tool evaluated the quality, external validity, bias and confounding from individual studies. In this modified tool, sample size calculation is considered in one question only, as opposed to five in the original tool that has 32 questions. Therefore, the maximum score for an individual study is 27, with a lower score indicating poor quality. The results of this assessment can be found in [Table 5.2].

In summary, the included studies all had significant weaknesses in their published work, with a median score of 16 and a range of (12 – 17). With the exception of O'Banion et al [135], all other papers did not clearly state the characteristics of the patients included in those studies. This can make pooling the results from those studies in a meta-analysis prone to show incorrect effect estimates biased by possible confounders. Similar concerns are raised again by the fact that only Mozaffar et al [138] clearly reported on possible confounders. Additionally, none of the studies attempted to run tests designed to adjust for known confounders. Adverse events were not reported in one of the studies [139], and all of the included studies failed to report on the characteristics of those lost to follow-up, raising concerns about reporting and attrition bias. None of the studies involved appropriate sample size calculation.

The assignment of patients into either group was not concealed in any of the studies. Similarly, no attempts were made to blind subjects or outcome assessors; this could have resulted in bias in performing the procedures if the operating surgeon favoured one technique over the other. However, maturation of fistulae included in those studies was assessed using a relatively objective method, either by ultrasound scans or by functional maturation defined as successful cannulation of those fistulae for HD. External validity components scored better among the included studies (all studies recruited patients from the same population, during the same period and used appropriate methods to assess outcomes).

Table 5.2: Results of the study quality assessment

| Number | Question | Khan [137] | O'Banion [135] | Mozaffar [138] | Ganie [139] | Galic [136] | Dunlop [140] | Wedgwood [133] |
|--------|---|---------------|-------------------|-------------------|----------------|----------------|-----------------|-------------------|
| 1 | Hypothesis/objective clear? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2 | Main outcomes clearly described in introduction or methods? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 3 | Are patients' characteristics clearly described? | No | Yes | No | No | No | No | No |
| 4 | Are interventions clearly described? | No | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | Are confounders equally distributed? | UTD | No | Yes | UTD | UTD | UTD | UTD |
| 6 | Are the main findings clearly described? | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 7 | Are estimates or variability provided? | No | Yes | Yes | No | No | No | No |
| 8 | Are important adverse events reported? | Yes | Yes | Yes | No | Yes | Yes | Yes |
| 9 | Are the characteristics of those lost to follow up described? | No | No | No | No | No | No | No |
| 10 | Are specific p value reported? | No | Yes | No | No | Yes | Yes | Yes |

| | | | | | | | | |
|----|--|-----|-----|-----|-----|-----|-----|-----|
| 11 | Were potentially eligible subjects representative of the population? | Yes |
| 12 | Were participating subjects representative of the population? | Yes |
| 13 | Were staff, places and facilities representative of the treatment most patients receive? | Yes |
| 14 | Was an attempt made to blind subjects to the intervention they received? | No |
| 15 | Was an attempt made to blind main outcome assessors? | No |
| 16 | If any results reflect data dredging, is this clear? | No |
| 17 | Do analyses adjust for length of follow up differences? | Yes |
| 18 | Were appropriate statistical analyses used? | No | Yes | No | No | Yes | Yes | Yes |
| 19 | Was compliance with the intervention reliable? | Yes |

| | | | | | | | | |
|--------------|--|-----|-----|-----|-----|-----|-----|-----|
| 20 | Were the main outcome measures valid and reliable? | Yes |
| 21 | Were study groups recruited from the same population? | Yes |
| 22 | Were subjects recruited over similar time-periods? | Yes |
| 23 | Were study subjects randomised to intervention groups? | No | No | Yes | No | No | No | Yes |
| 24 | Was treatment assignment concealed? | No |
| 25 | Was there adequate adjustment for confounders in the analysis? | No |
| 26 | Were losses of patients to follow-up taken into account? | Yes | Yes | UTD | UTD | Yes | Yes | Yes |
| 27 | Was an appropriate sample size calculation carried out? | No |
| | | | | | | | | |
| Total | Number of "Yes" results | 12 | 17 | 16 | 12 | 15 | 16 | 17 |

5.2.5 Data analysis:

The statistical tool Review Manager version 5.3 was used to perform the tests included in the meta-analysis section of the review [91]. The random effects model of DerSimonian and Laird was used to compare categorical outcome measures pooled as risk ratios [92]. Statistical heterogeneity among studies was assessed by the Cochran's Q-test. Statistically significant differences were reported if the p-value was less than 5%. In addition, publication bias was evaluated by comparing between the fixed and random effects models for outcomes in a sensitivity test to determine the impact of small-study effects [93].

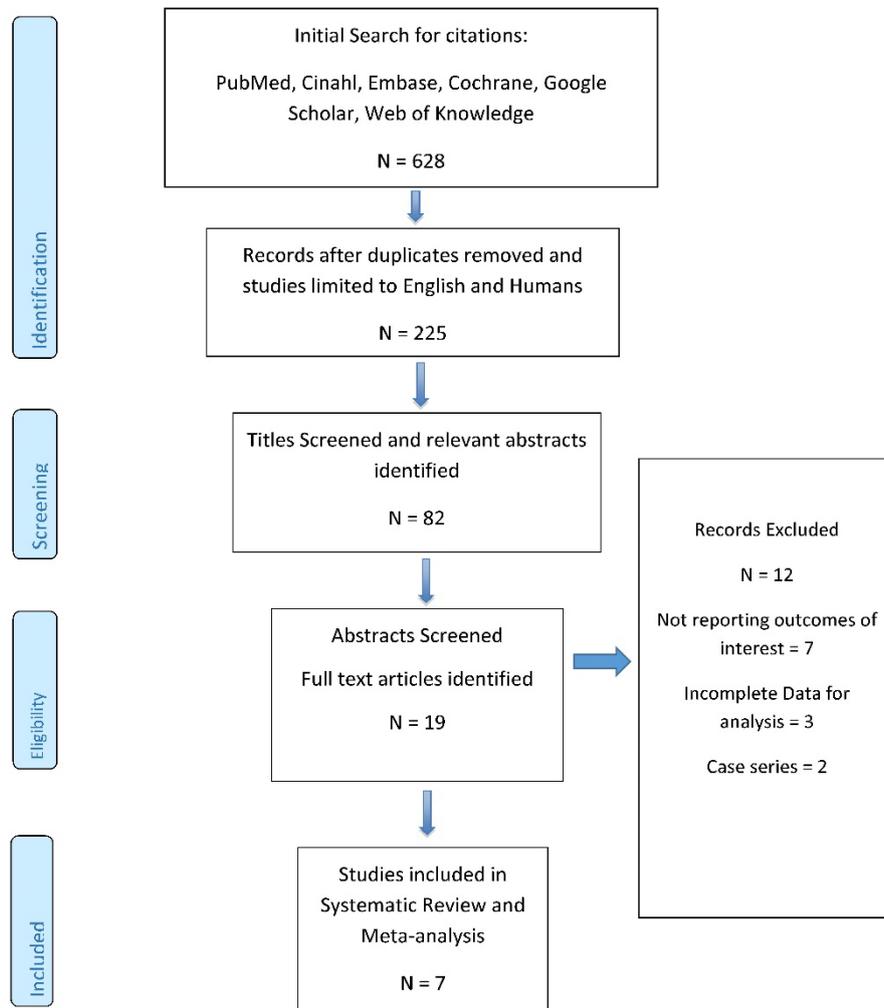
5.3 Results:

5.3.1 Study selection:

A summary of the selection process and is presented in the PRISMA flow diagram [Figure 5.1]. All related citations on haemodialysis vascular access that compared ETS to STS were searched. Initially started with 628, then following removal of duplicates and restricting our search to studies on human subjects that were published in English, 225 studies remained. The titles of the remaining citations were screened, and 82 possibly eligible studies were left. After reading the abstracts of the remaining citations, thirteen studies were considered for the review, however, reading the full articles revealed that only seven of those met our eligibility criteria and were therefore included in this systematic review [133, 135-140].

Of the seven studies included in this review, three were randomised controlled studies (RCTs) [133, 137, 138] and the remaining four were retrospective observational studies [135, 136, 139, 140]. All of the included studies compared patency rates of AVFs formed in ETS fashion to patency rates of those formed using a STS technique. All studies were reported on patients diagnosed with end-stage renal disease (ESRD) secondary to various aetiologies. All of the anastomosis in the ETS group were constructed between the end of the vein and the side of the artery, whereas all of the anastomosis in the STS group were made between the side of the vein and the side of the artery. In all studies, the artery used was the radial artery and the vein was the cephalic vein. Patency rates were reported from the time of access creation with 3 months being the shortest [133, 135], and 24 months being the longest follow-up period for reporting on cumulative access patency [136, 139, 140].

Figure 5.1: PRISMA flow diagram



5.3.2 Participants:

The seven studies included 986 patients, with 463 patients in the ETS group and 523 in the STS group. Of the seven studies, age of the participants was mentioned in four. In the study by Khan et al, the age of patients in the ETS group was 39.79 ± 0.41 , while it was 39.45 ± 0.51 for the STS group [137].

O'Banion et al studied older patients, as the age of patients in the ETS group was 55 ± 14.6 , and in the STS group it was 58 ± 12.5 [135]. In the study by Galic et al, age ranged between 17 to 90 years [136], while it ranged between 6 to 69 with a mean of 44.6 in the study by Dunlop et al [140]. The gender of participants was reported in five studies with 517 male and 288 female patients [133, 135-137, 140]. In the two studies that reported the prevalence of diabetes, there were 32 diabetics in the ETS group compared to 35 in the STS group [135, 138].

The main points in the study design, along with the inclusion and exclusion criteria - whenever available - and other baseline characteristics are summarised in [Table 5.1]. The author wants to highlight the fact that some of the included studies did not report clearly on many of the data considered relevant to outcomes from AVFs formation [Table 5.1]. This raises possible concern for a number of potential bias, including selection bias, reporting bias, information bias and attrition bias. Including those studies in a meta-analysis in their current shape should be considered a weakness of this systematic review. Important outcomes from included studies are outlined in [Table 5.2].

Table 5.3: Main outcomes from included studies

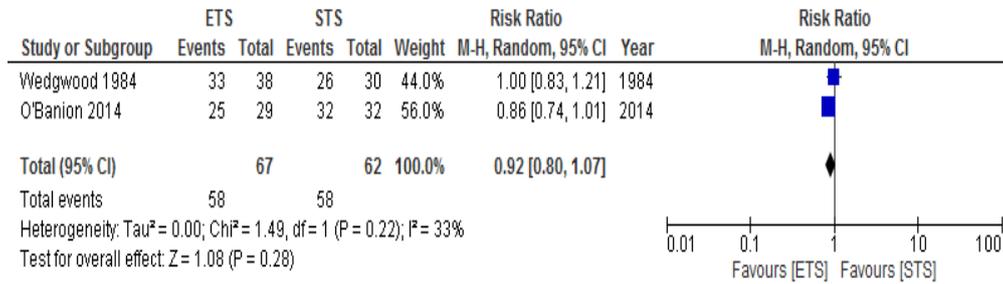
| Study | End-to-Side | | | | | Side-to-Side | | | | |
|-----------------------|-----------------------|--|--|-----------------|--------------|------------------------|--|--|-----------------|--------------|
| | Number of End-to-Side | Patency | Haematoma | Wound Infection | Steal | Number of Side-to-Side | Patency | Haematoma | Wound infection | Steal |
| Khan [137] | 168 | 150/168 at 6 months | In 24 hours: 15/168 In 1 month: 3/168 | - | - | 168 | 143/168 at 6 months | In 24 hours: 18/168 In 1 month: 7/168 | - | - |
| O'Banion [135] | 29 | 14% early thrombosis 86% 3-month primary patency rate 48% 6-month primary patency rate 75% secondary patency rate | - | - | - | 32 | No early thrombosis 100% 3-month primary patency rate 78% 6-month primary patency rate 81% secondary patency rate | - | - | - |
| Mozaffar [138] | 30 | 5/30 failed to mature due to early thrombosis | - | - | - | 30 | 4/30 failed to mature due to early thrombosis; while 2/30 failed due to venous hypertension | - | - | - |
| Ganie [139] | 26 | Patency in 12 months was 80% Patency in 24 months was 55% | - | - | - | 131 | Patency in 12 months was 77% Patency in 24 months was 50% | - | - | - |
| Galic [136] | 130 | Loss of primary patency in 6 months was 10.76%. | Over 2 years | Over 2 years | Over 2 years | 90 | Loss of primary patency in 6 months was 18.88%. Secondary | Over 2 years was 3/90 | Over 2 years | Over 2 years |

| | | Secondary patency in 2 years was 89.23% | was 1/130 | was 8/130 | was 0/130 | | patency in 2 years was 81.11% | | was 5/90 | was 2/90 |
|-----------------------|----|---|-----------|-----------|-----------|----|--|---|----------|----------|
| Dunlop [140] | 41 | Cumulative fistula patency was 21/41 after 6 months, 17/41 after 12 months and 12/41 after 24 months. | - | - | - | 40 | Cumulative fistula patency was 28/40 after 6 months, 19/40 after 12 months and 9/40 after 24 months. | - | - | - |
| Wedgwood [133] | 39 | Patency was 86.8 after 3 months, and 78.6 after 9 months. | - | - | - | 32 | Patency was 86.7 after 3 months and 79.2 after 9 months. | - | - | - |

5.3.3 Patency rate after 3 months:

Patency after 3 months was reported in two studies [133, 135]. The two studies had 129 patients, with 67 in the ETS group, and 62 in the STS group. In the ETS group 58/67 (87%) had patent fistulae, compared to 58/62 (94%) patent fistulae in the STS group. The difference between those groups was not statistically significant as shown in the pooled analysis (Pooled risk ratio = 0.92 [0.80, 1.07], 95% CI, P = 0.28) [Figure 2]. There was no heterogeneity detected (Cochran's Q = 1.49; degree of freedom (DF) = 1; P = 0.22; I² = 33%).

Figure 5.2: A Forest's Plot for patency rate in 3 months (random effects):



5.3.4 Patency rate after 6 months:

Five studies reported patency rates after 6 months of follow-up [135-138, 140] in 758 patients. In the ETS group 326/398 had patent fistulae in 6 months, compared to 292/360 patent fistulae in the STS group. The difference between the groups was not statistically significant (Pooled risk ratio = 0.98 [0.86, 1.13], 95% CI, P = 0.82) [Figure 5.3]. Heterogeneity was detected statistically (Cochran's Q = 10.75; degree of freedom (DF) = 5; P = 0.03; I² = 63%). This significant degree of heterogeneity might be explained by the fact that the author pooled data from two RCTs with data from three observational studies. A sensitivity test designed to detect publication bias by comparing the fixed effects (Pooled risk ratio = 1.00 [0.94, 1.07], 95% CI, P = 0.93) to the random effects above did not show any difference as the difference remained insignificant [Figure 5.4].

Figure 5.3: A Forest's Plot for patency rate in 6 months (random effects):

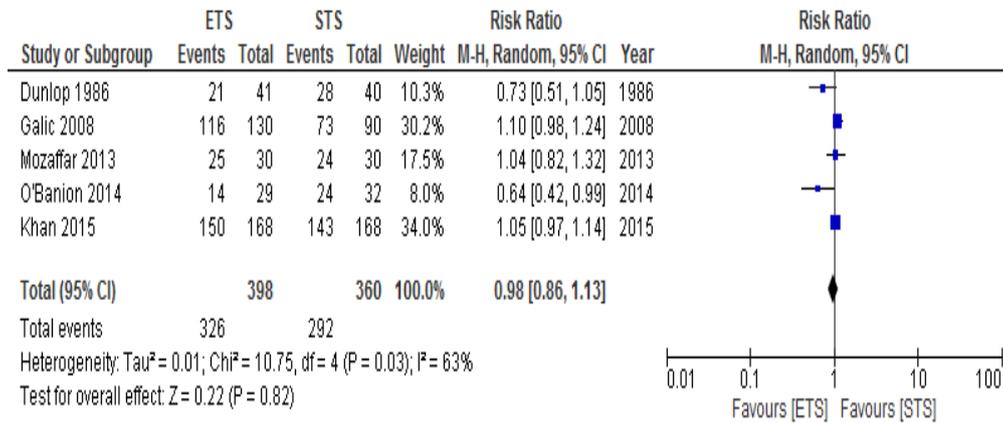
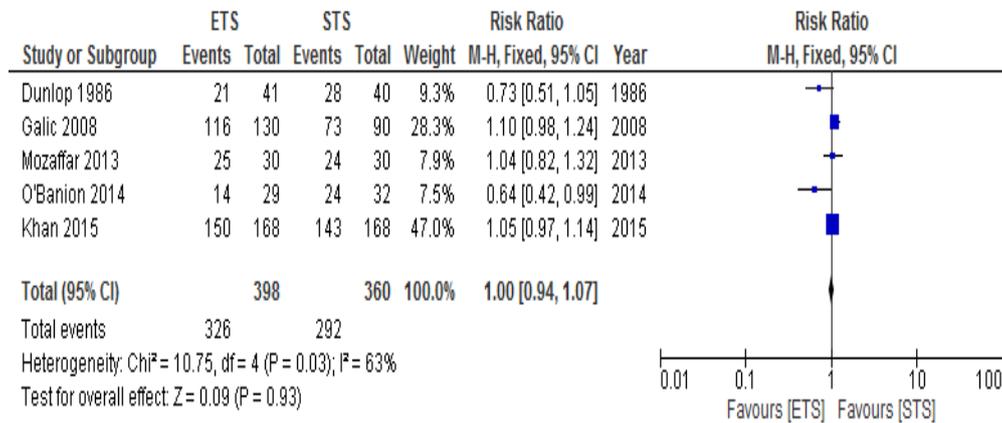


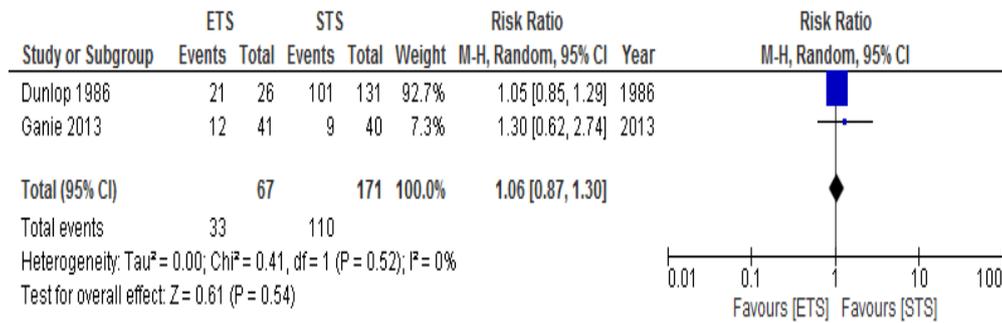
Figure 5.4: A Forest's Plot for patency rate in 6 months (a sensitivity test with fixed effects model):



5.3.5 Patency rate after 12 months:

This was reported in two studies [139, 140]. Of the 238 patients included in those studies, 33/67 fistulae remained patent after 12 months in the ETS group compared to 110/171 in the STS group. This difference was not found to be statistically significant (Pooled risk ratio = 1.06 [0.87, 1.30], 95% CI, P = 0.54). Heterogeneity was not detected statistically (Cochran's Q = 0.41; degree of freedom (DF) = 1; P = 0.52; I² = 0%) [Figure 5.5].

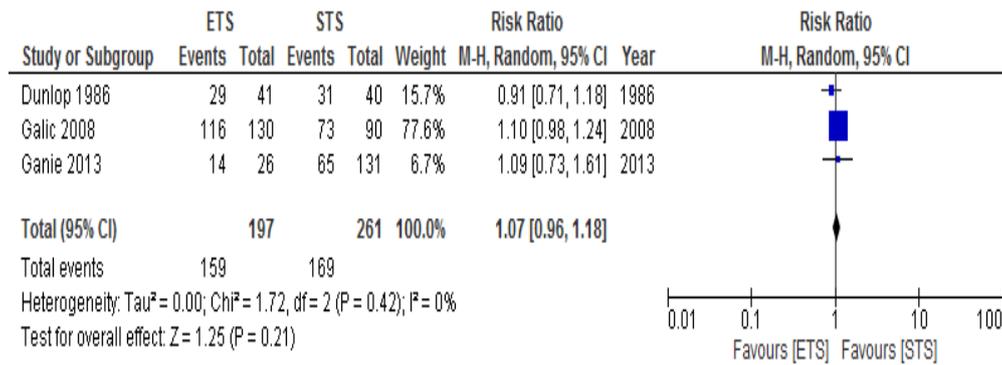
Figure 5.5: A Forest's Plot for patency rate after 12 months (random effects):



5.3.6 Patency rate after 24 months:

Three of the included studies reported data on patency rates after 2 years in 458 patients [136, 139, 140]. Of those, 159/197 fistulae were functional in two years in the ETS group, compared to 169/261 in the STS group. This difference was not significant (Pooled risk ratio = 1.07 [0.96, 1.18], 95% CI, P = 0.21) [Figure 5.6]. There was no heterogeneity detected statistically (Cochran's Q = 1.72; degree of freedom (DF) = 2; P = 0.42; I² = 0%).

Figure 5.6: A Forest's Plot for patency rate after 24 months (random effects):



5.3.7 Postoperative wound haematoma:

Two of the included studies reported on the incidence of postoperative wound haematoma in four weeks [136, 137]. Of the 556 patients shared in those studies, 4/298 patients in the ETS developed the complication, compared to 10/258 in the STS group. Although a trend favoured the ETS approach with fewer postoperative haematomas, however the difference was not statistically significant (Pooled risk ratio = 0.36 [0.12, 1.15], 95% CI, P = 0.09).

Heterogeneity was not detected statistically (Cochran's Q = 0.22; degree of freedom (DF) = 1; P = 0.64; I² = 0%) [Figure 5.7]. The results remained unchanged when the fixed effects model was used in a sensitivity test (Pooled risk ratio = 0.36 [0.12, 1.13], 95% CI, P = 0.08) [Figure 5.8].

Figure 5.7: A Forest's Plot for postoperative wound haematoma (random effects):

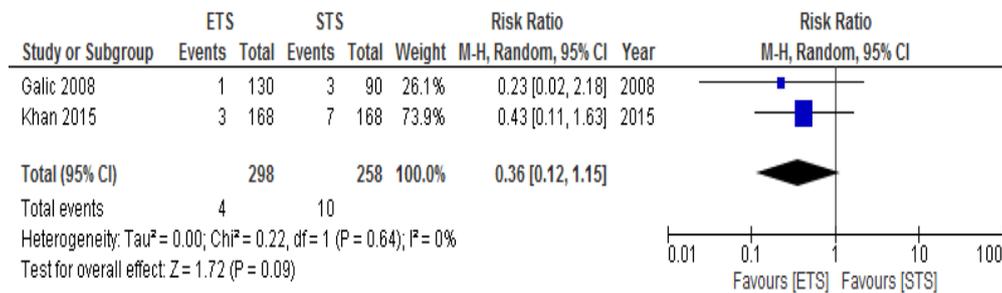
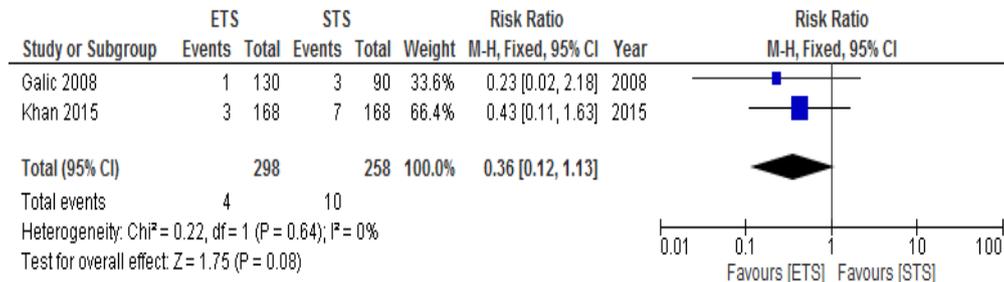


Figure 5.8: A Forest's Plot for postoperative wound haematoma (a sensitivity test with fixed effects model):



5.3.8 Arterial steal syndrome:

The development of postoperative arterial steal syndrome was reported in two studies, and was defined as the presence of ischaemic symptoms distal to the anastomosis that presented as claudication pain, muscle wasting, paraesthesia and/or trophic skin changes [136, 140]. Of the 301 fistulae included in those studies, none of the fistulae developed the condition in the ETS group, whereas 7/130 fistulae were found to have caused a degree of clinical steal syndrome. The difference between the groups was found to be statistically significant (Pooled risk ratio = 0.11 [0.01, 0.88], 95% CI, P = 0.04) [Figure 5.9]. Heterogeneity was not detected statistically (Cochran's Q = 0.05; degree of freedom (DF) = 1; P = 0.83; I² = 0%). A sensitivity test by performing the same test using the fixed effects model showed that the difference remained statistically significant with the same p-value in pooled analysis (Pooled risk ratio = 0.11 [0.01, 0.86], 95% CI, P = 0.04) [Figure 5.10].

In our review, only two studies have reported the incidence of arterial steal syndrome, of those only one was performed on brachiocephalic fistulas [140]. It was not immediately clear which anatomic types of AVFs were included in the second study [136].

Figure 5.9: A Forest's Plot for development of postoperative arterial steal (random effects):

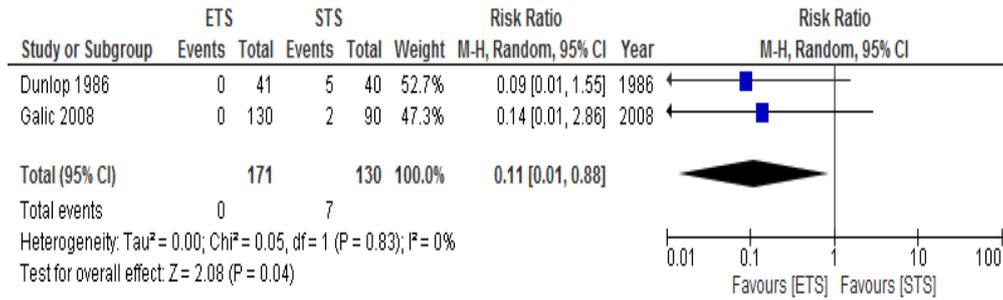
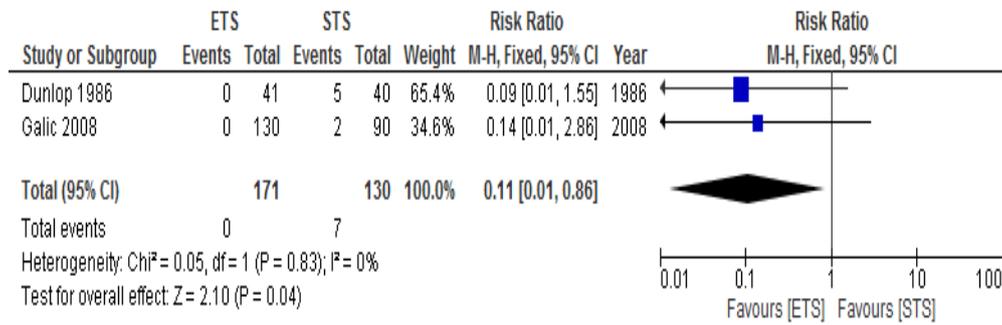


Figure 5.10: A Forest's Plot for development of postoperative arterial steal (a sensitivity test with fixed effects model):



5.4 Discussion:

A well-functioning AVF has been repeatedly shown to be the superior modality for vascular access creation in patients undergoing HD [130]. However, the main disadvantage with native AVFs has always been the relatively high rate of early thrombosis with as high as one-third of new fistulas at risk of early failure. Several factors have been studied, however with the exception of vessel diameters the evidence behind other predictors of access survival remain debatable at best [141]. The end-to-side (ETS) anastomosis has been favoured in forming AVFs; however, due to the high rate of primary failure, this configuration might be contributing to the significant haemodynamic changes leading to unfavourable conditions for the successful maturation of AVFs [142].

Seven studies were included in this systematic review [133, 135-140]; with 986 AVFs divided as 463 in the ETS group and 523 in the STS group. Five of the included studies reported on patency in six months [135-138, 140], and the difference was not statistically significant between the two groups (Pooled risk ratio = 0.98 [0.86, 1.13], 95% CI, P = 0.82). Similarly, patency rates in 3, 12 and 24 months did not differ significantly (P = 0.28, P = 0.54 and P = 0.21, consecutively). In addition, pooled analysis of the incidence of postoperative wound haematoma did not statistically favour either group, although fewer cases were reported in the ETS group (Pooled risk ratio = 0.36 [0.12, 1.15], 95% CI, P = 0.09). The only significant difference between the ETS and the STS techniques was found in the development of postoperative arterial steal syndrome. All cases of steal syndrome were reported in the STS groups (Pooled risk ratio = 0.11 [0.01, 0.88], 95% CI, P = 0.04).

Only three RCTs were included in this systematic review. One possible explanation is the fact that most surgeons are trained to perform an end-to-side anastomosis and they feel more comfortable with that technique. Another factor is probably the reported association between side-to-side AVFs and the development of arterial steal syndrome and venous hypertension. When we consider the similar maturation rates and patency rates reported using either technique, the lack of more RCTs becomes understandable. Therefore, even in the future, it will be difficult to see new RCTs comparing

the two techniques, as a genuine need for such studies seems to be lacking. Khan et al reported an overall survival rate of 89.3% in the ETS, compared to 85.1% in the STS groups ($p = 0.253$) [137]. They also compared the cumulative survival between groups according to gender. They found that 107(89.9%) male patients in the ETS, and 101(84.9%) in the STS had patent AVFs by the end of their study, a non-significant difference. Similarly, 43(87.8%) female patients in the ETS group and 42(85.7%) in the STS had functional fistulae by the end of the study, again, a non-statistically significant difference.

O'Banion et al found that the vein diameter of those in the ETS group (2.6 ± 0.68 mm) was significantly larger in comparison to the STS group (1.9 ± 0.59 mm), ($p < 0.001$) [135]. However, the STS group had better outcomes, as none of the 32 fistulae in this group suffered from early thrombosis compared to 14% in the ETS group ($p < 0.05$). In addition, primary patency rates were higher in the STS group (100%) compared to the ETS group (86%), ($p < 0.05$), and better cannulation rates (67% versus 30%, $p < 0.05$). Primary patency rates in 6 months of follow-up also favoured the STS configuration (78% versus 48%, $p < 0.03$), although the secondary patency rates were comparable between the groups with 75% of fistulae in the ETS, and 81% in the STS maintaining their cumulative patency.

Ganie et al reported a 90% patency rate in AVFs based on the brachial artery by the ETS technique after 12 months from creation [139]. In their study, AVFs based on the brachial and radial arteries both declined in terms of patency in the third year. They found a correlation between an audible murmur over a 6 cm distance over the fistula and flow rates of > 200 ml/min. Fistulae created in the ETS fashion had better flow rates, whereas those formed in the STS fashion had more arteriatised veins leading to easier cannulation by HD staff. Paraesthesia occurred more frequently in AVFs based on the radial artery, whereas STS fistulae based on the brachial artery provided less flow rates during HD sessions, possibly due to more collaterals in comparison to using the same technique in a radiocephalic AVF. Both early and late access failure was managed by formation of a new ETS fistula.

Galic et al found that threatening complications (infections, steal syndrome, thrombosis, haemorrhage and aneurysms) occurred less frequently in the STS (18.88%) group in comparison to the ETS group (62.5%) [136]. Thrombosis occurred in (2.31%) of STS fistulae compared to (5.56%) of ETS fistulae. Secondary patency rates in two years favoured the ETS technique (89.23%) when compared to the STS technique (81.11%).

Dunlop et al performed one of the earliest studies comparing between STS and ETS techniques in access formation. They diagnosed excess blood flow based on clinical or radiological assessment of high output cardiac failure [140]. The difference between the STS (7/40) and the ETS (4/41) groups concerning the development of this complication was not significant ($0.5 > P > 0.1$). In addition, venous hypertension was diagnosed in one fistula, which was formed using a STS anastomosis. All cases of aneurysms (two true and one false) were related to cannulation for HD, and were managed by a bypass vein graft.

Wedgwood et al reported that 4/39 (10.3%) fistulae created by the ETS technique suffered from primary failure compared to 3/32 (9.4%) in the STS group [133]. The only fistula salvaged following attempted thrombectomy belonged to the STS group. Patency rates were comparable in 9 months, as 22/28 (78.6%) in the ETS and 19/24 (79.2%) in the STS group remained patent. However, 7/32 patients in the STS group were diagnosed with hyperaemia of the hand compared to none in the ETS group, statistically significant difference. Patients who developed this complication were found to have increased caudal flow rates distal to the anastomosis intraoperatively; necessitating revision procedures in three of those cases. In their study, comparisons between preoperative and postoperative fistula flow rates correlated significantly with the maturation outcome in the ETS group only. Both groups had similar flow rates, venous pressure and blood pressure during HD sessions. Venous diameter was found to correlate significantly with AVF flow rates in both groups.

Sahasrabudhe et al reported findings from a retrospective study that showed the successful maturation rate when using the STS technique (76%) was

superior to the ETS approach (70%); however, the difference was not statistically significant [143]. It also needs to be highlighted that the STS was performed in proximal fistulae, whereas the ETS was used in all distal AVFs (wrist and forearm), leading to genuine concerns about confounding in comparing between the ETS and STS techniques in this study.

Similarly, Cassioumis et al found the difference in early patency rates between the ETS group (90%) and the STS group (88%) not to be significant [144]. However, when compared to the ETS group, the STS group had superior patency rates after 3 months of follow-up (85% vs 79%), and similarly after 12 months (80% vs 66%). In addition, 93% of AVFs in the STS group maintained satisfactory functional capacity during the study period, compared to 78% of fistulae in the ETS group. Similarly, Lynn et al found that the STS configuration was significantly superior to ETS ($P = 0.0001$) regardless of the side or site of the AVF in a retrospective analysis of 432 fistulas in patients receiving home HD [145].

The findings of this systematic review are limited by the quality of the included studies. Of the seven studies, three were RCTs and four were observational studies. All included studies had flaws in their study design, and lacked adequate risk stratification and sub-group analysis. In addition, data collection and analysis failed to reflect the baseline characteristics of some of the included studies, which increases the risk of bias and confounding. None of the studies included in this review performed power calculations to arrive at the sample sizes used by their authors, thus raising concerns about a potential type-2 error from small sample size. Those methodological weaknesses can be addressed and corrected in a future large RCT, possibly across multiple sites.

5.5 Conclusion:

The end-to-side anastomosis technique has been favoured by many vascular surgeons over the side-to-side technique in the formation of AVF for HD access. However, the evidence concerning early and late AVF patency rates does not support this practice. Arterial steal syndrome was significantly associated with the STS technique. More studies are required to make definitive recommendations.

VI Chapter Six: The Utility of a
Neutrophil-Lymphocyte Ratio derived
from preoperative blood tests in
predicting Arteriovenous Fistula
Maturation

6.1 Introduction:

The increase in the incidence of patients diagnosed with end stage renal disease (ESRD) is expected to strain the limited resources for haemodialysis (HD) in many hospitals [95, 96]. An arteriovenous fistula (AVF) is the best modality for haemodialysis; its superiority has been shown and is well established in the literature [97, 146-150]. Therefore, it is important to give patients with ESRD the best chance of having a functioning arteriovenous fistula (AVF) by the time they start haemodialysis. A well-functioning AVF capable of meeting the demands of repeated cannulation and maintaining enough blood flow through the formed conduit to successfully complete HD sessions is associated with less incidence of complications such as infections at the site of the fistula, sepsis, recurrent hospital admissions and access-related deaths [97-99]. The main disadvantage of fistulae is the high rate of primary failure – up to 50% in some studies [7, 100, 101].

An assessment of the relationship between the maturation of AVFs and the inflammatory response at the time of creation might provide a fast, cheap and readily available tool to predict stenosis and therefore non-maturation. This can help guide early intervention and pre-emptive angioplasty procedures to improve maturation rates. Fewer variables are required to calculate the neutrophil-lymphocyte ratio (NLR) as opposed to the use of more complex prediction models that are based on several factors. In addition, those factors have shown conflicted associations with non-maturation in the literature. Access failure secondary to stenosis and/or thrombosis is thought to be related to intimal hyperplasia (IH), a poorly understood phenomenon with several haematological and haemodynamic factors implicated in the pathophysiology of IH [116, 130].

The utility of the NLR in predicting stenosis in AVFs has been previously tested in chronic haemodialysis patients [116]. They found that patients who were diagnosed with AVF stenosis had a higher Mean \pm SD NLR (3.47 ± 0.46) compared to those with patent fistula (2.27 ± 0.22), this difference was significant ($p < 0.001$). The systemic inflammatory response involves changes in the level of the circulating components measured in a full blood count test

(FBC), namely neutrophils and lymphocytes. Neutrophilia has been shown to be associated with a relative lymphocytopaenia [151-153]. NLR has been suggested as a simple alternative to measure the systemic inflammatory response to surgical stress, systemic inflammation or sepsis in critically ill patients [154].

The author of this thesis hypothesised that inflammatory markers at the time of access formation can influence the process of fistula maturation through increased production of haematological factors associated with increased levels of Intimal hyperplasia. Calculating the NLR at the time of AVF creation can predict the maturation outcome.

6.2 Materials and Methods:

Patients who were referred to the vascular unit in the University Hospital Limerick (UHL) for formation of an upper limb AVF between 2009 and 2013 with a known fistula maturation outcome measured functionally in the haemodialysis unit were included in this study. Three surgeons performed the procedures. Patients included had a minimum age of 18 years. In those with multiple episodes of a new AVF formation, each episode was considered separately. All fistulae were created in the wrist or forearm.

Ethical approval for the study was obtained from the research ethics committee and the risk management department of the regional Health Service Executive (HSE West). All relevant data were extracted from the patients' medical records, including electronic records for discharge notes and laboratory blood tests. All records were anonymised and the data de-identified prior to processing.

6.2.1 Study objectives and definitions:

The author aimed to test the hypothesis that NLR – defined as the absolute neutrophils count divided by the absolute lymphocytes count – can predict fistula maturation. The NLR was calculated from blood tests obtained routinely on the morning of the fistula operation on all patients with the exception of in-patients who had their routine blood tests done the evening prior to the procedure. A functional maturation rate was used in this study, which was defined as the successful use of the arteriovenous fistula for six consecutive sessions of HD, and this was obtained from the dialysis records. This method has been validated and extensively used in the published literature [84-86, 155].

In addition, this study aimed to evaluate the association between certain demographics (age, gender, diabetes, smoking, hypertension, hyperlipidaemia, history of steroids use, history of Calcium channel blockers at the time of the access formation and the history of previous dialysis access)

and functional AVF maturation as secondary endpoints. The aetiology behind ESRD was also recorded whenever possible.

6.2.2 Statistical analysis:

Data were collected and recorded on spreadsheet. IBM SPSS version 22.0 was used for statistical analysis [87]. Categorical data are expressed in true value and as percentages and were compared using the Pearson Chi-Square (X^2) test. The independent sample t-test was used to compare normally distributed continuous data, which were reported as mean \pm SD; for abnormally distributed continuous data (reported as median and range), the author used the Mann-Whitney U test. Levene's test for equality of variances was used to determine the p value in the t-test regression analysis for continuous data [88]. Distribution of data was assessed by histograms, Q-Q plots and box-plots. The 5% level with a confidence interval of 95% was considered significant.

6.3 Results:

A total of 103 patients were included in this study with 123 AVFs; of which, 88 were created in men (71.5%) and 35 in women (28.5%). Overall, 109 fistulae (66 in men and 43 in women) had known maturation outcome with 55/66 (84.8%) matured in men compared to 23/43 (53.5%) in women; this difference was significant ($P = 0.001$). The missing fistulae (14/123) belonged to patients who never started HD. Age of included patients (mean \pm SD) was 60 ± 17.6 , and showed skewed distribution between males and females, as men aged 62.7 ± 16.3 with a median of 67 (20 – 89) while women aged 53.6 ± 19.3 with a median of 55 (21 – 81) [Figure 6.1]. The age difference between men and women was statistically significant ($P = 0.012$).

The most frequent aetiology behind ESRD was diabetes ($n = 42/123$; 37.4%) followed by congenital renal agenesis (11/123; 8.9%), hypertension (9/123; 7.3%), ischaemic injury (8/123; 6.5%) polycystic kidney disease (7/123; 5.7%) and obstructive uropathy (7/123; 5.7%). The rest of the demographic data, comorbidities and regular drug therapy at the time of fistula creation are shown in [Table 6.1]. A summary of age and baseline blood results for all patients can be found in [Table 6.2].

Figure 6.1: A box Plot showing age distribution per gender:

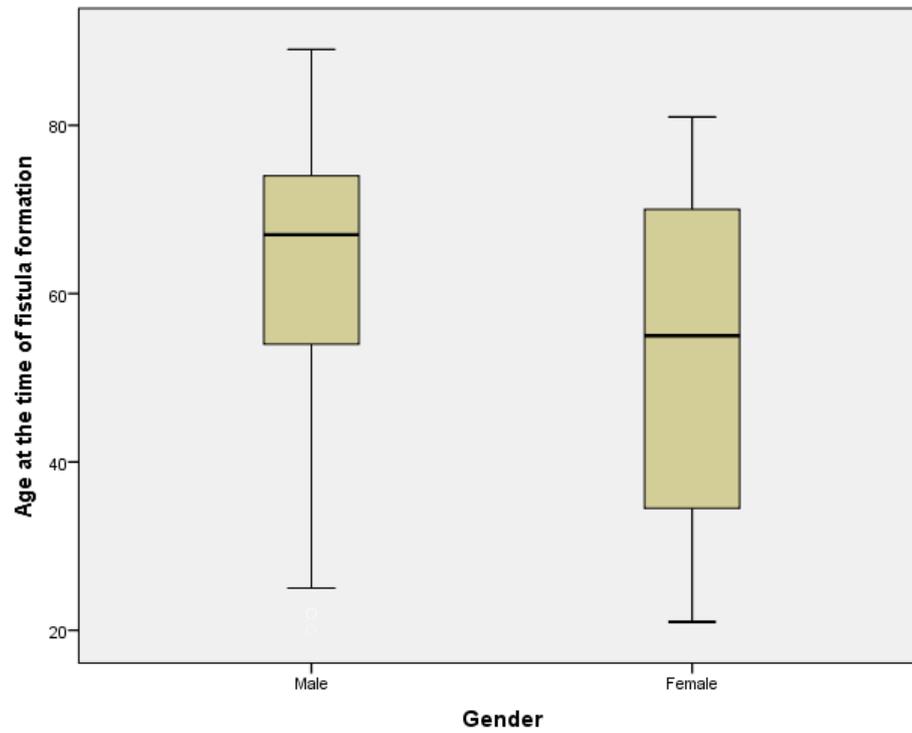


Table 6.1: Characteristics of patients in study:

| Baseline characteristic | Frequency and percentage of the positive (yes) values | |
|--|---|--|
| | Frequency (Expected %) N = 123 | Valid % (Excluding missing values) |
| Functional maturation | 66 (53.7) | 60.6 |
| Female gender | 35(28.5) | 28.5 |
| Male gender | 88 (71.5) | 71.5 |
| Diabetes | 46 (37.4) | 37.7 |
| Smoking | 40 (32.5) | 34.2 |
| Hypertension | 104 (84.6) | 86.7 |
| Hyperlipidaemia | 89 (72.4) | 73.6 |
| Coronary artery disease | 46 (37.4) | 38 |
| Atrial fibrillation | 19 (15.4) | 15.7 |
| Warfarin | 19 (15.4) | 15.7 |
| Congestive cardiac failure | 29 (23.6) | 24 |
| Insulin | 22 (17.9) | 18.3 |
| Calcium channel blockers | 38 (30.9) | 31.9 |
| Previous history of haemodialysis | 84 (68.3) | 70.6 |
| Dialysis through Venous Catheter | 78 (63.4) | 67.2 |
| Previous kidney transplant | 18 (14.6) | 15.8 |
| Previous Arteriovenous fistula | 26 (21.1) | 32.1 |
| Site of AVF: Wrist | 60 (48.8) | 52.2 |
| Site of AVF: Forearm | 55 (44.7) | 47.8 |
| Salvage procedures to maintain patency | 26 (21.1) | 30.2 |

Table 6.2: Characteristics of continuous variables:

| | Age at creation of fistula | Haemoglobin (g/dl) | Platelets (10 ⁹ /L) | White Cells Count (10 ⁹ /L) | Neutrophils Count (10 ⁹ /L) | Lymphocytes Count (10 ⁹ /L) | NLR |
|----------------|-------------------------------|-----------------------|--------------------------------|---|---|---|--------|
| Mean | 60.19 | 11.085 | 244.77 | 7.6655 | 5.3478 | 1.270 | 5.091 |
| Std. Deviation | 17.578 | 1.5575 | 105.092 | 2.08274 | 1.82714 | 0.5503 | 3.0709 |
| Median | 63.00 | 11.000 | 226.00 | 7.2850 | 4.9600 | 1.160 | 4.263 |
| Minimum | 20 | 7.2 | 96 | 3.58 | 2.20 | 0.4 | 1.7 |
| Maximum | 89 | 14.6 | 1007 | 14.04 | 12.11 | 3.6 | 15.7 |

The overall AVF functional maturation rate was 53.7% (66/123); however, if the 14 patients who did not have a clearly identifiable maturation outcome in their medical records were excluded from the analysis, the functional maturation rate would be 60.6% (66/109).

Of our 123 fistulae, 55/78 (70.5%) matured in men compared to 11/31 (35.5%) in women; this difference was statistically significant ($P = 0.001$). Gender was the only demographic factor significantly associated with fistula outcome in this study. Age was not found to be significantly associated with maturation (patients with functional access had (mean \pm SD) age of (61.4 ± 16) compared to (59.1 ± 19.6) in patients with failed fistulae ($P = 0.836$; Mann-Whitney U test) [Figure 6.2].

Similarly, history of either diabetes or hypertension was not found to significantly influence fistula maturation (60 % and 62% in patients with mature AVFs compared to 40% and 46% in those with failed access, ($P = 0.976$) and ($P = 0.249$), respectively). The rest of the association analysis between fistula maturation and patients' characteristics are shown in [Table 6.3].

Figure 6.2: A box Plot showing age distribution per functional maturation

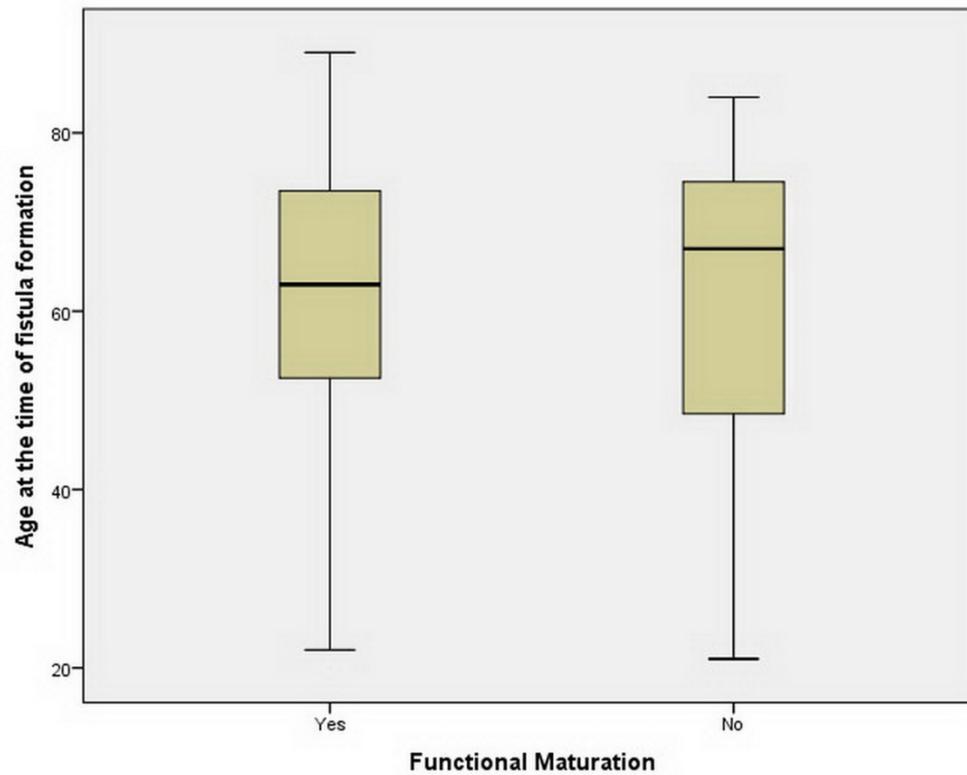


Table 6.3: Categorical variables association with functional maturation

| Variable | Functional maturation | N | % | P value |
|-------------------------|-----------------------|----|------|---------|
| Female gender | Yes | 11 | 35.5 | 0.001 |
| | No | 20 | 64.5 | |
| Male gender | Yes | 55 | 70.5 | |
| | No | 23 | 29.5 | |
| Diabetes | Yes | 24 | 60 | 0.976 |
| | No | 16 | 40 | |
| Smoking | Yes | 20 | 54.1 | 0.261 |
| | No | 17 | 45.9 | |
| Hypertension | Yes | 58 | 62.4 | 0.249 |
| | No | 35 | 37.6 | |
| Hyperlipidaemia | Yes | 50 | 60.2 | 0.906 |
| | No | 33 | 39.8 | |
| CAD | Yes | 25 | 61 | 0.944 |
| | No | 16 | 39 | |
| Atrial fibrillation | Yes | 10 | 62.5 | 0.863 |
| | No | 6 | 37.5 | |
| PVD | Yes | 11 | 52.4 | 0.394 |
| | No | 10 | 47.6 | |
| HD history | Yes | 44 | 60.3 | 0.978 |
| | No | 26 | 39.7 | |
| HD by catheter | Yes | 41 | 59.4 | 0.705 |
| | No | 28 | 40.6 | |
| Previous AVF | Yes | 14 | 56 | 0.731 |
| | No | 11 | 44 | |
| Site of AVF: Wrist | Yes | 32 | 56.1 | 0.324 |
| | No | 25 | 43.9 | |
| Site of AVF: Forearm | Yes | 34 | 65.4 | |
| | No | 18 | 34.6 | |

| | | | | |
|--------------------------------|-----|----|------|-------|
| History of salvage procedures | Yes | 17 | 70.8 | 0.032 |
| | No | 7 | 29.2 | |
| Renal transplant history | Yes | 15 | 93.8 | 0.002 |
| | No | 1 | 6.2 | |
| C ² channel blocker | Yes | 26 | 83.9 | 0.001 |
| | No | 5 | 16.1 | |
| Warfarin | Yes | 9 | 56.3 | 0.703 |
| | No | 7 | 43.7 | |
| Insulin | Yes | 14 | 70 | 0.339 |
| | No | 6 | 30 | |

6.3.1 Predictive value of the NLR:

The NLR (Mean \pm SD) for all of the patients included in the study was (5.091 \pm 3.091), with a median of 4.263 and a range of (1.7 – 15.7). The NLR ratio was skewed when patients were grouped based on functional maturation [Figures 6.3 and 6.4], therefore the author opted to report the findings as median (range) and used a non-parametric test (Mann-Whitney U) to calculate statistical significance. Patients with mature AVFs had NLR of 4.850 (1.8 – 15.7) compared to 3.554 (1.7 – 15.0); the difference was statistically significant (P = 0.024).

Figure 6.3: A box Plot showing NLR distribution per Maturation

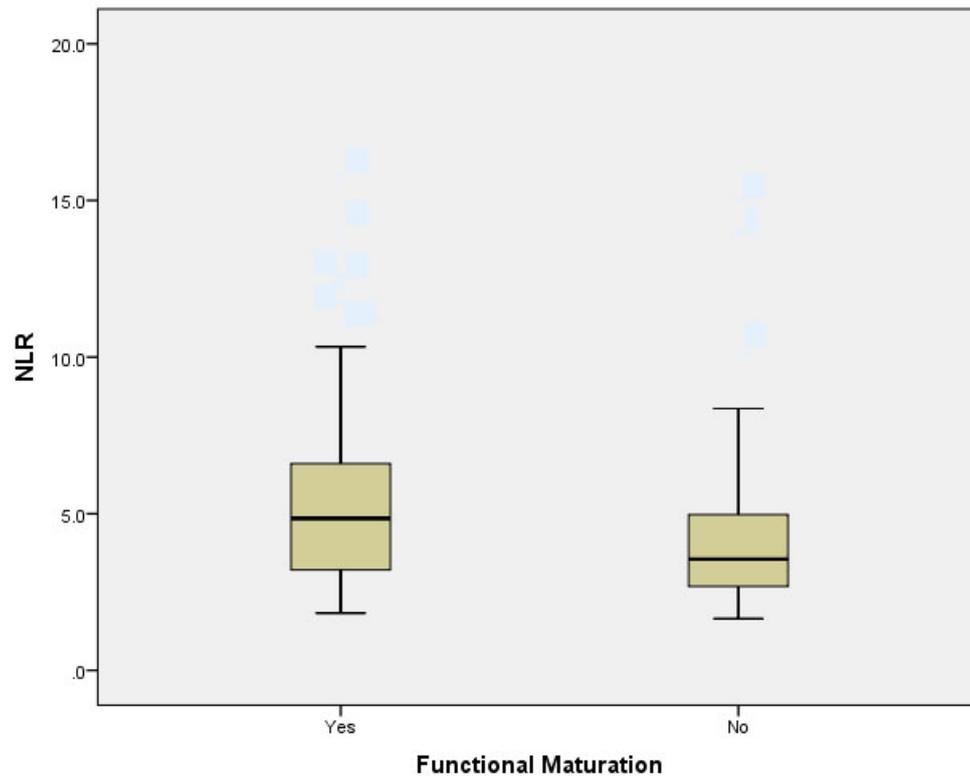
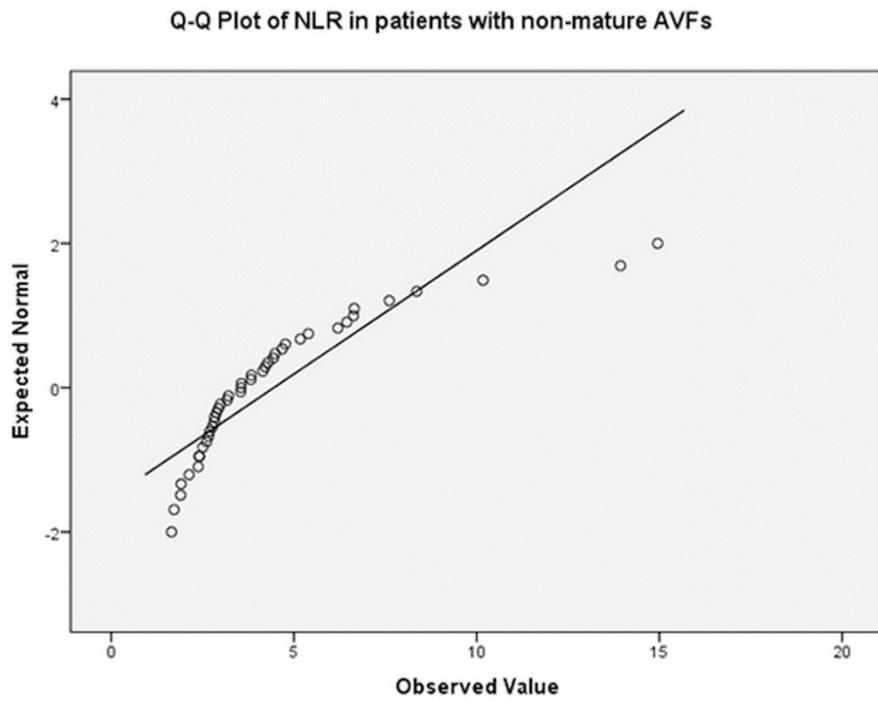
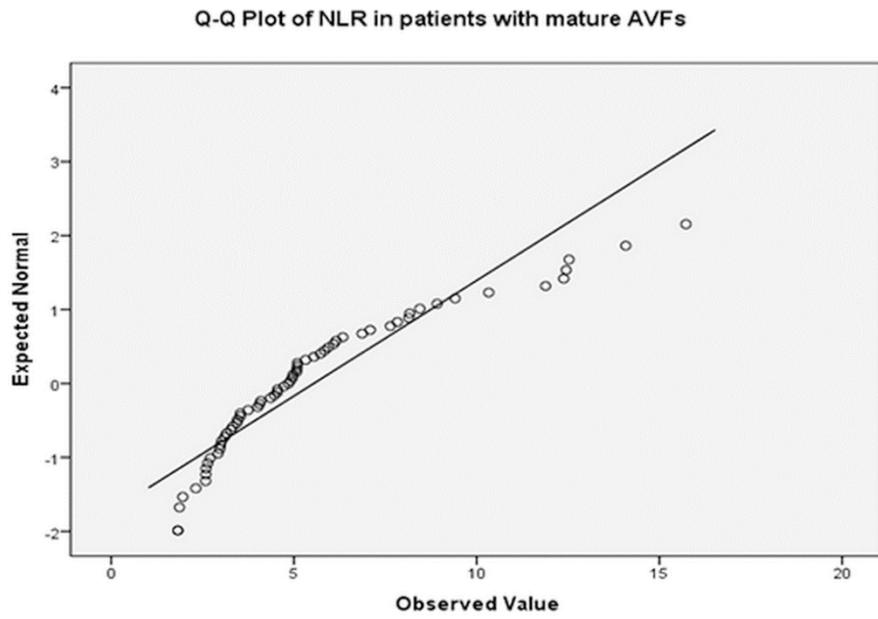
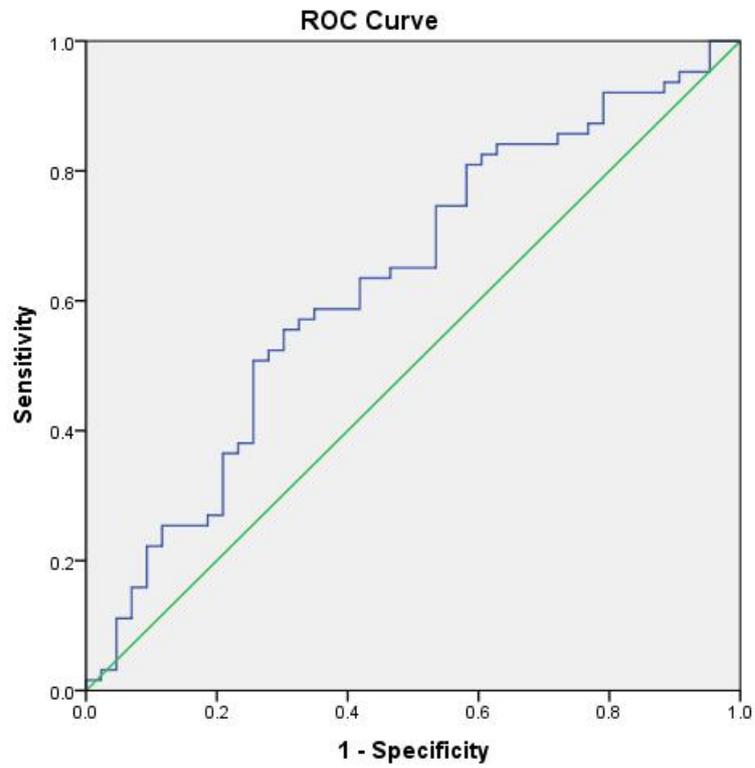


Figure 6.4: Q-Q Plots showing NLR distribution per mature/non-mature:



A logistic regression test that included all of the variables found to be significantly associated with fistula maturation (age, gender, history of secondary intervention to maintain patency, history of taking a calcium-channel blocker agent, haemoglobin level and history of a previous kidney transplant) was performed. In this test, female gender ($P = 0.008$) and a history of previous renal transplant ($p = 0.004$) were found to significantly predict fistula maturation. When the NLR was added to the logistic regression model, female gender was the only significant predictor of outcome ($P = 0.006$). However, in stepwise regression analysis, the NLR was found to be the third predictor of maturation after female gender and a previous renal transplant ($P = 0.190$). A receiver operator curve (ROC) for the NLR is shown in [Figure 6.5]. The area under the curve (AUC) for this test was (0.63).

Figure 6.5: ROC Curve (area under the curve = 0.63):



6.4 Discussion:

Several studies have tried to establish a link between the possible outcomes of a newly created AVF and factors that can influence the process of its maturation, and therefore, predict those outcomes. The process of fistula maturation is complex with several biomechanical factors involved in order to create a low resistance conduit capable of dilatation to accommodate the increased blood flow required for successful HD sessions [97]. Prediction models based on patients' characteristics have been suggested [156, 157], however they tend to be complicated and are associated with both internal and external validity concerns considering the wide variations of independent measures used in those models. In addition, those models incorporate demographic data such as age, gender and history of medical comorbidities, most commonly diabetes. The problem with that is the lack of universal evidence to associate fistula maturation with those factors. For instance, while many studies reported that female gender was associated with fistula non-maturation [108, 110, 158]; others have disputed that association [28, 112, 114]. The same can be said regarding age [101, 110, 111], and the history of diabetes mellitus [28, 107-109] in predialysis patients.

The use of vein diameter – and to a lesser degree, arterial diameter – has been tested as a predictor for fistula maturation with reasonable success. There is an increasing agreement that a minimal arterial diameter > 2mm and venous >2.5mm should be considered as a cut-off point, as anything less than that is likely to be associated with non-maturation [1, 121, 159]. However, vein diameter will not predict fistula non-maturation in those with adequate size vessels based on preoperative venous mapping, but it remains a valuable predictive tool, in particular in choosing those who would require a basilic vein fistula (BVT) [160]. Unfortunately, the findings in this study could not be stratified by the diameter of the vein used in creating the anastomosis, as most of the patients included had their fistulas formed before the routine use of preoperative venous assessments in our unit.

The functional maturation rate was 53.7% in our study; however, by excluding 14 patients with unclear maturation outcomes, the maturation rate was 60.6%. Since a functional definition was used to determine fistula maturation, it is important to highlight that the main disadvantage of this method is the inability to differentiate between true non-maturation and mis-cannulation by dialysis staff. It is possible that the use of an imaging based definition – like the rule of (6s) adopted by the K-DOQI [1] – might have deemed more fistulae to be mature.

The author found that female gender was associated with poor maturation rate as 11/66 fistulae matured successfully in females and 20/43 failed to meet the definition of functional maturation used in the study, compared to 55/66 and 23/43 in men, respectively; a significant difference ($P = 0.001$). Also, history of previous renal transplant ($p = 0.004$) was found to be associated with successful maturation ($P = 0.004$). Whereas history of diabetes, hypertension, hyperlipidaemia, smoking, steroids treatment, peripheral vascular disease, atrial fibrillation, warfarin, and history of a previous AVF were all not significantly associated with fistula maturation. Age also did not show a significant association with fistula outcome ($P = 0.836$; Mann-Whitney U test).

Patients with mature AVFs had NLR of 4.850 (1.8 – 15.7) compared to 3.554 (1.7 – 15.0) in those with failed fistulas, a significant difference ($P = 0.024$). Our findings suggest an association between pro-inflammatory markers and improved AVF maturation. Due to the lack of similar studies, it was not possible to compare our results to other studies concerning the values of NLR associated with one outcome or the other. The association between NLR and the maturation of fistulas was non-linear in our sample, as patients with significantly higher values of NLR suffered invariably from poor maturation outcome, suggesting a complex relationship between NLR and AVF maturation.

The author of this thesis hypothesises that this finding can be explained by increased production of nitric oxide (NO) as part of a systemic response to inflammation. NO is a known vasodilator and is associated with decreased cellular proliferation [38], however, this remains speculative and more studies

examining the relationship between inflammation, NO and AVF maturation process are required. Additionally, it needs to be highlighted that our study was underpowered due to a relatively small sample size, and this could have affected our results.

The use of a simple, widely available test such as NLR has been shown to be beneficial in patients with other vascular abnormalities. Spark et al evaluated the use of the NLR to predict mortality in patients with chronic critical limb ischaemia. They found that an elevated NLR along with a high troponin level (>0.1) were the only independent predictors of mortality in those patients [161]. Also, in study of 83 patients who underwent infrapopliteal percutaneous interventions for critical limb ischemia, Chan et al reported that those with $\text{NLR} \geq 5.25$ had an increased risk of death (hazard ratio, 1.97; 95% confidence interval, 1.08-3.62; $P = 0.03$) [162]. Yilmaz et al reported that in chronic HD patients with established AVF access, patients who developed late stenosis were found to have higher level of NLR [116]. It is possible that the reversed NLR association seen in our study – successful AVF maturation more likely in patients with higher NLR - is due to differences in local response to pro-inflammatory markers between fistulae and bypass grafts in the lower limb.

A logistic regression test that included all the variables found to be significantly associated with fistula maturation showed that only female gender ($P = 0.008$) and a history of previous renal transplant ($P = 0.004$) significantly predicted fistula maturation. NLR was not found to significantly predict fistula outcome when added to the regression model above, with female gender being the only predictor of outcome in the new logistic model ($P = 0.006$).

The main limitation of this paper is the retrospective nature of the study and missing data from patients' medical records. In addition, most of our old patients did not have routine postoperative US to determine patency and differentiate between primary failure and mis-cannulation. A maturation definition based on ultrasound measurements rather than functional maturation would have been better, and certainly prospective studies should opt for such definitions in particular the one adopted by the NKF-KDOQI[1]. In addition, a type-2 error due to the small sample size cannot be excluded. It

should also be mentioned that haemodialysis could have altered the NLR as it has been shown that HD reduced both the number and phagocytic ability of neutrophils in dogs for a period of 24 hours following HD [163]. Therefore, the timing of taking the blood sample, in particular in patients on HD, could have confounded the results.

6.5 Conclusion:

NLR has not been found to independently predict AVF maturation in our study; however, the use of a functional maturation definition coupled with a relatively small size means more studies – particularly large prospective RCTs – are required to make a final recommendation on the utility of NLR in the prediction of AVF maturation.

VII Chapter Seven: One-Stage Vs Two-
Stage Brachio-Basilic Arteriovenous
Fistula for Dialysis Access: A Systematic
Review and a Meta-Analysis

7.1 Introduction:

The superiority of arteriovenous fistulas (AVFs) created as haemodialysis (HD) access in patients with end stage renal disease (ESRD) has been shown before. Stenosis and thrombosis is less likely to occur in a well-functioning and mature AVF when compared to arteriovenous grafts (AVGs) and central venous catheters (CVCs), resulting in prolonged patency rates for AVFs as has been described previously [97]. In addition, AVFs carry a lower risk for infection [95, 164]. However, around 20% - 50% of all fistulas fail to mature into a useful HD access [11-14].

The preferred location for placing an AVF for the first time is distally at the radius, thus making it possible to place a second fistula proximally if the first one failed to mature. The order of preference for creating an AVF [5, 159, 165]:

- I. Distal Radio-Cephalic
- II. Proximal Radio-Cephalic
- III. Brachio-Cephalic
- IV. Brachio-Basilic (superficialised/transposed Basilic vein)

This order is in agreement with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines [1]. However, fistulas created distally at the wrist are less likely to mature compared to proximal AVF, at the same time proximal AVF require less intervention and are likely to last longer [166]. The decision of placing an AVF can be helped by preoperative vascular mapping using ultrasound imaging, which is expected to improve chances of creating an AVF that will likely mature into a useful dialysis access [167, 168]. Placement of a primary forearm fistula is feasible in 40% to 50%, with an upper arm fistula possible in an additional 25% to 35% of patients [6]. An AVF prevalence of $\geq 65\%$ has been recommended in the KDOQI guidelines for patients undergoing HD [1], this prevalence is currently higher in Europe (67% - 91%) compared to the US (24% - 47%) [6, 100, 103, 169]; however, the prevalence of AVFs in the US varies significantly among different dialysis units [6, 170].

Dagher was the first to describe the use of the basilic vein to create an AVF in the upper arm between the end of the basilic vein and the side of the brachial artery for long term haemodialysis access [171]. Since then, the procedure has seen several changes and modifications. Superficialisation of a brachio basilic fistula in order to make it more susceptible to cannulation, can be achieved either by an elevation technique without mobilisation; this will bring the vein superficial to the surgically reconstructed deep fascia and subcutaneous tissue in the anatomic location of the basilic vein [172]. Alternatively, superficialisation can be achieved by mobilising the entire length of the basilic vein to position it anterolaterally through a subcutaneous flap; this procedure is known as transposition of the basilic vein [173].

Some of the debate surrounding brachio basilic arteriovenous fistulas (BB-AVF) has been focused on the decision to choose between performing the procedure in one-stage, or a two-stage technique. The one-stage procedure aims to create a fistula between the basilic vein and the brachial artery in the upper arm in one procedure. This would require a long incision to gain access and mobilise the basilic vein making sure the anastomosis is not placed under tension and no obvious stenosis is present proximally. The main advantage of this technique is the shorter waiting time required to cannulate the fistula. In addition, the one-stage will prevent the patient from having to undergo another procedure and is more cost effective as hospital resources will be used only once. One of the main disadvantages of this technique is the long incision that will require a longer time to heal and carries a higher risk for wound-related complications. In addition, the procedure takes longer and is more demanding [174-176]. Moreover, in a study by Anaya-Ayala et al assessing the anatomy of the basilic vein, they found that only 66% of patients are expected to have a “normal” basilic vein entering one of two paired brachial veins close to the axilla. Up to 34% will have an “abnormal” variant, which can lead to higher non-maturation rates [177].

The two-stage procedure allows the basilic vein to become arterialised and as such, more resistant to torque and will become easier to mobilise in the second procedure as it is transformed into a bigger and stronger structure. The aim of the two-stage approach is to reduce operative difficulty and complications, which can lead to improved patency rates [178].

This review was designed to systematically assess the differences between both procedures in terms of access maturation and survival, as well as postoperative complications and interventions required to maintain patency for haemodialysis.

7.2 Methods:

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89]. No published protocol exists for this review.

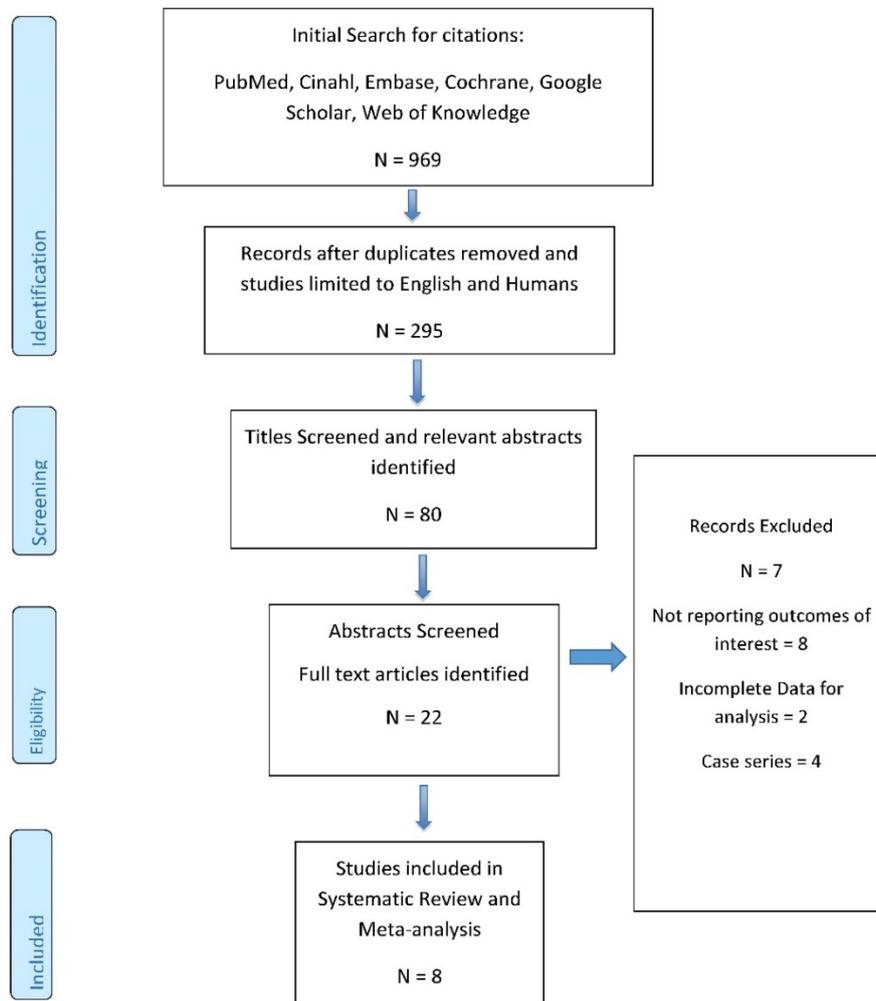
7.3 Eligibility Criteria:

A search was conducted looking for randomised controlled trials (RCTs) and observational studies that compared the one-stage technique with the two-stage technique used to create brachiobasilic arteriovenous fistulas (BB-AVFs) for haemodialysis access. Case series and review articles were excluded from this review. Only studies published in English language were included in this systematic review. The author accepts that pooling results from RCTs and observational studies together to perform a meta-analysis can result in significant heterogeneity because of the distinctively different methodological approaches intrinsic to each study type. One recognised method of dealing with this limitation when it results in significant heterogeneity is to perform a sensitivity test by pooling data from RCTs and observational studies in separate tests and compare the difference – if any - in the statistical significance.

7.4 Search strategy:

A search of the literature for relevant studies was conducted in August 2014 using the following terms: ([“Basilic Vein” OR “Basilic”] AND [“Fistula” OR “Arteriovenous” OR “Access”] AND “dialysis”). The author searched the online databases of Medline, CINAHL, EMBASE, the Cochrane library and Google Scholar. The search was not restricted by publication date or status, however, only studies published in English language and those conducted on humans were included. In addition, the bibliographies of included trials were screened for additional studies. A summary of the study selection process can be found in the PRISMA flow diagram below [Figure 7.1]. Studies were not restricted based on the duration of follow-up.

Figure 7.1: PRISMA flow diagram



Eligibility for inclusion was determined by two researchers separately (KB, DH) by going through the abstracts of the relevant citations. Differences were settled by examining the full article by both authors, and then any remaining uncertainties regarding the eligibility of studies were settled following a discussion with a third author (SRW).

The main outcome measures for this review were successful maturation and development of postoperative complications, namely wound haematoma, wound infection and steal syndrome. Secondary outcomes were primary and secondary patency rates. Definitions for “maturation”, “primary patency” and “secondary patency” were those specified in the individual studies.

7.5 Data Collection:

KB and DH independently extracted the data from the included studies on a Microsoft Excel spreadsheet. Any differences in recording the outcomes of interest were discussed between two authors (KB, DH), and if remained unsettled, a third author was consulted to resolve the issue (SRW). The following characteristics regarding participants were recorded: age, sex, presence of co-morbidities, primary patency rate, secondary patency rate, maturation rate and postoperative complications (Haematoma, wound infection and steal syndrome). Usability of fistula for Haemodialysis, time to first use for HD and interventions needed to maintain patency were recorded when possible. Additionally, the author extracted the data related to compliance with the Society for Vascular Surgery (SVS) recommended standards for reports dealing with arteriovenous haemodialysis accesses [179]. To this end, the author assessed whether studies provided SVS standard-based grading of factors that affect outcomes and whether studies provided SVS standard-based grading of severity of arteriovenous access complications. The inclusion and exclusion criteria of the individual studies were recorded [Table 7.1].

Table 7.1: characteristics of individual studies

| Author | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics 1 stage | Number 2 stage | Characteristics 2 stage |
|---------------------|----------------|--|--|----------------|--|--|---|---|--|--|---|--|
| Vrakas [173] | 2013 | Retrospective cohort study at King's College Hospital London. Mean follow up of BB-AVF patients was 559 days (SD33). Median interval between first and second operations in the two-stage group was 90 days. Allocation to groups was based upon preferences of the two surgeons. Patients with small veins mostly would have had 2-stage procedure. | Consecutive patients who underwent BB-AVF between January 1st 2009 and December 31st 2011. | None specified | Basilic vein dissected and mobilised with preservation of the medial cutaneous nerve of the forearm. End to side arteriovenous anastomosis in the antecubital fossa. | First, BB-AVF created at the cubital fossa, then 4 - 6 weeks later a second procedure carried (following US assessment to determine if a second stage is necessary) for mobilisation and superficialisation of the fistula | Primary, primary assisted and secondary functional patency rates. Complications such as thrombosis, haematoma, steal syndrome, infection, venous hypertension, stenosis, mortality. | Two stage procedure patients had better functional primary, primary assisted and secondary patency rates at 1 and 2 years. Complication rates were similar. | Data were provided using number of BB-AVFs as the denominator rather than the number of patients. 65 one-stage procedures were performed. Number of patients was unclear. | Mean age was 58 years (SD15). 32/65 were female. 25/65 had DM. 53/65 had hypertension. Mean BMI was 29 (SD6). 29/65 were black. Mean vein size was 4.0mm (1.1SD). The only significant difference was in vein size (p=0.041). Factors that affect outcome were not described in accordance with the SVS guidelines. | 84 two-stage procedures were performed. Number of patients was unclear. | Mean age was 58 years (SD15). 44/84 were female. 33/84 had DM. 67/84 had hypertension. Mean BMI was 27 (SD7). 39/84 were black. Mean vein size was 4.0mm (1.1SD). The only significant difference was in vein size (p=0.041). Factors that affect outcome were not described in accordance with the SVS guidelines. |
| Ozcan [180] | 2013 | Retrospective cohort study at the authors' institutions. Allocation to groups was based upon surgeon preference and often patients with basilic vein diameter <3mm had the 2-stage procedure. The second stage of the two-stage procedure took place at 30 days. Mean follow up was for 36 months. | Patients who underwent BVT in the authors' institution(s) between January 2007 and January 2012. | None specified | Basilic vein dissected and mobilised with preservation of the medial cutaneous nerve of the forearm. End to side arteriovenous anastomosis in the antecubital fossa. HD was allowed after one month. | First, BB-AVF created at the cubital fossa, then 4 weeks later a second procedure carried for mobilisation and superficialisation of the fistula | Primary and secondary patency rates, postoperative complications such as thrombosis, haemorrhage, haematoma, infection, venous aneurysm development, mortality. Rate of fistula maturation and time to fistula maturation. Auxiliary interventions for patency. | Two stage procedure patients had a higher rate of maturation but 1 stage BVTs matured faster. Thrombosis, bleeding, haematoma incidence were lower in the two stage group. The two-stage group required fewer interventions for patency within the first 10 days but after that, there was no difference. | Data were provided using number of BVTs as the denominator rather than the number of patients. 47 one stage procedures on 47 patients were included and Total number of patients was 96 therefore some patients were included twice. | Mean age was 43.1 years (SD16) for men and 42.5 years (SD13) for females. 28/47 were male. Mean duration of ESKD was 63.1 months (SD17) for men and 64.5 (SD18) for women. 15/47 had hypertension. 9/47 had DM. 4/47 had heart disease. 2/47 had PVD. 9/47 were smokers. Mean basilic vein diameter was 3.46mm (SD0.2). The only | 59 two-stage procedures on 59 patients were included. | Mean age was 44.9 years (SD14) for men and 44.1 (SD13) for females. 36/59 were male. Mean duration of ESKD was 61.7 months (SD20) for men and 63.3 (SD21) for women. 14/59 had hypertension. 11/59 had DM. 3/59 had heart disease. 3/59 had PVD. 11/59 were smokers. Mean basilic vein diameter was 2.79mm (SD0.1). The only |

| | | | | | | | | Primary and secondary patency rates were better in the two-stage group but no statistical analysis was performed for this outcome. | | significant difference between groups was in vein size (p<0.001). Factors that affect outcome were not described in accordance with the SVS guidelines. | | significant difference between groups was in vein size (p<0.001). Factors that affect outcome were not described in accordance with the SVS guidelines. |
|---------------------|------|--|--|----------------|---|--|--|---|---|--|---|---|
| Kakkos [181] | 2010 | Retrospective cohort study at Henry Ford Hospital Detroit USA on 173 consecutive patients who were scheduled for BVT. Allocation to groups was based on surgeon's preference. The length of follow up was not described explicitly although the report suggests that follow ended when fistulas were used in dialysis. | Patients who underwent BVT at the authors' institution during a 5-year period between xx and xx. | None specified | Basilic vein dissected and mobilised with preservation of the medial cutaneous nerve of the forearm. Arteriovenous anastomosis in the antecubital fossa via the brachial or proximal radial or ulnar artery. HD was allowed only after least 6 weeks. | First, BB-AVF created at the cubital fossa, then 4 - 6 weeks later a second procedure carried for mobilisation and superficialisation of the fistula | Maturation rates and complications such as haematomas, dehiscence, infection, steal syndrome, venous hypertension. 30-day mortality. | One-stage procedures had significantly higher complication rates. Haematomas and venous hypertension occurred significantly more often in one-stage procedures. Maturation rates were similar although time to first use was longer in the two-stage group. | Data were provided using number of BVTs as the denominator rather than the number of patients. 76 one-stage procedures were performed. One patient in the study had two distinct BVT procedures and was thus included twice but it was not clear which procedures this patient underwent. | Mean age was 59 years (SD15). 46/76 were male. 61/76 were black. 45/76 had DM. 51/76 had previous dialysis access. 6/76 were pre-haemodialysis patients. 16/76 had general anaesthesia and 60/76 were performed under local anaesthesia. The only significant baseline differences were that more patients in one stage group had a history of previous access and they were more likely to have general anaesthesia. Notably there were no data on baseline vein diameters. Factors that affect outcome were not described in accordance with the SVS guidelines. | 98 patients underwent two stage procedures. 98 had the first stage and 72 subsequently underwent the second stage. One patient in the study had two distinct BVT procedures and was thus included twice but it was not clear which procedures this patient underwent. | Mean age was 62 years (SD16). 41/98 were male. 73/98 were black. 57/98 had DM. 30/98 had previous dialysis access. 14/98 were pre-haemodialysis patients. 4/98 had general anaesthesia and 94/98 were performed under local anaesthesia. Notably there were no data on baseline vein diameters. Factors that affect outcome were not described in accordance with the SVS guidelines. |

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|------------------------|------|--|---|----------------|--|---|--|---|--|---|---|---|
| El Mallah [182] | 1998 | Prospective randomised controlled trial at El Menoufia University Hospital Egypt. Allocation to groups was performed randomly and the groups had similar age and gender characteristics. No details on the randomisation process were provided. Follow up was for 6-24 months. | It involved 40 patients who were admitted for secondary vascular access procedures between June 1993 and December 1995. | None specified | BB-AVFs were made using the traditional one stage technique. | First, BB-AVF created at the cubital fossa by anastomosing a mobilised segment of basilica vein to the brachial artery. Then 2 - 4 weeks later a second procedure carried for mobilisation and superficialisation of the fistula. | Patency at 4 weeks and patency at end of follow up period. Aneurysm formation and infection. | Early patency was achieved in 12/20 in the one stage group versus 18/20 in the two-stage group. Patency at end of follow up was 10/20 versus 16/20. The authors did not use an intention to treat analysis. When an intention to treat analysis was used, the difference was not significant. There was no significant difference in infection or aneurysm rates. | 20 patients who underwent 20 one-stage procedures were included. | Mean age was 32.5 years (SD5.8). 12/20 were male. Mean period of follow up was 16 months (SD3.5). Factors that affect outcome were not described in accordance with the SVS guidelines. | 20 patients who underwent 20 two-stage procedures were included. One fistula occluded in the interval between stages and thus was excluded. | Mean age was 35.8 years (SD7.3). 11/20 were male. Mean period of follow up was 14.8 (SD5). Factors that affect outcome were not described in accordance with the SVS guidelines. |
| Syed [183] | 2012 | Retrospective cohort study on 106 patients who underwent BVT at the Methodist DeBakey Heart & Vascular Centre in Texas. Choice of one stage BVT or two stage BVT was based upon surgeon preference. Follow up was for 3 years. | It involved 106 patients who underwent BVT between June 2006 and June 2010. It is unclear whether the cases were consecutive. Data came from a computerised database. | None specified | Brachial artery to brachial vein anastomosis along with the superficial transposition, all in the same procedure | The anastomosis was created in the first stage and, subsequently, the vein was transposed in the second stage | Primary, primary assisted and secondary patency up to three years, reinterventions, mortality, major complications, fistula maturation and complications such as infections, steal syndrome, | Primary patency and assisted primary patency rates were better in the one stage group. Other outcomes were not significantly different. | 29 patients underwent one stage BVT | Mean age was 54 years (SD21). 14/29 were male. 16/29 had current catheter usage at the time of the surgery. 16/29 had prior ipsilateral access. Average BMI was 28.1, 16/29 had DM, 28/29 had hypertension, 5/29 had coronary artery disease, 2/29 had congestive heart failure. 13/29 had GA and the others had regional arm block. The only significant differences in baseline characteristics between groups was in regards to history of catheter use and prior ipsilateral access | 77 patients underwent the two-stage procedure. | Mean age was 54 years (SD14). 29/77 were male. 67/77 had current catheter usage at the time of surgery. 16/77 had prior ipsilateral access. 39/77 had prior failure of an arteriovenous fistula. Average BMI was 28.1, 42/77 had DM, 71/77 had hypertension, 21/77 had congestive heart failure. 13/29 had GA and the others had regional arm block. The only significant differences in baseline characteristics between groups was in regards to history of catheter use and prior ipsilateral access |

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|----------------------|------|---|--|---|---|---|---|---|---|---|--|---|
| | | | | | | | | | | procedure. Factors that affect outcome were not described in accordance with the SVS guidelines. | | |
| Agarwal [184] | 2014 | Retrospective cohort study involving 144 consecutive patients who underwent BVT at a US hospital. Patients with basilic vein diameter of <4mm were chosen for the two stage procedure. Mean follow up duration was unclear. Some patients were followed for greater than 4 years. | It involved consecutive patients who underwent BVT creation between January 2005 and December 2009 and who received all access-related care (surgical and radiological) up to a 4-year follow up point in December 2013. | Patients were excluded if interventions or follow up had taken place at an outside institution. | Not specified | Not specified | Maturation rates, mean time to initiation of fistula use, intensity of percutaneous interventions per patient year on dialysis, primary patency, primary assisted patency and secondary patency annually. | Modest reduction in primary and secondary patency rates in the two stage group compared to the one stage group | 61 patients underwent 61 one stage BVTs | Mean age was 59.1 years. No other were provided on baseline characteristics. Factors that affect outcome were not described in accordance with the SVS guidelines. | 83 patients underwent 83 two stage BVTs. | Mean age was 61.5 years. No other data were provided on baseline characteristics. Factors that affect outcome were not described in accordance with the SVS guidelines. |
| Hossny [172] | 2003 | Cohort study involving 70 brachio basilic fistulas in 70 patients at Menofia University Egypt. It is unclear whether it was prospective or retrospective although it seems to be prospective. The study compared basilic vein transposition versus a one-stage elevation procedure versus a two-stage elevation | It involved 70 brachio basilic fistulas that were performed in 70 patients over an unspecified 2-year period at the author's institution. | None specified | 30 fistulas created using a traditional one stage BVT to create a BB-AVF 20 fistulas created in a one stage elevation technique, the basilic vein was brought superficial to the deep fascia and subcutaneous tissue rather than through a subcutaneous tunnel | 20 fistulas created in a two stage elevation technique, the basilic vein was brought superficial to the deep fascia and subcutaneous tissue rather than through a subcutaneous tunnel | Ability to access fistula for dialysis, cumulative secondary patency, complications (oedema, haematoma, thrombosis, venous hypertension, lymph leakage), perioperative mortality, | The one stage BVT had a lower complication rate and was favoured by the dialysis staff compared to basilic vein superficialisation techniques | 20 patients underwent 20 one stage BVTs, while 20 patients underwent one stage basilic vein elevation procedure | For the one stage BVT: Mean Age = 45.7 (16-98), 12/40 were created in male patients, 17/20 had diabetes and 10/20 had hypertension For the one stage basilic vein elevation: Mean age = 49.3 (26-71), 12 had diabetes and 7 had hypertension. Factors that affect outcome were not | 20 patients underwent two stage basilic vein procedure | Mean Age = 54 (32-71), 8 were created in male patients. Diabetics = 4/20 and 5/20 had Hypertension. Factors that affect outcome were not described in accordance with the SVS guidelines. |

| | | | | | | | | | | | | |
|--------------------|------|---|---|--|---|---|---|--|--|---|---|--|
| | | procedure. It is unclear on what grounds patients were selected for different procedures. Mean follow up time was 25.8 months. | | | | | | | | described in accordance with the SVS guidelines. | | |
| Effat [185] | 2013 | Cohort study involving 104 patients who underwent 106 Brachio-basilic fistulas at Zagazig University Hospital from October 2010 to December 2011. It is unclear whether it was prospective or retrospective. Comparison between one stage BVT, Two stage BVT, two-stage superficialisation. Allocation to groups was based upon the preferences of the surgeons or patients preferences. The period of follow up was not specified. | Scheduled for brachio-basilic fistula with a basilic vein >2.5mm diameter and a brachial artery >3mm. | Patients were excluded if vein diameter <2.5mm, failure of BB-AVF to mature in staged groups, steel or massive venous hypertension after creation of the brachio-basilic shunt and failed to be corrected, patients who refused the second stage or who were lost to follow up between stages. | All fistulas created using a traditional one stage BVT to create a BB-AVF | 38 fistulas were created using a two stage BVT technique, stage one involved forming a BB-AVF, the second stage involved mobilisation and superficialisation of the fistula. In 40 fistulas, they carried a two stage superficialisation procedures without transposing the basilic vein | functional patency (ability to access the fistula for haemodialysis), mean time to use the fistula, complications such as haematomas requiring exploration, wound dehiscence or infection, thrombosis, steal syndrome, venous hypertension requiring intervention, failure to mature. | Lower patency rates for the one stage technique and increased chance of developing postoperative complications compared to the two stage technique | 28 one stage BVTs performed. Number of patients unclear. | Mean age = 43.6 ± 11.9, 13/28 were male, 13/28 had diabetes and 16/28 had hypertension. Factors that affect outcome were not described in accordance with the SVS guidelines. | 38 two stage BVTs and 40 two stage superficialisation. Number of patients unclear | For the two stage BVT: Mean age = 48.4 ± 10.2, 20/38 were created in male patients. 19/38 had diabetes and 22/38 had hypertension For the two-stage elevation: Mean age 47.5 ± 8.4, 16/40 were created in male patients, 23/40 had diabetes and 26/40 had hypertension. Factors that affect outcome were not described in accordance with the SVS guidelines. |

7.5.1 Quality assessment for risk of bias:

The Downs and Black Tool was used for quality assessment [90]. This tool consists of 32 questions assessing the quality of reporting, external validity and internal validity generating scores ranging from zero to 32, which includes a score of 0-5 for sample size justification. The author of the thesis modified the tool by awarding one point for studies that reported on sample size calculations, and zero for those that did not report their methods of sample size calculation. Hence, the modified score ranged from zero to 27, with higher scores reflecting higher quality. Details of the quality assessment can be found in [Table 7.2].

Studies included in this systematic review were of mixed quality, with a median of 19.5 and a range of (15 – 20). Three of the studies had score of 20, which make them of reasonable methodological quality [172, 173, 183]. The paper by Agarwal et al [184] did not clearly describe the characteristics of the patients included in their study. Without knowing the distribution of baseline characteristics in both groups, it would be difficult to exclude bias from reported confounders in the literature such as old age, and female gender. Effat et al failed to describe clearly their main findings, which can potentially lead to wrong associations by pooling results from this study into a meta-analysis [185]. Treatment assignment was not concealed in any of the studies.

Only El-Mallah et al [182] managed to report the characteristics of those lost to follow-up, which raises significant concerns about attrition bias. In all studies, no attempts were made at blinding of either the subjects or the assessors; this could have resulted in bias in performing the procedures if the operating surgeon favoured one technique over the other. The external validity of the included studies scored better than their internal validity, as they all recruited patients from same population, during the same period and used appropriate methods to assess outcomes. Patients lost to follow-up were not accounted for in the study by El-Mallah et al [182], additionally, they did not adjust for confounders. None of the studies reported an appropriate method for sample size calculation.

Table 7.2: Results of the study quality assessment

| Number | Question | Vrakas 2013 | Ozcan 2013 | Kakkos 2010 | El- Mallah 1998 | Syed 2012 | Hossny 2003 | Agarwal 2014 | Effat 2013 |
|--------|---|----------------|---------------|----------------|-----------------------|--------------|----------------|-----------------|---------------|
| 1 | Hypothesis / objective clear? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| 2 | Main outcomes clearly described in introduction or methods? | Yes | Yes | No | No | Yes | Yes | Yes | No |
| 3 | Are patients' characteristics clearly described? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| 4 | Are interventions clearly described? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | Are confounders equally distributed? | Yes | Yes | Yes | UTD | Yes | Yes | UTD | Yes |
| 6 | Are the main findings clearly described? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |

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|-----------|--|------------|------------|------------|------------|------------|------------|------------|------------|
| 8 | Are important adverse events reported? | Yes |
| 9 | Are the characteristics of those lost to follow up described? | No | No | No | Yes | No | No | No | No |
| 10 | Are specific p value reported? | Yes | No | Yes | No | Yes | Yes | Yes | Yes |
| 11 | Were potentially eligible subjects representative of the population? | Yes |
| 12 | Were participating subjects representative of the population? | Yes |
| 13 | Were staff, places and facilities representative of the treatment most patients receive? | Yes |

| | | | | | | | | | |
|-----------|---|-----|-----|-----|-----|-----|-----|-----|-----|
| 14 | Was an attempt made to blind subjects to the intervention they received? | No |
| 15 | Was an attempt made to blind main outcome assessors? | No |
| 16 | If any results reflect data dredging, is this clear? | No |
| 17 | Do analyses adjust for length of follow up differences? | Yes | Yes | No | No | Yes | Yes | Yes | Yes |
| 18 | Were appropriate statistical analyses used? | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes |
| 19 | Was compliance with the intervention reliable? | Yes |

| | | | | | | | | | |
|-----------|--|------------|------------|------------|------------|------------|------------|------------|------------|
| 20 | Were the main outcome measures valid and reliable? | Yes |
| 21 | Were study groups recruited from the same population? | Yes |
| 22 | Were subjects recruited over similar time periods? | Yes |
| 23 | Were study subjects randomised to intervention groups? | No | No | No | Yes | No | No | No | No |
| 24 | Was treatment assignment concealed? | No |
| 25 | Was there adequate adjustment for confounders in the analysis? | Yes | Yes | Yes | No | Yes | Yes | UTD | Yes |

| | | | | | | | | | |
|--------------|---|------------|------------|------------|-----------|------------|------------|------------|------------|
| 26 | Were losses of patients to follow-up taken into account? | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes |
| 27 | Was an appropriate sample size calculation carried out? | No | No | No | No | No | No | No | No |
| | | | | | | | | | |
| Total | Number of "Yes" results | 20 | 19 | 18 | 15 | 20 | 20 | 17 | 16 |

7.5.2 Data analysis:

Statistical analysis was performed using Review Manager version 5.3 [91]. The random effects model of DerSimonian and Laird was used [92] to calculate pooled risk ratios for categorical outcomes measures. The Cochran's Q test was used to determine statistical heterogeneity among studies. The confidence interval was set to 95%, and P-values < 5% were used to determine statistical significance. The author compared between the fixed and random effects modelling to produce a sensitivity analysis aimed at detection of the influence of publication bias of small-study effects[93]. In addition, the author of this thesis performed an additional sensitivity analysis limited to published articles only as part of the meta-analysis.

7.6 Results:

7.6.1 Study selection:

The results of the study selection process are summarised in the PRISMA flow diagram [Figure 7.1]. The initial search yielded a total of 969 citations. Following the removal of duplicates and limiting the search criteria to studies conducted on humans and in English language, 295 citations were left. Then, the titles of those papers were screened, and 80 potentially relevant citations were found. The abstracts of those titles were examined for relevant outcomes, and 22 papers were evaluated for eligibility criteria, of those, eight citations met our criteria and were included in the systematic review [172, 173, 180-185]. Of those eight studies, one was a randomised controlled study (RCT) [182]. Five were retrospective cohort studies [173, 180, 181, 183, 184] and two studies were cohort studies but it was unclear whether they were retrospective or prospective [172, 185]. This last citation was a conference presentation which the author included in the review; however, a number of sensitivity tests excluding the data from this citation and including data extracted from published papers only were performed [185].

Six of the included studies compared outcomes between 1-stage versus 2-stage BB-AVF formation techniques [173, 180-184]. Hossny et al compared three different groups, first group of patients had traditional 1-stage basilic vein transposition (BVT), while the second group had 1-stage basilic vein elevation, and the third group underwent a 2-stage BB-AVF. For the sake of this meta-analysis, the first 2 groups were pooled from this particular study together [172]. Similarly, Effat had three groups of patients in his conference paper, the first group had standard 1-stage BVT, whereas the second group had a 2-stage BVT and the last group consisted of patients who had 2-stage superficialisation of the basilic vein to create BB-AVFs. Data extracted from the 1-stage groups in this last study were combined together for the purpose of the meta-analysis [185].

7.6.2 Participants:

The studies included a total of 849 patients who had 859 fistulas, of those, 366 fistulas were formed using a 1-stage technique, while the remaining 493 fistulas were created in a 2-stage technique. Overall, 432 were male patients versus 417 female patients. Kakkos et al [181] did not specify the male to female ratio in the 72 patients who underwent a 2-stage procedure in their study, however, in the remaining studies, 181 men had 1-stage fistula procedure compared to 164 in the 2-stage group. Similarly, 226 in the 1-stage group were female patients compared to 150 in the 2-stage group. Of the six studies [172, 173, 180, 181, 183, 185] that reported past history of diabetes, 143/295 diabetic patients were in the 1-stage group while 202/390 were in the 2-stage group. History of hypertension was reported in five studies [172, 173, 180, 183, 185], with 123/219 patients in the 1-stage group and 202/390 in the 2-stage group having the diagnosis. All the studies were conducted on adult patients with end stage renal disease (ESRD). El-Mallah [182] had the youngest patients (23.5 ± 5.8 years for the 1-stage group, and 35.8 ± 7.3 years for the 2-stage group), while the remaining studies included patients in their fifties and sixties [Table 7.1]. Inclusion and exclusion criteria of studies among other characteristics are outlined in [Table 7.1]. Main outcomes reported in studies are summarised in [Table 7.3].

Table 7.3: Main outcomes from included studies

| Study | 1-stage procedure | | | | | 2-stage procedure | | | | |
|---------------------|---|--|---|---|--|---|--|--|---|--|
| | Number of 1-stage fistulas | Patency | Haematoma | Wound Infection | Steal | Number of 2-stage fistulas | Patency | Haematoma | Wound infection | Steal |
| Vrakas [173] | 65 one-stage procedures were performed. Number of patients was unclear. | Primary functional patency at 1 and 2 years was 71% and 53%. Assisted Primary functional patency at 1 and 2 years was 77% and 57%. Secondary functional patency at 1 and 2 years was 79% and 57%. The definitions for patency outcomes were based upon the SVS guidelines. | 3 / 65 No SVS grading was provided | 3 / 65 | 2 / 65 No SVS grading was provided | 84 two-stage procedures were performed. Number of patients was unclear. | Primary functional patency at 1 and 2 years 87% and 75%. Assisted Primary functional patency at 1 and 2 years was 95% and 77%. Secondary functional patency at 1 and 2 years was 95% and 77% | 3 / 84 No SVS grading was provided. | 2 / 84 | 3 / 84 |
| Ozcan [180] | 47 one stage procedures on 47 patients were included and Total number of patients was 96 therefore some patients were included twice. | Primary patency at 1, 2 and 3 years was 33/47 (70%), 30/47 (64%), and 27/47 (54%) Secondary patency at 1, 2 and 3 years was 36/47 (76%), 43/47 (72%), and 31/47 (66%). The definitions for patency outcomes were unclear. | 8 / 47 No SVS grading was provided | 6 / 47 No SVS grading was provided | 4 / 47 No SVS grading was provided but all required surgical management | 59 two-stage procedures on 59 patients were included. | Primary patency at 1, 2 and 3 years was 41/59 (84%), 36/59 (73%), and 34/59 (69%). Secondary patency at 1, 2 and 3 years was 44/59 (90%), 40/59 (82%), and 38/59 (77%) | 3 / 59 No SVS grading was provided | 5 / 59 No SVS grading was provided | 3 / 59 No SVS grading was provided but all require surgical treatment |
| Kakkos [181] | 76 one-stage procedures were performed. One patient | Not reported | 10 / 76 No SVS grading | 5 / 76 No SVS grading | 3 / 76 No SVS grading was | 98 patients underwent two | Not reported | 3 / 72 No SVS grading was provided | 0 / 72 No SVS grading was | 2 / 72 No SVS grading |

| | | | | | | | | | | |
|------------------------|--|--|--|--|--|---|--|--|--|--|
| | in the study had two distinct BVT procedures and was thus included twice but it was not clear which procedures this patient underwent. | | ng was provided. Across the whole study, most were grade 1 or 2 and 3 were grade 3 | was provided | provided but all were managed conservatively | stage procedures. 98 had the first stage and 72 subsequently underwent the second stage. One patient in the study had two distinct BVT procedures and was thus included twice but it was not clear which procedures this patient underwent. | | d. Across the whole study, most were grade 1 or 2 and 3 were grade 3 | provided | was provided but all were managed conservatively |
| El Mallah [182] | 20 patients who underwent 20 one-stage procedures were included. | Early patency (4 weeks) = 12/20 (60%), Overall patency (at the end of follow-up) = 10/20 (50%), The definitions for patency outcomes were unclear. | - | 3 / 20 No SVS grading was provided but they were described as mild infections | 0 / 20 | 20 patients who underwent 20 two-stage procedures were included. One fistula occluded in the interval between stages and thus was excluded. | Early patency (4 weeks) 2-stage = 18/20 (90%). Overall patency at the end of the study = 16/20 (80%) | - | 1 / 20 No SVS grading was provided but they were described as mild infections | 0 / 20 |

| | | | | | | | | | | |
|----------------------|---|---|--|--------|--------|--|---|--|--|--|
| Syed [183] | 29 patients underwent 20 one stage BVT | Primary patency at 1, 2 and 3 years was 82%, 81%, and 51%. Assisted primary patency at 1, 2 and 3 years was 91%, 77%, and 48%. Secondary patency at 1, 2 and 3 years was 91%, 80%, and 58%. The definitions are similar to those in the SVS guidelines. | 2 / 29 No SVS grading was provided. | 0 / 29 | 0 / 29 | 77 patients underwent the two-stage procedure. | Primary patency at 1, 2 and 3 years was 67%, 27%, and 18%. Assisted primary patency at 1, 2 and 3 years was 77%, 41%, and 24%. Secondary patency at 1, 2 and 3 years was 81%, 61%, and 45% | 6 / 77 No SVS grading was provided. | 3 / 77 No SVS grading was provided. | 3 / 77 No SVS grading was provided. |
| Agarwal [184] | 61 patients underwent 61 one stage BVTs | Primary unassisted patency at 1 and 2 years was 26% and 7%. Primary assisted patency at 1, 2, 3 and 4 years was 67%, 38%, 21% and 8%. Secondary patency at 1, 2, 3 and 4 years was 86%, 75%, 69% and 57%. The definitions are similar to those in the SVS guidelines. | - | - | - | 83 patients underwent 83 two stage BVTs. | Primary unassisted patency at 1 and 2 years was 13% and 0%. Primary assisted patency at 1, 2, 3 and 4 years was 66%, 39%, 7% and 0%. Secondary patency at 1, 2, 3 and 4 years was 76%, 71%, 49% and 25% | - | - | - |
| Hossny [172] | 20 patients underwent 20 one stage BVTs, while 20 patients underwent one stage basilic vein elevation procedure | The study reported 87% cumulative secondary patency rate at 1 year across all groups, with 86.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the 2-stage elevation group. 1 death was excluded from final analysis. Cumulative secondary patency rate at 2 years for all groups was 75%, with 82.8% for the BVT group, 70% for the 1-stage elevation group and 68.4% for the 2-stage elevation group. 2 deaths | 6 / 50 No SVS grading was provided. | - | 0 / 50 | 20 patients underwent two stage basilic vein procedure | The study reported 87% cumulative secondary patency rate at 1 year across all groups, with 86.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the 2-stage elevation group. 1 death was excluded from final analysis. Cumulative secondary patency rate at 2 years for all groups was 75%, with 82.8% for the BVT group, 70% for the 1-stage elevation group and 68.4% for the 2-stage | 5 / 20 No SVS grading was provided. | - | 0 / 20 |

1-stage vs 2-stage BVT

| | | | | | | | | | | |
|-------------------------------|--|------------------------------------|--|---|---|---|--|---|--|---|
| | | were excluded from final analysis. | | | | | elevation group. 2 deaths were excluded from final analysis. | | | |
| Effat conference [185] | 28 one stage BVTs performed. Number of patients unclear. | Not reported | 2/28 No SVS grading was provided. | 2/28 No SVS grading was provided | 2/28 No SVS grading was provided | 38 two stage BVTs and 40 two stage superficialisation. Number of patients unclear | Not reported | 7/78 No SVS grading was provided | 12/78 No SVS grading was provided | 0/78 No SVS grading was provided |

7.6.3 Successful Maturation rate:

Successful maturation rates were reported in six of the included studies [172, 173, 181-184]; the criteria used for reporting maturation are found in [Table 7.4]. Those studies had a combined total of 683 fistulas, 301 of those were created in the one stage group, whereas 382 were created in the two-stage group. The difference between the two groups was not significant in pooled analysis (Pooled risk ratio = 0.95 [0.82, 1.11], 95% CI, P = 0.53) [Figure 7.2].

Heterogeneity was detected statistically (Cochran's Q = 14.48; degree of freedom (DF) = 5; P = 0.001; I² = 65%). This significant degree of heterogeneity might be explained by the fact that the author pooled data from the RCT by El-Mallah with data from observational studies.

The significance of the results was not altered when using the fixed effects analysis model as a sensitivity test to detect publication bias (Pooled risk ratio = 0.92 [0.84, 1.01], 95% CI, P = 0.07) [Figure 7.3].

Table 7.4: Maturation outcomes

| Study | One stage | Two stage | Source of data | comments |
|-----------------|-----------|-----------|---|--|
| Vrakas [173] | 36 / 65 | 49 / 84 | Primary failure rates were reported. This was defined as an AVF that was never used for dialysis. Primary failure may have resulted from inadequate maturation, early thrombosis, failure of first cannulation, and other complications that made AVF unusable. Successful maturation rates were derived from these data. | The number of AVFs that required intervention to assist maturation is unclear. |
| Kakkos [181] | 67 / 76 | 69 / 98 | Maturation rates were reported. Maturation was based upon clinical judgement (development of basilic vein dilatation and thrill for a sufficient length). | Includes fistulas that required intervention to assist maturation for dialysis. 7 one-stage fistulas required such intervention and 3 two-stage fistulas required such intervention. |
| El-Mallah [182] | 12 / 20 | 18 / 20 | Patency at 4 weeks was reported and the author used this figure to determine successful maturation. The authors did not provide a definition for patency. | The number of AVFs that required intervention to assist maturation is unclear. |
| Syed [183] | 6 / 29 | 14 / 77 | Maturation rates were reported. Fistula maturation was defined | The number of AVFs that required intervention to |

| | | | | |
|---------------|---------|---------|---|--|
| | | | as dilation of the vein to allow cannulation and support dialysis at a minimum flow rate of 350ml/min for at least 3 sessions. | assist maturation is unclear. |
| Agarwal [184] | 55 / 61 | 62 / 83 | Maturation rates were reported. Maturation was defined as the use of the fistula for haemodialysis for any amount of time or, if it was not used, documentation in surgical or renal records that the fistula was mature and ready for use based upon successful cannulation and/or physical examination by vascular surgery. | Includes an unspecified number of fistulae that needed percutaneous intervention to assist maturation. |
| Hossny [172] | 47 / 50 | 19 / 20 | Numbers of fistulas that were successfully used for dialysis at 6 weeks were reported. | No patients needed reintervention to assist achievement of successful dialysis at 6 weeks. |

Figure 7.2: A Forest's Plot for successful maturation rate (random effects):

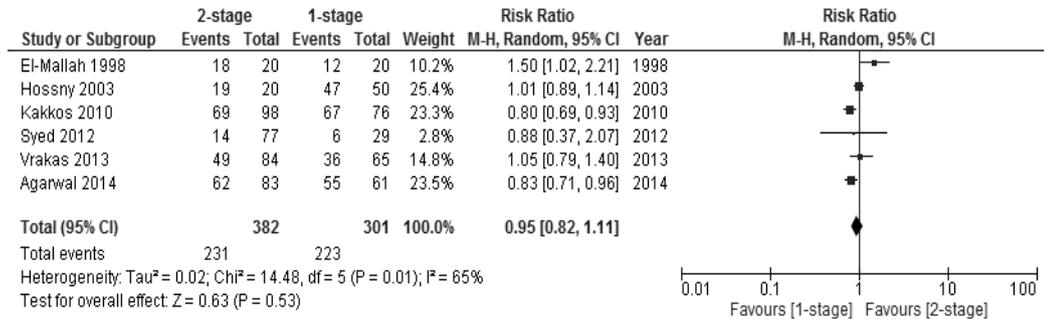
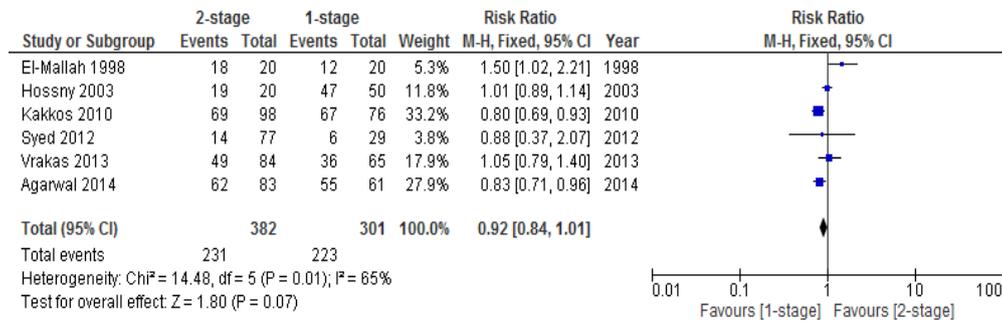


Figure 7.3: A Forest's Plot for successful maturation rate (A sensitivity test using fixed effects):



7.6.4 Postoperative complications:

7.6.4.1 *Haematoma:*

The incidence of postoperative wound haematoma was reported in six of the included studies [172, 173, 180, 181, 183, 185] with a total of 711 fistulas, of those, 295 fistulas were created in the 1-stage group and 416 fistulas in the 2-stage group. Analysis of pooled data showed the difference was not significant (Pooled risk ratio = 0.73 [0.34, 1.58], 95% CI, P = 0.43) [Figure 7.4].

Heterogeneity was not detected statistically (Cochran's Q = 9.76; degree of freedom (DF) = 5; P = 0.08; I² = 49%). The results were not changed significantly when using the fixed effects analysis model as a sensitivity test to detect publication bias (Pooled risk ratio = 0.67 [0.41, 1.11], 95% CI, P = 0.12).

A sensitivity test by excluding the data from the conference paper by Effat [185] was carried out, and no significant difference was found in the incidence of postoperative haematoma between the two groups (Pooled risk ratio = 0.67 [0.27, 1.64], 95% CI, P = 0.38) [Figure 7.5].

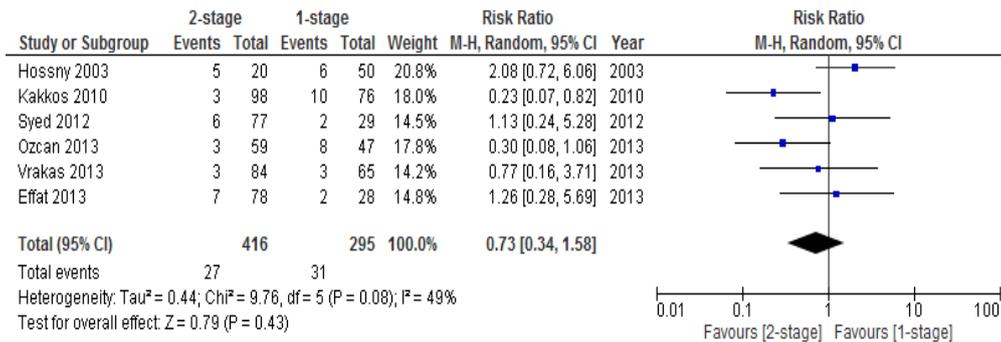
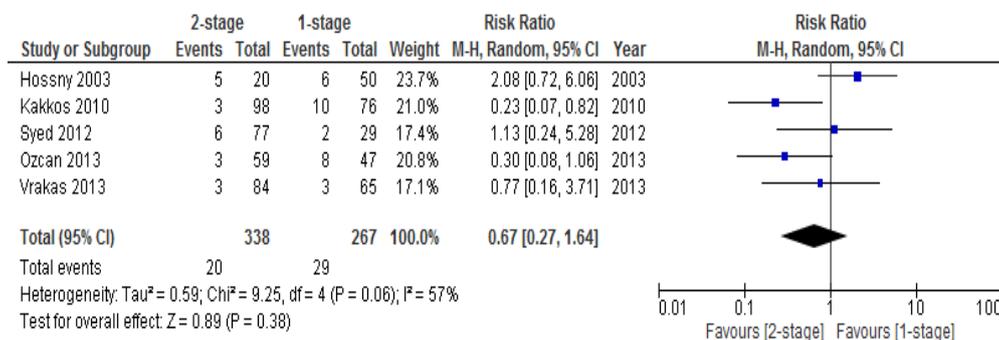
Figure 7.4: A Forest's Plot for postoperative haematoma (random effects):

Figure 7.5: A Forest's Plot for postoperative haematoma (a sensitivity test using fixed effects):



7.6.4.2 *Wound infection:*

Six of the included studies [180-183, 185] reported on the incidence of postoperative wound infection with a total number of 681 fistulas, 265 of those belonged to the 1-stage group, while 416 to the 2-stage fistulas. Meta-analysis of the pooled data showed the difference was not significant (Pooled risk ratio = 0.77 [0.35, 1.68], 95% CI, P = 0.51) [Figure 7.6].

There was no evidence of statistical heterogeneity (Cochran's Q = 5.76; degree of freedom (DF) = 5; P = 0.51; I² = 13%). The results were not changed significantly when using the fixed effects analysis model (Pooled risk ratio = 0.73 [0.39, 1.37], 95% CI, P = 0.32).

A sensitivity test by excluding the data from the conference paper by Effat [185] was carried out, and no significant difference was found in the incidence of postoperative wound infection between the two groups (Pooled risk ratio = 0.57 [0.25, 1.27], 95% CI, P = 0.17) [Figure 7.7].

Figure 7.6: A Forest's Plot for postoperative wound infection (random effects):

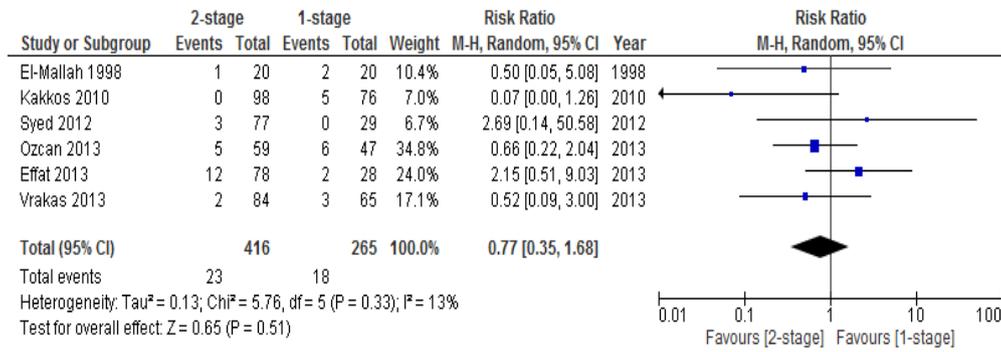
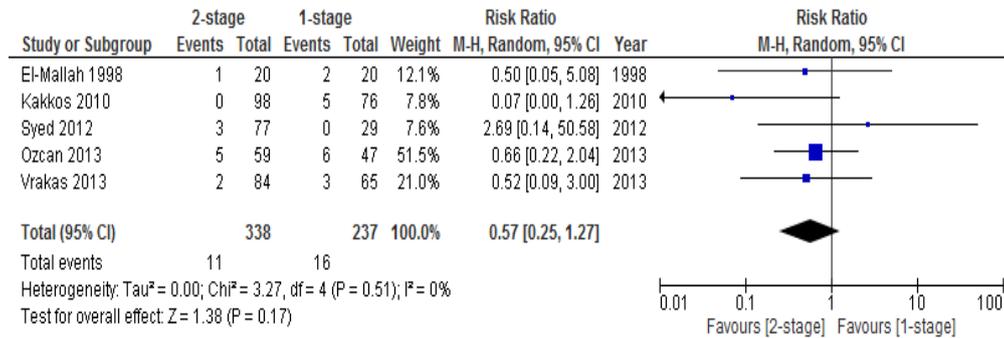


Figure 7.7: A Forest's Plot for postoperative wound infection (a sensitivity test using fixed effects):



7.6.4.3 *Steal Syndrome:*

Six of the studies [173, 180-183, 185] reported on the risk of developing significant postoperative ischaemia (steal syndrome). Those studies had a combined total of 681 patients, of those, 265 belonged to the 1-stage group, while 416 to the 2-stage group. Analysis of pooled data showed the difference was not significant (Pooled risk ratio = 0.65 [0.27, 1.53], 95% CI, P = 0.32) [Figure 7.8].

Heterogeneity was not detected statistically (Cochran's Q = 3.42; degree of freedom (DF) = 4; P = 0.49; I² = 0%). The results were not changed significantly when using the fixed effects analysis model (Pooled risk ratio = 0.64 [0.29, 1.40], 95% CI, P = 0.26).

A sensitivity test by excluding the data from the conference paper by Effat [185] was carried out, and no significant difference was found in the incidence of postoperative haematoma between the two groups (Pooled risk ratio = 0.79 [0.32, 1.94], 95% CI, P = 0.60) [Figure 7.9].

Figure 7.8: A Forest's Plot for the development of steal syndrome (random effects):

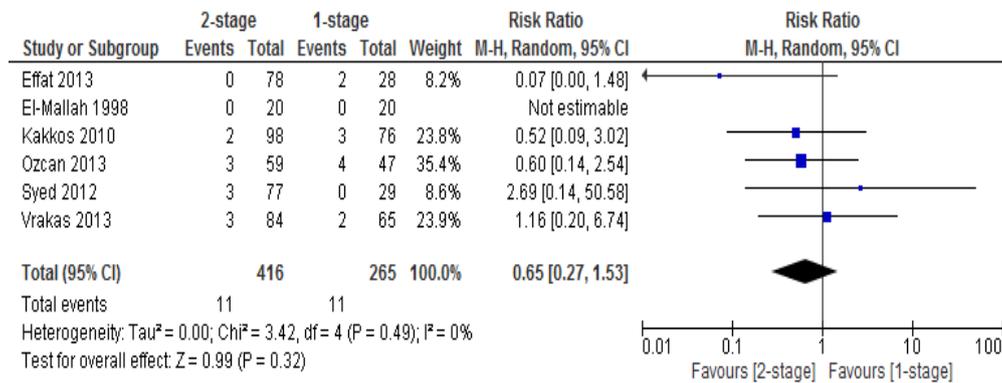
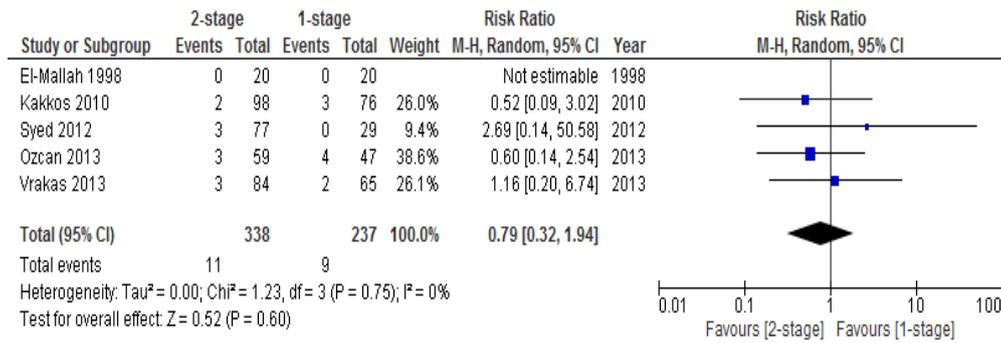


Figure 7.9: A Forest's Plot for the development of steal syndrome (a sensitivity test using fixed effects):



7.7 Systematic review:

El-Mallah in his paper titled “Staged basilic vein transposition for dialysis angioaccess” published in 1998 [182] compared outcomes in two groups randomly allocated to receive either 1-stage BVT or 2-stage BVT. The difference in early patency rates was significant and favoured the 2-stage approach (60% of 1-stage vs 90% of 2-stage, $P < 0.05$), as well as the difference in the overall patency rates at the end of follow-up (50% of 1-stage vs 80% of 2-stage, $P < 0.05$) [182]. Postoperative wound infection rate also favoured the 2-stage approach with one case compared to three in the 1-stage group. There was no difference in postoperative aneurysmal dilatation, and there was no significant ischaemia (steal syndrome) reported in either of the two groups [182].

Hossny looked at the different surgical techniques used in creation of a BB-AVF in 2003 [172]. He compared patency rates and dialysis related complications in 70 patients divided into 3 groups, 30 of those patients had traditional BVT whereas 20 patients had 1-stage BB-AVF with elevation and the remaining 20 patients had 2-stage fistula with elevation of the vein [172]. Cumulative secondary patency rates were comparable among the 3 groups at 1 year and 2 years; at 1 year it was 86.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the last group, while at 2 years the rate was 82.8%, 70%, and 68.4%, respectively [172]. Similarly, no significant difference was found in his study in postoperative early thrombosis across the groups. Postoperative arm oedema occurred in 14 patients, all of whom had temporary subclavian access catheters sited on the same arm on which the new fistula was created. All 14 cases were managed conservatively with success. The difference in developing postoperative haematoma significantly favoured the traditional BVT approach compared to the two elevation methods with fewer haematomas reported in the first group. Interestingly, the dialysis staff were more satisfied with the 1-stage BVT technique, whereas only 53.3% reported satisfaction with the elevation technique (1-stage and 2-stage techniques combined) ($P < .001$) [172].

Kakkos et al also tried to answer the question of “What is the Optimal Technique” for performing a BVT in a retrospective study of 173 patients published in 2010 [181]. They found that the incidence of venous hypertension (17% vs 4%, $P = 0.004$), wound infection (13% vs 3%, $P = 0.012$) and all complications (43% vs 11%, $P < 0.001$) were significantly higher in patients who had 1-stage BVT when compared to those who had a 2-stage BVT [181]. Time to fistula use in HD was – expectedly – shorter in the 1-stage group (Median = 68 (49 – 103) days) compared to the 2-stage group (Median = 132 (102 – 166) days). This difference was significant ($P < 0.001$) [181]. However maturation rates were similar (85% for the 1-stage group versus 82% for the 2-stage group, $P = 0.49$). Median time to use the fistulas for HD in the 2-stage group was 66 in patients who developed postoperative complications, compared to 50 days in those who did not ($P = 0.019$). They also found that wound infection occurred more in patients who were operated under general anaesthetic compared to those who had their procedures done under local anaesthetic (OR 38, $P < 0.001$). Also, venous hypertension was found to occur more frequently in patients who developed postoperative wound haematoma, but the difference was not statistically significant (18% vs 6%, $P = 0.12$) [181]. A trend was noted towards steal being more common in patients with previous vascular access than in those who did not have such history (4.9% vs 1.1%, $P = 0.19$) [181].

Syed et al carried out a similar study comparing the outcomes of 1-stage (29 patients) and 2-stage (77 patients) BVT and published their findings in 2012 [183]. In the 1-stage group, 79% of the patients had a history of a previously failed access for HD compared to 51% of the 2-stage group. They found that the rate of primary failure was comparable between both groups (21% vs 18%) [183]. In their study, patients who had 1-stage BVT had better patency rates when compared to those who had 2-stage procedures at 1 year (82% vs 67%), 2 years (81% vs 27%) and 3 years (51% vs 18%) respectively. The same finding was reported for secondary patency (91%, 80% and 58% for 1-stage BVT compared to 81%, 61% and 45% for the 2-stage group at 1, 2 and 3 years respectively) [183]. Reintervention rate in this study was 62% for the 1-stage vs 66% for the 2-stage group. It is worth noting that 87% of the patients in the 2-stage group were using catheters for dialysis, whereas 55% of the 1-stage group were dialysing through a catheter at the time of access formation [183].

Ozcan et al published a paper in 2013 with preliminary results from their study comparing between the 1-stage and the 2-stage BVT techniques in creating AVF access in HD patients [180]. They retrospectively divided their patients to those with a basilic vein > 3 mm and who had a 1-stage BVT procedure, and those with a basilic vein < 3 mm who had a 2-stage procedure. Although the diameter of the basilic vein was statistically higher in the first group (3.46 ± 0.2 mm) compared to the second group (2.79 ± 0.1 mm) ($P < 0.005$), the rate of fistula maturation was significantly lower in the first group (66% vs 77%, $P < 0.005$) [180]. Also, postoperative complications were significantly higher among the first group of patients who had 1-stage BVT. Thrombosis occurred in 34% compared to 23% of patients who had a 2-stage procedure, haemorrhage in (36% vs 14%) and haematoma in (17% vs 6%) respectively. Time required for the fistula to mature was significantly shorter in the first group (Mean 41 ± 14 days) compared to the second group (Mean 64 ± 28 days) ($P < 0.05$) [180]. Early interventions (≤ 10 days) for fistula thrombosis occurred more frequently in the first group (21% vs 12%, $P < 0.05$), although there was no significant difference in terms of late interventions (≥ 10 days) required to deal with access thrombosis (20% in the first group vs 22% in the second) [180]. Also they reported superior primary patency rates at 6, 12, 18, 24, 30 and 36 months for those who had 2-stage BVT fistulas compared to the first group of patients (1-stage 83%, 70%, 68%, 64%, 60% and 57% versus 88%, 84%, 80, 73%, 71% and 69% for the 2-stage respectively). Similarly, the 1-stage had lower secondary patency rates at 6, 12, 18, 24, 30 and 36 months when compared to the 2-stage group (85%, 76%, 74%, 72%, 70% and 66% versus 94%, 90%, 84%, 82%, 80% and 77% respectively) [180].

Similarly, Vrakas et al evaluated the difference in outcomes between 1-stage (65 fistulas) and 2-stage (84 fistulas) BB-AVFs performed in 141 patients [173]. They performed ultrasound scans 4 – 6 weeks after the first stage procedure to determine if a second stage was required. Patients who had their fistulas created in a 1-stage approach had a bigger preoperative basilic vein diameter (4.0 ± 1.1 mm vs 3.6 ± 1.3 mm, $P = 0.041$) [173]. There was no difference in primary failure between the groups (45% vs 42%, $P = 0.718$), however the 1-stage BB-AVF had significantly lower primary (71% vs 87%; $P = 0.034$), assisted primary (77% vs 95%; $P = 0.017$), and secondary (79% vs 95%; $P = 0.026$) functional patency rates compared to the 2-stage BB-AVF [173]. Multivariate

Cox regression analysis showed that the 1-stage procedure was 3.2 times more likely to fail ($P = 0.028$), and male gender was associated with loss of access ($P = 0.054$). In the first group, 66% of the fistulae were used successfully for HD compared to 60% in the 2-stage group ($P = 0.407$), and the number of interventions required before first successful HD sessions was equivalent between both groups (21% vs 11%, $P = 0.201$) [173]. Overall, 93 (62%) fistulas were successfully used for HD (66% 1-stage vs 60% 2-stage; $P = 0.407$), of the remaining 56 (38%), 19 fistulas (34%) failed before needling, 2 (4%) received a renal transplant, 7 (13%) died, and 28 (50%) BB-AVFs remain patent in patients awaiting to start HD [173].

Agarwal et al examined the outcomes of 1-stage vs 2-stage BVT-AVF. They included patients who underwent percutaneous angioplasty (assisted maturation) in calculating the overall maturation rate which was 90% for the 1-stage group (55/61 patients) compared to 75% of the 2-stage group (62/83 patients) ($P = 0.02$). Subgroup analysis showed that both men (54/66 patients) and women (64/78) in this study had a maturation rate of 82% ($P = 0.97$) [184]. Primary unassisted patency rates were comparable between the groups (69%, 52%, 26%, and 7% for the 1-stage BVT at 3 months, 6 months, 1 and 2 years; compared to 58%, 35%, 13%, and 0% of the 2-stage group, respectively ($p = 0.12$) [184]. Similarly, no significant difference was found in secondary patency on an intent to-treat basis (86%, 75%, 69%, and 57% at 1, 2, 3, and 4 years for 1-stage group; compared to 76%, 71%, 49%, and 25% of the 2-stage group, respectively); ($p = 0.12$) [184]. The intensity of percutaneous interventions in their study was 1.84/patient-year of dialysis (PYD) for the 1-stage group versus 2.15/PYD for the 2-stage group ($P = 0.57$) [184]. They suggested that although the 2-stage BB-AVF technique resulted in modest reduction in maturation and patency rates, it should still be favoured to the use of synthetic grafts in patients who would not be suitable for a 1-stage BB-AVF procedure [184].

The number of AVFs that failed to progress from the first stage to the second stage in the two-staged BVT approach were unclear in four studies [173, 180, 184, 185]. In the remaining four, El-Mallah [182] reported 1/20 patient failed to progress to the second stage (occluded shunt), while Hossny [172] also had 1/20 patient failing to progress due to spontaneous thrombosis within the

first 4 weeks postoperatively. Syed [183] had 2/77 patients that never progressed to the second stage of the procedure. Kakkos [181] reported that 26/98 of his patients never had a second stage procedure (thrombosed (n=4), failed to mature and was abandoned during the re-exploration (n=12), patient refused the procedure (n=3), lost to follow-up (n=1), died (n=2), venous hypertension (n=2), venous monomelic neuropathy (n=1) requiring ligation, moved out of state (n=1)).

Number of interventions required to maintain patency or to improve the fistula maturation rates were not reported clearly in all studies. Hossny reported that in the one-stage group, one patient underwent ligation and another had a surgical revision, same numbers occurred in the two-stage group. All ligations were done to treat venous hypertension, whereas all revisions were performed to improve poor flow [172]. Kakkos reported that in the two-stage group, six patients had endovenous angioplasty interventions; three had surgical revisions compared to three patients and one patient in the one-stage group, respectively [181]. Syed et al performed 37 angioplasty interventions, 7 surgical revisions and 7 thrombectomy procedures in their one-stage group, compared to 36, 11 and 6 patients in the two-stage group, respectively [183]. The remaining studies did not report data related to fistula salvage procedures or they were reported poorly making it difficult to quantify those interventions.

With the exception of the studies by El-Mallah et al [182] and the one by Vrakas et al [173] (both reported significantly superior patency rates in the two-stage groups), and the paper by Syed [183] which conversely reported a significantly better patency rates in the one-stage BVT group, the remaining studies all reported comparable patency rates [172, 180, 181, 184, 185], [Table 7.3]. However, it is important to point out that patency rate data were reported as percentages with the lack of clearly identifiable denominators in the majority of those studies, thus making pooling those data in a meta-analysis not feasible. In addition, definitions used in individual studies included in this review for patency rates (primary, assisted primary and secondary) differed significantly.

7.8 Discussion:

The number of patients with end stage renal disease (ESRD) requiring haemodialysis (HD) is steadily rising, a trend that is expected to continue [95]. A well-functioning AVF is superior to grafts and central catheters in providing efficient access for haemodialysis; moreover, AVFs provide the least rate of access related complications. This has lead vascular surgeons to resort to the basilic vein, which by virtue of its anatomical position is less likely to be damaged by repeated cannulation contrary to the more superficial veins of the arm and forearm. However, a consensus on how to form a brachiobasilic AVF does not exist as some surgeons opt for a one-stage operation, while others prefer a two-stage procedure. In the two-stage approach, the first procedure usually involving making the anastomosis between the basilic vein and the brachial artery, while in the second stage the arterialised vein is mobilised and brought closer to the skin surface to facilitate cannulation.

This review identified eight studies [172, 173, 180-185], including data from a conference paper [185] in order to increase the rigour of the review. The pooled data referred to 849 patients with a total of 859 fistulas, 366 of those fistulas belonged to patients who underwent a 1-stage BB-AVF, while 493 fistulas were performed using a 2-stage technique to create the access. The data from six of the included studies [172, 173, 180, 181, 183, 185] were used to compare the difference between the two groups in developing postoperative haematoma which was not significant (Pooled risk ratio = 0.69 [0.30, 1.56], 95% CI, P = 0.37). Excluding the data from the conference paper by Effat [185] in a sensitivity test did not alter the result (Pooled risk ratio = 0.61 [0.23, 1.60], 95% CI, P = 0.31).

The incidence of postoperative wound infection was reported in five studies [180-183, 185], and the difference between the 1-stage group and the 2-stage groups was not found to be significant (Pooled risk ratio = 0.82 [0.31, 2.18], 95% CI, P = 0.69). This remained unchanged in a sensitivity test excluding the data by Effat [185] (Pooled risk ratio = 0.57 [0.21, 1.51], 95% CI, P = 0.27).

Similarly, the difference between the two groups was not found to be significant when it came to postoperative ischaemia (steal syndrome) in the six studies which reported this complication [173, 180-183, 185] (Pooled risk ratio = 0.51 [0.20, 1.30], 95% CI, P = 0.16). A sensitivity test was performed by excluding the data by Effat [185] from the pooled data, and the result was not altered (Pooled risk ratio = 0.63 [0.23, 1.69], 95% CI, P = 0.35).

Ozcan et al [180] allocated patients to groups based on vein diameter. Those with basilic vein > 3 mm received a 1-stage BVT, while patients with basilic vein < 3 mm received a 2-stage BVT. Even with this seemingly advantageous difference in favour of the 1-stage approach, they reported superior patency rates and maturation rates in patients who had a 2-stage procedure with primary patency at 1, 2 and 3 years for the 1-stage group of (70%), (64%), and (54%) versus (84%), (73%), and (69%) in the 2-stage group. Secondary patency rates at 1, 2 and 3 years for the 1-stage group were (76%), (72%), and (66%) versus (90%), (82%), and (77%) in the 2-stage group.

Similarly, Vrakas et al reported a smaller mean vein diameter of (3.6 ± 1.3 mm) for the 2-stage group, compared to (4.0 ± 1.1 mm) for fistulas created in the 1-stage group. However, the results favoured the 2-stage approach with primary functional patency at 1 and 2 years for the 1-stage group of 71% and 53% versus 87% and 75% in the 2-stage group. Assisted Primary functional patency at 1 and 2 years for the 1-stage group was 77% and 57% versus 95% and 77% in the 2-stage group, while secondary functional patency at 1 and 2 years for the 1-stage group was 79% and 57% versus 95% and 77% in the 2-stage group.

Conversely, in study by Agarwal et al [184], their patients in the 1-stage group achieved better maturation rate than those who had a 2-stage BVT fistulas (90% vs 75%, P = 0.02). They did not include any analysis between the two groups based on vein diameter. Vein diameter has been shown to influence maturation and patency rates in AVFs, and is one of the main predictors of outcomes in fistulas [80, 117], and indeed has been shown to be the only independent predictor of maturation in some studies [119, 121]. Syed et al reported similar findings with better primary and cumulative patencies in the 1-stage group. The primary patency rate at 1, 2 and 3 years was 82%, 81% and

51% for the 1-stage groups, versus 67%, 27% and 18% for the 2-stage group, respectively. The secondary patency rate at 1, 2 and 3 years was 91%, 80% and 58% for the 1-stage BVT and 81%, 61% and 45% for the 2-stage group. Variations in vein diameter between the groups were not reported in this study.

Kakkos et al [181] did not find a significant difference in maturation between the two groups, as 15% of fistulas in the 1-stage group did not mature, compared to 18% in the second group ($P = 0.49$). They did however find significant difference in developing postoperative haematoma (13% vs 3%, $P = 0.012$), venous hypertension (17% vs 4%, $P = 0.004$) and overall complications (43% vs 11%, $P < 0.001$), all in favour of the 2-stage BVT technique.

Kim et al compared the 2-stage approach to all other AVF procedures including 1-stage BVT, radiocephalic and brachiocephalic fistulas. All of the 2-stage BB-AVFs in their study successfully matured compared to a pool consisting of all different types that showed a combined maturation rate of 52% ($P = 0.001$) [186]. Fistula failure occurred in 7% of the 2-stage BVT compared to 59% of other fistulas ($P = 0.001$), and more 2-stage BVT fistulas were used successfully for HD compared to all other fistula types (87% vs 48%, $P = 0.024$). In addition, the patency rate at 1 year was superior in the 2-stage group compared to other AVFs (91% vs 47%, $P = 0.003$).

Several factors would drive the decision of the operating surgeon to choose one technique over the other. The size of both the basilic vein and the brachial artery used to create the anastomosis is possibly the single most important factor to determine which technique should be used, along with the quality of those vessels. Another factor is the preference of the operating surgeon, as some surgeon will prefer to perform all BB-AVF in two stages.

One of the limitations of this review is the low number of randomised trials included – only one study was randomised, while the remaining seven were cohort studies. Most of the cohort studies were retrospective in nature, making them prone to all the limitations known to be intrinsic to retrospective studies. Another limitation is the variation in surgical

approaches; those variations include technical differences in performing the procedure, as well as differences in equipment used and expertise among participating surgeons. Some surgeons transpose the basilic vein, where other surgeons might prefer a superficialisation approach only without lateralisation of the vein. Those variations in technique combined with the likely selection bias in the retrospective cohort studies included in this systematic review should be taken into account when considering the estimated pooled effects reported in this study. Those limitations can be addressed by conducting a large randomised multi-centre trial that would adhere to a rigid protocol in selecting patients and performing the procedures. Another limiting factor is the lack of sufficient sub-group analysis among included studies, particularly analysis taking into account factors that are known to be associated with fistula maturation such as vein diameter. Finally, the author wants to highlight that included studies were not compliant with SVS reporting recommendations regarding baseline factors that affect outcomes or severity of complications.

7.9 Conclusion:

Although more studies seem to favour the 2-stage BVT approach, evidence in the literature is not sufficient to draw a final conclusion, as the difference between the 1-stage and the 2-stage approaches for creation of a BB-AVF is not statistically significant in terms of the overall maturation rate and postoperative complications. Patency rates (primary, assisted primary and secondary) were comparable in the majority of studies. Large randomised properly conducted trials with adequate sub-group analysis are needed before making a final recommendation. Future studies should aim for compliance with established reporting standards.

VIII Chapter Eight: Role of Far Infra-Red
therapy in dialysis Arterio-venous Fistula
maturation and survival: A Systematic
review and meta-analysis

8.1 Introduction:

The number of patients with end stage renal disease (ESRD) requiring haemodialysis (HD) is steadily rising, a trend that is expected to continue [95]. Vascular access is a critical component in the provision of successful HD. A well-functioning arteriovenous fistula (AVF) is the best modality for HD vascular access [1-5]. AVF maturation is a complex process of remodelling. The newly formed fistula has to form a low resistance circuit capable of dilation to accommodate the increased blood flow required for HD. The AVF also has to be cannulated repeatedly with ease. The need for re-intervention to maintain patency should be minimal [1-3, 5, 39].

AVFs' main disadvantage is the high rate of maturation failure, with approximately one third (20% - 50%) not maturing into useful access [7, 100, 101]. AVFs have higher primary failure rates to mature when compared to grafts [7, 104, 105]. However, they last longer, and with the exclusion of fistulas that fail to mature primarily, the cumulative patency rate from formation to permanent failure is superior to grafts. AVFs also require fewer secondary interventions in the form of angioplasty, stenting or thrombectomy [6-10]. AVFs are associated with fewer complications if compared to AVG and CVC in terms of infection, death, vascular access salvage procedures and hospitalizations [9, 10]. In addition, a mature AVF has a lower incidence of thrombosis and stenosis. This translates into prolonged patency rates and lower risk of infection [95, 164, 187-189].

Maturation of the AVF depends on variable biomechanical forces. Remodelling of the arterial limb is characterised by vessel dilatation and outward hypertrophic remodelling of the intimal layer. Remodelling at the venous end can be accompanied by an aggressive form of intimal thickening resulting in inward hypertrophic remodelling. Intimal hyperplasia (IH) is defined as the abnormal migration and proliferation of vascular smooth muscle cells provoked by injury, inflammation or stretch with the associated deposition of extracellular matrix in the intimal layer of the vein [17-19].

Far Infra-Red (FIR) therapy, which is a form of heat therapy, has been implicated in the improvement of endothelial function and haemodynamics in coronary arteries. Probably through the up-regulation of the endothelial nitric oxide synthase (eNOS) expression in arteries leading to improved cardiac function in patients with chronic heart diseases [190]. Additionally, repeated leg hyperthermia using FIR technology has been shown to reduce oxidative stress in bed ridden type II diabetics [191].

FIR has also been reported to show encouraging results in the control of phantom limb pain [192], stimulation of the secretion of Transforming Growth Factor beta-1 (TGF- β -1) and activation of fibroblasts. Those effects may promote better wound healing independent of skin blood flow and skin temperature [193, 194], reduction of both stress and fatigue levels of patients with end stage renal disease (ESRD) and stimulates the autonomic nervous system in those who are receiving regular haemodialysis (HD) [195].

This review was designed to examine the effects of FIR on AVF maturation using primary and secondary patency rates as the main outcomes of interest.

8.2 Methods:

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [89].

8.2.1 Eligibility Criteria

Observational studies or randomised controlled trials (RCTs) that examined FIR therapy in patients with AVFs and ESRD were included in this study. Eligible studies reported on AVF patency rates in both the FIR and non-FIR groups after at least one year of follow up after the initiation of therapy. Case series and case reports were excluded. There was no restriction with regard to publication status or language.

8.2.2 Search strategy

A search of the literature for relevant studies was conducted in March 2014. Databases searched included Medline without date restriction using the free text “far infra-red”. Additionally, the author used the strategy ([“far infra-red” OR “far infrared” OR “post conditioning”] AND [“arteriovenous fistula” OR “dialysis” OR “end stage renal disease” OR “dialysis access” OR “access survival” OR “primary patency” OR “secondary patency” OR “fistula maturation”]) to search CINAHL, EMBASE, the Cochrane library and Google Scholar. Bibliographies of included studies were searched for additional studies.

Abstracts of the relevant titles were subsequently obtained and evaluated for eligibility (KB, DH). Any remaining uncertainty was resolved by examination of the full article (KB, DH). Discussion with a third author (SRW) resolved discrepancies in cases of disagreement regarding eligibility.

The relevant outcomes for this review were primary patency – defined as unassisted AVF patency rates after at least 12 months of follow up - and

secondary patency – defined as assisted patency rates after at least 12 months of follow up. The incidence of salvage procedures (endoluminal procedures or surgical procedures) for dysfunctional fistulas during follow up was a secondary outcome.

8.2.3 Data Collection

Data were extracted and checked for accuracy by two reviewers (KB, DH) independently and recorded on a Microsoft® Excel spreadsheet. Any disagreements in extracting data were discussed between the two reviewers (KB, DH), and if not settled this was resolved by consulting with a third reviewer (SRW). The following information regarding the characteristics of participants were recorded: age, sex, , presence of co-morbidities, start of HD, primary and secondary patency rates, AVF salvage procedures, underlying cause of ESRD, definition of first AVF malfunction and overall access survival. The inclusion and exclusion criteria of the studies were also recorded.

8.2.4 Quality assessment for risk of bias

The risk of bias for each study was assessed according to the criteria outlined in the in the Cochrane Handbook for Systematic Reviews of Interventions [94]. For each included study, the methods used to perform random sequence generation, allocation concealment and blinding were described. The study was then scrutinised for incomplete data outcomes, selective reporting and other potential sources of bias. Where possible, study protocols were obtained from trial registries to ascertain whether there was selective reporting within studies [Table 8.1].

Table 8.1: Results of the quality assessment of the studies

| Included study | Domain | Support for judgement | Judgement |
|------------------------------|--|---|-------------------|
| Lai 2013 ESVS [196] | Random sequence generation | The method of generating the random sequence was not described. | Unclear |
| | Allocation concealment | No description of methods for maintaining allocation concealment. | Unclear |
| | Blinding of participants and personnel | Participants and personnel were not blinded. Dysfunctional access signs and other referral criteria could have a subjective component. | High risk of bias |
| | Blinding of outcome assessment | Outcome assessors were not blinded. Dysfunctional access signs and other referral criteria could have a subjective component. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was minimal. Analysis was not by intention to treat. 9/59 control group patients crossed over to the intervention group potentially leading to bias in favour of the intervention | Unclear |
| | Selective reporting | No link to the protocol was given | Unclear |
| | Other sources of bias | None | Not available |
| Lin 2007 J Am Soc Neph [197] | Random sequence generation | A computerised minimisation algorithm was used | Low risk of bias |
| | Allocation concealment | Allocation sequence was kept by a study nurse who would not disclose allocations until time of intervention. Diagnosing malfunction in a fistula could have had a subjective element. | Unclear |

| | | | |
|---------------------|--|---|-------------------|
| | Blinding of participants and personnel | Participants and personnel were not blinded. | High risk of bias |
| | Blinding of outcome assessment | Outcome assessors were not blinded. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was minimal and was similar between groups and was unlikely to influence results | Low risk of bias |
| | Selective reporting | Protocol was not available. | Unclear |
| | Other sources of bias | None | Not available |
| Lin 2013 AJKD [198] | Random sequence generation | A computer generated sequence was used | Low risk of bias |
| | Allocation concealment | Sealed opaque envelope were used to conceal allocation. There was no information in the manuscript or protocol on who had access to the envelopes and whether they were opened sequentially | Unclear |
| | Blinding of participants and personnel | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Blinding of outcome assessment | Ultrasonographers were blinded; however, patients were not blinded. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was similar between groups and unlikely to influence results | Low risk of bias |
| | Selective reporting | Link to protocol was provided (NCT01138254). Trial was not prospectively | High risk of bias |

| | | | |
|-------------------------------------|--|--|-------------------|
| | | registered and there were several changes made including changes to outcomes. | |
| | Other sources of bias | None | Not available |
| Lin 2013 Neph Dial Transplant [199] | Random sequence generation | A computer generated sequence was used | Low risk of bias |
| | Allocation concealment | Sealed opaque envelope were used to conceal allocation. Two study nurses had access to the envelopes and there was no information in the manuscript or protocol on whether they were opened sequentially | Unclear |
| | Blinding of participants and personnel | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Blinding of outcome assessment | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was similar between groups and unlikely to influence results | Low risk of bias. |
| | Selective reporting | All outcomes that were mentioned in the protocol were reported. The subgrouping based on polymorphisms of heme oxygenase-1 was not prespecified | Low risk of bias |
| | Other sources of bias | None | Not available |

8.2.5 Data analysis

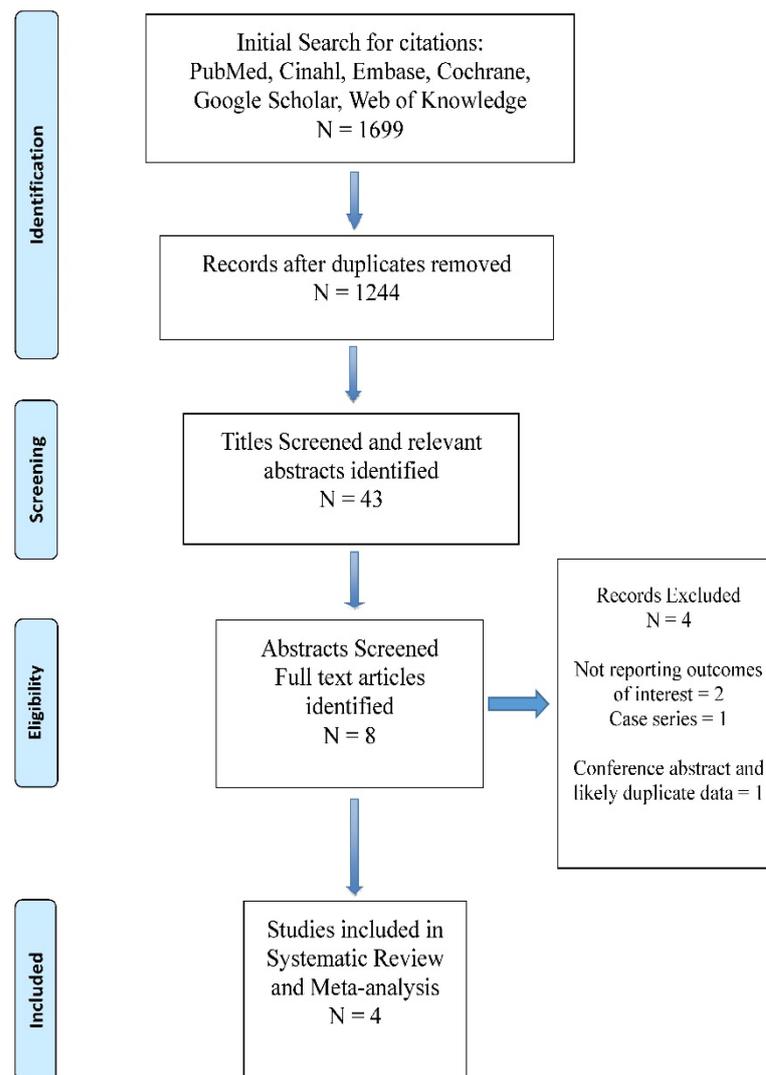
Statistical analyses were performed using Review Manager version 5.2.8 [91]. Pooled risk ratios were calculated using the random effects model of DerSimonian and Laird [92]. For continuous outcome variables, the weighted mean difference (WMD) was calculated. The presence of statistical heterogeneity between studies was evaluated using the Cochran's Q statistic. P-values less than 5% were considered as statistically significant. Publication bias was assessed visually using funnel plots, and additionally by comparing fixed and random effects modelling in sensitivity tests – this is a recognised method that can detect the influence of small-study effects [93]

8.3 Results:

8.3.1 Study Selection

The results of the study selection process are summarized in the PRISMA flow diagram (Figure 8.1).

The initial search yielded 1669 citations, with 1244 citations remaining following removal of duplicates. The titles of these citations were screened with 43 titles deemed potentially relevant. The abstracts of those titles were examined and eight full text articles were subsequently retrieved and examined. After assessing the eligibility according to the criteria decided at the time of conducting the online search, four RCT's were included in the review [196-199]. Three of those four studies reported on patients with history of previous AVFs who had been on HD prior to FIR therapy [196, 197, 199], while one study reported on patients with newly formed AVF not on HD [198]. Another study by Lin et al [200] could not be included as it had a follow up period of 3 months for primary patency rates. This was a conference abstract only, which the author of this thesis had concerns that the data in this study was possibly used in another study by the same author [199] that has already been included in this review. Three studies were excluded from the final analysis after going through the full articles. Shipley et al followed their patients for six months in a case series of 20 patients – no control group - and reported maturation in 10 of those patients [201]. Two studies did not report on the outcomes of interest to the author of this systematic review [195, 202].

Figure 8.1: PRISMA flow diagram

8.3.2 Characteristics of included studies

8.3.2.1 Far Infrared (FIR) technique

All of the included studies used the same technique to deliver FIR therapy. WS TY101 FIR emitter (WS Far Infrared Medical Technology Co., Ltd., Taipei, Taiwan) was used in all studies, which generates electromagnetic waves with wavelengths in the range between 5 and 25 (peak at 5- 8.2 μm). The top radiator was set at a height of 20 – 30 cm above the surface of the AVF with the treatment time set at 40 min - during HD sessions - three times per week.

8.3.3 Participants

The four studies included 666 patients, with 340 patients randomised to receive FIR therapy – median age 62.3 ± 14.5 SD, while 326 were randomised to the control group – median age 62.0 ± 14.5 SD. There were 348 male patients – 180 in FIR group and 168 in the control group, while there were 318 female patients, of those 160 received FIR therapy and 158 were controls.

Inclusion and exclusion criteria of studies are outlined in [Table 8.2], along with the definitions of AVF malfunction used in each of the included studies.

Table 8.2: Inclusion & exclusion criteria and definition of AVF malfunction for included studies

| Study | Inclusion criteria | Exclusion criteria | Definition of AVF malfunction |
|---------------------|--|---|---|
| Lin 2007 [197] | (1) Receiving 4 h of maintenance HD therapy three times weekly for at least 6 months at Taipei Veterans General Hospital, (2) Using a native AVF as the current vascular access for more than 6 months, without interventions within the last 3 months, and (3) Creation of AVF by cardiovascular surgeons in our hospital with the standardized surgical procedures of venous end-to-arterial side anastomosis in the upper extremity. | During the 1-yr follow-up, patients would be excluded from the study because of the following censoring criterion: (1) Renal transplantation, (2) Death with a functioning access, (3) Shifting to peritoneal dialysis, and (4) Loss of follow-up. | The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning AVF that cannot sustain an extracorporeal blood flow > 200 ml/min during HD after exclusion of the following stenosis-unrelated events: Infectious complication, progressive aneurysmal formation, or steal syndrome. |
| Lin 2013_AJKD [198] | (1) Aged 18-80 years, (2) Had CKD with estimated glomerular filtration rate (eGFR) of 5-20 mL/min/1.73 m ² , (3) Were not anticipated to receive dialysis or kidney transplantation within the next 3 months, and (4) Were undergoing AVF creation with venous end-to-arterial side anastomosis in the upper extremity. | (1) Those receiving an arteriovenous graft or cuffed tunnelled double-lumen catheter as the type of permanent vascular access, (2) Heart failure of New York Heart Association functional class III or IV, and (3) Episode of cardio- or cerebrovascular event or receiving intervention therapy within 3 months prior to screening. | The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning fistula which could not sustain an extracorporeal blood flow >200 mL/min during HD after excluding the following stenosis-unrelated events, such as infectious complication, progressive aneurysmal formation or steal syndrome. |
| 2013 [196] | (1) Received two or more PTA on the target lesions at upper extremities, with the last PTA successfully performed within the week before patient enrolment, and (2) After successful completion of at least 1 week of HD treatment, the patients with AVF or AVG were consecutively enrolled and randomly assigned to either a post-PTA FIR radiation group or a control group receiving the usual form radiation therapy at a 1:1 ratio | (1) Received HD treatments other than three times a week, (2) Had previously received FIR radiation Therapy, (3) Received implantation of an endovascular stent, (4) Had multiple lesions that a single radiation field did not cover or the central lesion was considered too deep to be irradiated, (5) Missed FIR radiation treatments exceeding 10%, (6) Underwent renal transplantation, (7) Switched to peritoneal dialysis treatments, and (8) Had any severe disease with an estimated life expectancy of less than 1 year. | A significant lesion was defined as a lumen loss of 50% or more compared with adjacent normal vessel on angiography following dysfunctional diagnosis based on clinical signs suggestive of stenosis |

| | | | |
|-------------------------------|--|---|---|
| <p>Lin_2013_NDT [199]</p> | <p>(1) Receiving 4 h of maintenance HD therapy three times weekly for at least 6 months at Taipei Veterans General Hospital, (2) Using a native AVF as the present vascular access for >6 months, without interventions within the last 3 months, and (3) Creation of AVF by cardiovascular surgeons in our hospital with the standardized surgical procedures of venous end-to-arterial side anastomosis in the upper extremity.</p> | <p>Received an AV graft as the first vascular access.</p> | <p>The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning fistula which could not sustain an extracorporeal blood flow >200 mL/min during HD after excluding the following stenosis-unrelated events, such as infectious complication, progressive aneurysmal formation or steal syndrome.</p> |
|-------------------------------|--|---|---|

Apart from Lin et al who evaluated the effects of FIR in pre-dialysis patients with newly formed AVFs [198], the remaining RCTs included patients who were already started on HD. Mean time on HD in months for Lin et al [197] was 85.2 ± 41.1 for the FIR group and 79.2 ± 42.2 for the control group, for Lai et al [196] FIR = 50.4 ± 42 and control = 58.8 ± 56.4 and for Lin et al in 2013 [199] FIR = 66.0 ± 59.1 and control = 75.9 ± 58.0 . All patients in included trials received FIR therapy for 40 minutes per session three times a week for the duration of the study.

Lai et al studied patients with history of dysfunctional AVFs and repeated angioplasties. The mean life of the AVFs for their patients was 21.8 ± 23.0 months for the FIR group and 23.5 ± 22.6 months for the controls [196]. In the RCT by Lin et al in 2007, 33 patients from 72 in the FIR group had history of AVF malfunction, 14 patients of those required surgical interventions, while 20 patients had 49 angioplasty procedures. In the control group, 34 patients from 73 had history of AVF malfunction; 13 of those required surgical interventions, and 20 patients had 46 angioplasty procedures [197]. Similarly, in the study by Lin et al in 2013, 47 patients had history of AVF malfunction with 12 patients requiring surgery from 139 and 35 patients underwent 79 angioplasty procedures in the FIR group. In comparison, there were 45 patients with history of malfunction, 13 patients of those required surgery and 32 patients underwent angioplasty salvage procedures in the control group [199]. All patients in both the FIR and the control groups had angioplasty procedures prior to recruitment in the study by Lai et al [196], while none of the patients included by Lin et al had a history of either surgical or angioplasty salvage procedure since they were all first time AVFs [198]. Lai et al had nine of their patients who were initially randomised to the control group crossing over to the FIR group based on their request [196]. Clinical maturation was reported in 49 (81.7%) patients of 60 who received FIR therapy by Lin et al, compared to 37 (59.7%) from the 62 control subjects [198]. Sub-group analysis by age, gender and diagnosis of hypertension was not possible as this was not included in the studies, and the author did not have access to the raw data used by the authors. Other characteristics are detailed in [Table 8.3].

Table 8.3: Patients' Characteristics across included studies:

| Study | Patients | | Age | | Gender M:F | | Diabetes | | Hypertension | | Hx of AVF failure | | Time on HD | | Withdrawals |
|---------------------|----------|---------|-----------|-----------|---------------|---------|----------|---------|--------------|---------|-------------------|---------|--------------|--------------|--|
| | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | |
| Lin 2007 [197] | 63/72 | 64/73 | 61.9±14.4 | 59.2±19.0 | 37:35 | 38:35 | 25 | 24 | 40 | 39 | 33 | 34 | 85.2±41.1 | 79.2±42.2 | Creation of another vascular access because of the poor response to angioplasty: 1 patient receiving FIR therapy and four patients in control group. Patients were censored in case of renal transplantation ($n = 3$), death with a functioning access ($n = 5$), shifting to peritoneal dialysis ($n = 4$) or loss of follow-up ($n=1$). |
| Lin 2013_AJKD [198] | 60 | 62 | 63.2±18.5 | 63.0±14.4 | 32:28 | 35:27 | 28 | 23 | 18 | 20 | - | - | Pre-dialysis | Pre-dialysis | Lost to F/U: FIR=1, Control=1. Shifting to PD: FIR=1, Control=1. Death e AVF: FIR=2, Control=3. Renal transplantation: FIR=1. New AVF (Infection): Control=1. D/C intervention: FIR=2; Control=1 |

| | | | | | | | | | | | | | | | |
|--------------------|---------|-------------|---------------|---------------|-------|-------|----|----|----|----|-----|-----|---------------|---------------|--|
| Lin 2013_NDT [199] | 119/139 | 120/14 1 | 61.3±14. 1 | 62.8±1 5.9 | 79:60 | 71:70 | 45 | 47 | 80 | 90 | 47 | 45 | 66.0±59 .1 | 75.9±58 .0 | Underwent creation of another vascular access due to non-stenotic lesions: 3 patients receiving FIR therapy and 2 patients in the control group. Patients were censored in case of renal transplantation (n = 5), death with a functioning access (n = 15), shift to peritoneal dialysis (n = 5) or loss of follow-up (n = 9). |
| Lai 2013 [196] | 69 | 50 | 62.7±10. 9 | 63.1±1 2.5 | 32:37 | 24:26 | 42 | 28 | 48 | 38 | All | All | 50.4±42 .0 | 58.8±56 .4 | Crossover patients: 9 from Control to FIR |

8.3.4 Primary - unassisted - patency rates at 1 year:

All of the four included studies (610 patients) reported on unassisted (primary) patency rate at 12 months from the start of FIR therapy. In total, 228/311 patients in the FIR group had patent AVFs compared to 185/299 patients in the control group. Pooled results showed significant difference between the two groups, with those who received FIR showing better primary patency rates compared to control (Pooled risk ratio = 1.23 [1.12, 1.35], 95% CI, $p = 0.00001$) [Figure 8.2].

There was no evidence of statistical heterogeneity (Cochran's $Q = 0.33$; degree of freedom (DF) = 3; $p = 0.96$; $I^2 = 0\%$). The funnel plot did not suggest bias [Figure 8.3], and the result was unchanged when fixed effects modelling was used (pooled risk ratio 1.24 [1.13-1.37], 95% CI, $p < 0.0001$).

Figure 8.2: A Forest Plot showing Primary AVFs patency at 12 months (random effects):

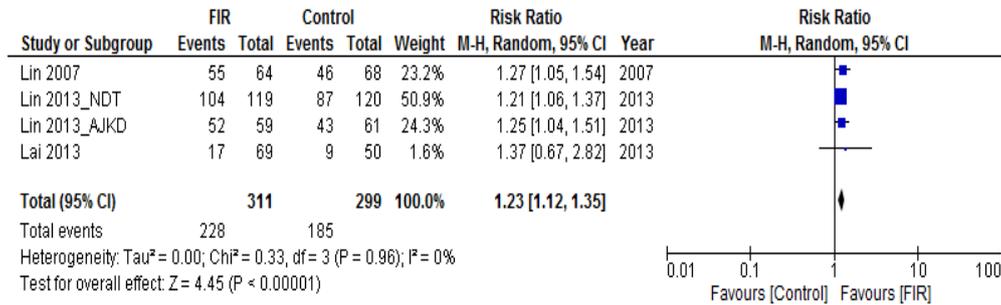
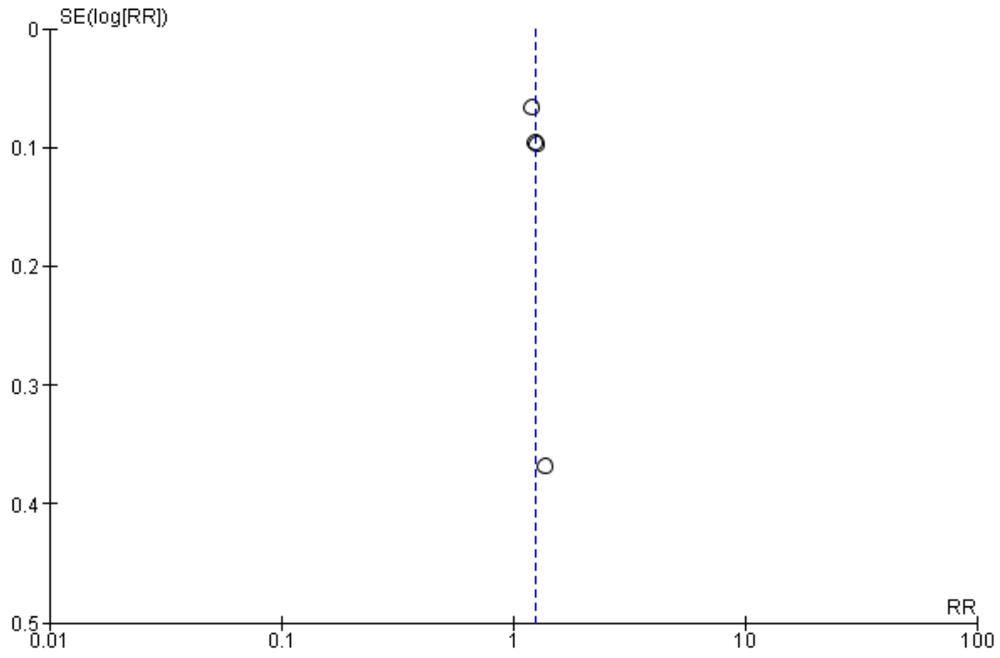


Figure 8.3: Funnel plot for Primary AVFs patency at 12 months:



Excluding the RCT by Lin et al on newly formed AVFs in pre-dialysis patients [198] from the analysis for the primary patency rate after 12 months, the remaining studies (490 patients) reported better results in the FIR group with 176/252 AVFs remaining patent at 12 months compared to 142/238 in the control group [196, 197, 199]. This difference was statistically significant (Pooled risk ratio = 1.23 [1.10, 1.37], 95% CI, $p = 0.0001$) [Figure 8.4]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.31$; degree of freedom (DF) = 2; $p = 0.86$; $I^2 = 0\%$).

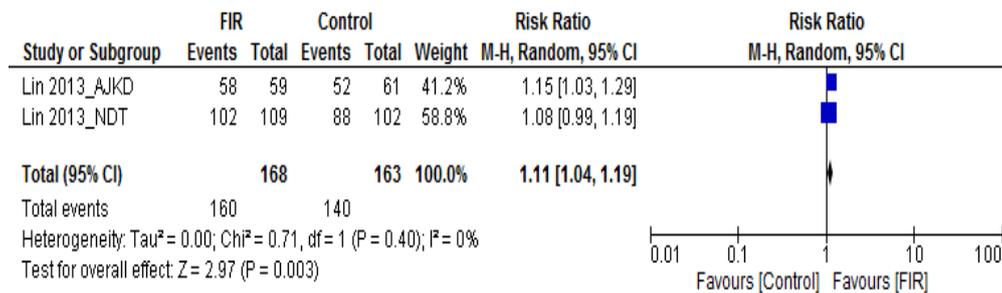
Figure 8.4: A Forest Plot showing Primary AVFs patency at 12 months, Lin et al RCT on new AVFs excluded (random effects):



8.3.5 Secondary - assisted - patency rates:

Data could be retrieved from two studies (331 patients) for the analysis of assisted (secondary) patency rates at 12 months following salvage procedures [198, 199]. In the FIR group, 160/168 patients had patent AVFs following intervention for dysfunctional fistulas, compared to 140/163 patients in the control arm. Pooled results showed statistically significant difference favouring FIR therapy (Pooled risk ratio = 1.11 [1.04 - 1.19]; 95% CI, $p = 0.003$) [Figure 8.5]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.71$; degree of freedom (DF) = 1; $p = 0.40$; $I^2 = 0\%$).

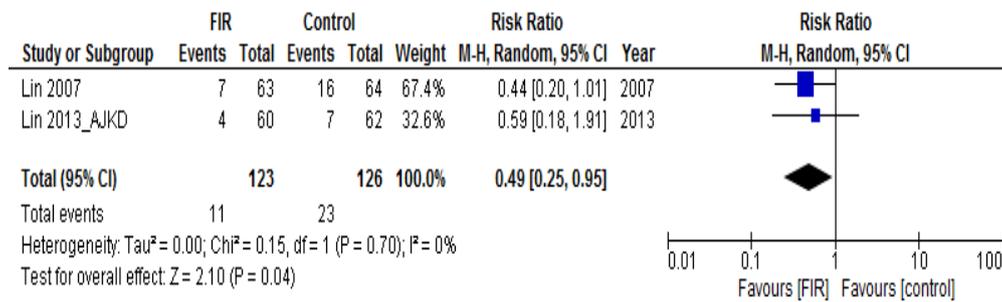
Figure 8.5: A Forest plot showing assisted patency rates at 12months (random effects):



8.3.6 Intervention:

Two studies [197, 198] (249 patients) reported the need for interventions to salvage dysfunctional fistulas. Patients who received FIR therapy required less interventions, 11/123 patients compared to 23/126 patients in the control group. The difference was statistically significant (Pooled risk ratio = 0.49 [0.25 – 0.985; 95% CI; p = 0.04] [Figure 8.6]. There was no evidence of statistical heterogeneity (Cochran's Q = 0.15; degree of freedom (DF) = 1; p = 0.70; I² = 0%).

Figure 8.6: A Forest plot showing surgical intervention for AVF malfunction (random effects):

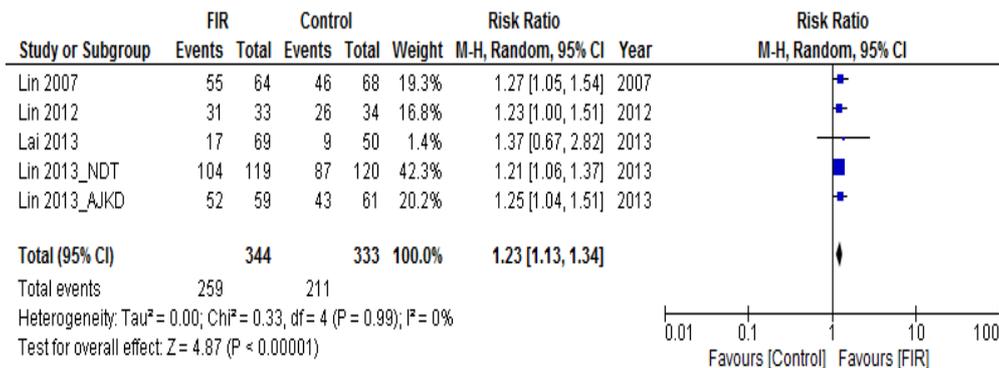


8.4 Discussion:

This review identified four studies (666 patients) which evaluated the use of FIR therapy to improve primary and secondary patency rates for AVFs in patients with ESRD. They all reported significant improvements in the outcomes assessed in this review in favour of FIR therapy. Three of those studies (490 patients) were carried out on patients that were already started on HD, and one study (122 patients) focused on pre-dialysis first time AVF maturation. All four trials were randomised, and the demographics of patients in the included studies did not differ significantly. Pooled analysis showed that primary (unassisted) patency was significantly better in the FIR group (pooled risk ratio of 1.23[1.12-1.35], p value of 0.0001). Secondary (assisted) patency was reported in two studies (279 patients) and was found to be significantly better in those who received FIR therapy (pooled risk ratio of 1.19[1.07-1.31], p value of 0.0008).

Post-conditioning using Far Infra-Red therapy has been shown to increase the level of heme oxygenase-1 (HO-1) expression that protects against Ischaemia/reperfusion injury in study by Tu et al [203]. HO-1 is a known vasodilator, and at the same time inhibits the proliferation of vascular smooth muscle cells, platelet aggregation, and vasospasm leading to favourable conditions for maturation of AVFs. In addition, Ikeda et al repeated thermal therapy was shown to up-regulate endothelial nitric oxide synthase expression in Syrian hamsters [190], a finding that was validated by Akasaki et al, who also reported increased angiogenesis via (eNOS) following repeated thermal therapy in mice with hind-limb ischemia. [204]. Kipshidze et al irradiated cultures of rabbit endothelial cells and smooth muscle cells with different doses of non-ablative infrared. They found that non-ablative infrared laser inhibited neointimal hyperplasia after coronary arteries angioplasty in cholesterol-fed rabbits for up to 60 days [205]. FIR therapy is still considered a novel treatment for AVF although the technique has been described since 2007 by Lin et al [197]. This review demonstrated a beneficial use of FIR therapy that improved both primary and secondary patency rates in all of the included studies. This statistically significant difference was consistent even when one excluded study for having only 3 months of follow-up was added to the sensitivity analysis [200] [Figure 8.7].

Figure 8.7: A Forest Plot showing Primary AVFs patency at 12 months (Study with maturation rate measured in 3 months added as a sensitivity test (random effects)) :



In addition, excluding the only RCT found by the authors on newly formed AVFs did not alter the outcome of the pooled analysis in terms of significance.

FIR therapy was also shown to improve access flow (Qa). The study by Lin et al, which was one of the RCTs included in this review, showed that 40 minutes of FIR therapy in a single HD session could increase access flow of AVF by about 50 mL/min. After one 1-year of follow up, FIR improved access flow (Qa) by up to 150 mL/min and resulted in increased unassisted patency of AVF by about 18% in comparison with controls [197]. Currently, the evidence behind when to stop the use of FIR therapy for dialysis fistulae remains vague; however, it seems most studies have used the technology for a period of at least 3 months, with 12 months being the average in published RCTs. More studies are required to determine if the positive effects reported from using the technology will be permanent after discontinuing the use of FIR, and if so, the time required achieving that. The studies published in this systematic review seem to suggest the continuous use of FIR in patients receiving HD.

A serious limiting factor of this systematic review is that the four RCTs came from the same institution (Yang-Ming University in Taiwan), and three of the four were authored by the same two authors (Lin-cc and Yang-wc) [197-199]. Dr Lin-cc reported that he was receiving lecture fees from WS Far Infrared Medical Technology, the company that makes the infrared machines used in the studies, thus raising the potential of bias, as there is a clear conflict of interest involved - although this has been declared by those authors on the published work relating to the studies. This group of authors are pioneers of using this technology in AVFs; however, the financial interest they stand to gain from promoting the use of the devices should always be kept in mind when considering the evidence published from their studies.

In addition, none of the included RCTs were blinded, which can influence outcomes as demonstrated by the fact that in one study nine patients opted to join the FIR group despite initially being allocated as controls. Blinding in clinical trials involving FIR therapy would involve additional costs in making machines that resemble the ones used to deliver FIR therapy. Those machines should be convincing to both staff and patients if effective double blinding is

to be considered. However, blinding can be attempted by placing a screen between the FIR device and the patient. In addition, double blinding can be achieved by placing a box over the device and then creating simple mock devices that also appear as boxes.

This review provides a thorough examination of published evidence supporting the use of FIR therapy to promote AVF access maturation in patients with ESRD in HD, and for those who are likely to require dialysis in the near future. The meta-analysis showed overwhelming support for the regular use of FIR therapy, however there were limitations that need to be considered. Future studies from outside China conducted by a different group of researchers, in particular ones without ties to the industry involved in making and promoting the technology remains lacking. A search of registered trials (clinicaltrials.gov) revealed two more studies on the effects of FIR on fistulae, however, they were both from China; therefore, they are bound to carry the same limitations in terms of the generalisability of their findings concerning the sample population and publication bias. Finally, this review may serve to guide future advances in using repeated thermal therapy in post-conditioning of AVFs.

8.5 Conclusion:

Results from four RCTs suggest that the regular use of FIR therapy in haemodialysis and pre-haemodialysis patients with ESRD (in particular those with AVFs) can positively influence access function. However, more blinded randomised controlled, multicentre and international clinical trials are required. In addition, the author of this thesis hopes to see sub-group analysis in those studies, particularly by age (e.g. using 65 as cut-off), gender and the diagnosis of hypertension.

DISCUSSION

IX Chapter Nine: Discussion

9.1 Introduction:

The number of patients with end-stage renal disease (ESRD) has been growing steadily, thus increasing the demand for haemodialysis (HD) [206, 207].

Arteriovenous fistula (AVF) has been shown to be the best route for delivering HD [1, 3, 4]. The main disadvantage of AVF is the relatively high rate of non-maturation, as the newly formed conduit needs to mature into a low resistance circuit, allowing frequent cannulation with increased flow rates.

There is no universal definition for a mature AVF; the one adopted in the updated NKF-KDOQI guidelines has been widely in use. KDOQI introduced the role of 6s to define maturation (Flow of 600 ml/min, an AVF located less than 6 millimetres from the skin surface to facilitate successful repeated cannulation by HD staff, and finally a minimal diameter of 6 millimetres) [4].

A mature fistula should be consistently cannulatable, and should allow blood flow of at least 300 to 400 ml per minute [100, 101]. This review summarises current knowledge about why so many fistulae fail to mature.

9.2 Patient characteristics: Sex, age and diabetes mellitus

Various patient factors have been suggested to be associated with poor AVF maturation, including diabetes mellitus (DM), female sex and old age. However, those factors are less important when preoperative ultrasound mappings show adequate size vessels. Preoperative US venous mapping has been proven to aid significantly the decision of placing an AVF that will have better odds of successful maturation [104, 167, 168].

Salmela et al, found that diabetes mellitus, female sex and thrombophilia were associated with decreased primary fistula patency rates [108]. Conversely, Sedlacek et al reported that diabetes was not found to be an independent risk factor for AVF non-maturation, and furthermore, the presence of diabetes had no effect on the prevalence of AVF creation [109]. Recently, Allon et al reported that both diabetes and age did not influence AVF maturation outcomes, although both were significantly linked to increased intimal hyperplasia [28].

Diabetes potentially exerts its influence on AVF maturation by affecting the bioavailability of Nitric Oxide (NO) as most of the metabolic abnormalities that take place in diabetic patients can disrupt the balance between production of NO and its degradation [208]. In addition, diabetes is a known risk factor for atherosclerosis, which can also limit blood flow through a newly created AVF. Overall, there is little evidence that diabetes influences AVF maturation; consequently, the rate of AVF formation in diabetics is similar to non-diabetics

Elderly patients (e.g. above 65 years) are thought to have worse patency rates [110, 111]. Lok et al argued that age should not be a limiting factor when considering vascular access options for HD as their study showed equal survival and secondary (salvage) procedural rates in patients above or under 65 years of age [101]. A study of cumulative access survival in AVF found that age, race, diabetes, gender and peripheral vascular disease did not show significant association with access survival [112]. The number of salvage procedures was the only significant factor associated with cumulative access

survival in this study, as more interventions were required in elderly patients to maintain patency [112]. In the very elderly with multiple comorbidities, consideration should be given to dialysis via central venous catheters (CVCs) as the primary access choice to reduce the surgical burden from repeated salvage procedures usually required to maintain patency.

Some studies suggested a significant negative association between female gender and fistula patency rates and prolonged maturation [108, 110, 158]. In addition, others have suggested that elderly female patients (65+) are at higher risk of fistula non-maturation than men [28, 111]. Recently, Bashar et al found that female gender, history of a kidney transplant and calcium channel blocker agents at the time of fistula creation all influenced AVF maturation, with non-maturation associated with a female gender in their series ($P = 0.004$) [130]. However, several studies disputed the association between female sex and a higher risk of AVF non-maturation [28, 112, 114].

Lee et al studied factors implicated in AVFs maturation. They found that race, diabetes, age, gender and peripheral vascular disease did not statistically influence the outcome, with the sole predictor of access cumulative failure being the number of secondary procedures required to maintain patency [112]. Feldman et al in a series of 348 HD patients found that non-maturation was associated with a previous history of stroke, transient ischaemic attack, increasing age and dependence on dialysis when the fistula was created [117].

In summary, there are papers suggesting that diabetes mellitus, female sex and increasing age among other factors can decrease fistula maturation and increase failure; however, other papers dispute this. Certainly none of these factors should influence the decision to proceed to AVF formation in these groups.

9.3 Pathophysiology of AVF non-maturation:

Maturation of the new AVF depends on variable biomechanical forces induced in the vascular system following AVF formation. Remodelling of the arterial limb is characterised by outward hypertrophic remodelling of the intimal layer leading to vessel dilatation; while at the venous side, the process can result in excessive intimal thickening resulting in narrowing of the venous limb [97]. This can lead to stenosis and early thrombosis, and eventually, non-maturation. The degree of intimal hyperplasia developing in a vessel depends on the length and depth of any (surgical) injury. It increases in proportion to direct injury to the smooth muscle layer[18]. In the absence of significant injury, wall stretch can lead to less marked smooth muscle cells proliferation [18, 23]. Intimal hyperplasia usually causes failure of fistulae in the long-term; however, it can also cause failure of primary maturation [209].

9.4 Timing of initial cannulation and previous access:

The NKF-KDOQI guidelines recommend allowing fistulae to mature for at least one month before cannulation [210]. Cannulation within 14 days of creation reduces long-term fistula survival, with a 2.1-fold increased risk of subsequent fistula failure compared to fistulae cannulated beyond 14 days [100]. No significant difference in non-maturation rates was observed in fistulae cannulated between 15 and 28 days compared to those used after 43 to 84 days [100].

Several studies have suggested that the use of a previous ipsilateral CVC to initiate HD is associated with higher primary failure rates for subsequent AVFs. Pisoni et al showed that both AVFs and grafts displayed better survival if used when initiating HD compared with being used after patients began dialysis with a catheter [103]. Rayner et al in a prospective observational study of 3674 patients found that the risk of AVF failure was increased for patients with a prior ipsilateral temporary access [100]. A review in 2004 of vascular access results from the DOPPS reported that tunnelled catheters pose a higher mortality risk than permanent access and are associated with increased risk of failure of a subsequent fistula [102]. CVCs can also result in central vein stenosis that will reduce the chances of AVF maturation if placed on the same side of a previous catheter. Contrast venography or other imaging should be performed preoperatively to evaluate the patency of central veins in patients with previous CVCs.

In general, AVFs created before patients start HD (i.e. pre-emptive) have higher primary patency rates compared to those created after the start of HD. Baldrati et al showed that AVF created prior to starting HD had 94.6% patency rate immediately and 72.2% in 2 years, compared to 86.5% immediately and 54.8% in 2 years in patients with AVF created after starting HD [211]. This can probably be explained by the influence of uraemia on the vascular response to the haemodynamic changes created by the formation of a new AVF; as well as the concern that early cannulation may occur in patients urgently needing dialysis without waiting long enough for their AVFs to mature.

9.5 Surgical Technique, site and ultrasound mapping:

Study by Saran et al looked into prospective data from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). They found that primary failure rate was 34% lower when the fistula was created by a surgeon who performed ≥ 25 AVFs in training, underlining the impact of surgical experience on fistula maturation [212]. This has been validated by other studies; therefore, AVFs should be performed by surgeons with sufficient experience in the field [213, 214].

In the interest of preserving “venous real estate” AVFs are usually created distally at the wrist, however distally created fistulae have a greater risk of non-maturation, are likely to require more interventions and are associated with inferior cumulative patency rates compared to those placed proximally [166, 215]. The siting of a new AVF should be based on preoperative vascular mapping. Preoperative ultrasound venous mapping has been proven to improve AVF maturation significantly [104, 167, 168]. A Forearm fistula can be placed in 40% to 50%, while 25% to 35% more fistulae can be placed in the upper arm in patients referred initially for AVF formation [6].

9.6 Vein Diameter:

Venous diameter is an independent predictor of maturation. A diameter < 2.5 mm is usually associated with non-maturation, particularly if the vein lacks distensibility following the application of a tourniquet, whereas successful maturation can be expected if the vein measures ≥ 4 mm in preoperative US assessment [141]. Lauvao et al reported in a series of 158 patients that vein diameter was the main independent predictor of functional maturation; also, vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis [119]. Mendes et al used the smallest cephalic vein diameter distally at the wrist to predict AVF maturation. Of the 22 fistulae that were created using a cephalic vein ≤ 2 mm, 19 failed to mature, whereas 19/25 (76%) fistulae successfully matured of those created using a cephalic vein diameter of > 2 mm ($P = 0.0002$) [80].

In the older patients, conservation of venous real estate is not such a priority. In the author's current institute, the practice is not to use a cephalic vein at the wrist that measures < 2.5 mm in elderly patients; instead, the aim should be to create a fistula at the elbow, or utilise a PTFE graft for brachio-axillary bypass. On the other hand, in younger patients using veins > 2 mm in the wrist seems reasonable.

9.7 Anatomic lesions within vessels:

Focal stenosis either at the anastomosis (juxta-anastomotic) or in the draining vein, presence of a large accessory vein and very deep fistulae are the three most common observed anatomic variations, with juxta-anastomotic stenosis being the most common [6, 7]. Lesions proximal to the cannulation site are classified as inflow stenosis, whereas those distal to cannulation are called outflow lesions. The KDOQI guidelines recommend that all fistulae should be monitored, and advised referral for a contrast fistulogram if flow was < 400 to 500 ml/min, or the derived static venous pressure (VAPR) - the ratio of venous access pressure to mean arterial pressure - was > 0.55 [1]. It needs to be highlighted that measuring the VAPR is intrinsically limited by design in detecting inflow stenosis as the pressure drops distal to the stenosis.

Venoplasty or surgical revision can assist maturation or salvage stenosed fistulae; accessory veins can be ligated and deep fistulae can be superficialised for better access [6, 216]. Planken et al in 2007 in small series of 15 patients found that accessory veins with a diameter $> 70\%$ of the cephalic vein diameter had a sensitivity of 80% and specificity of 100% of predicting non-maturation of AVFs, and they advised routine identification and surgical management of accessory veins [217]. Most anatomical causes of failure can be managed effectively with endovascular intervention, although this may be associated with higher restenosis rate which is thought to be due to intimal hyperplasia (IH) and remodelling of the AVF [218].

9.8 Far-Infra Red therapy:

Heat application by means of Far Infra-Red (FIR) therapy may enhance AVF maturation, improving both primary and secondary patency rates, as well as overall cumulative rates [196, 199]. FIR is a form of post-conditioning, which has been shown to increase the levels of Haeme Oxygenase-1 (HO-1) expression, a potent vasodilator and inhibitor of vascular smooth muscle cells proliferation as well as platelet aggregation and vasospasm [72]. This is delivered by a radiator that generates electromagnetic waves (5 to 12 μm); the device is placed 25 cm above the fistula site. Treatment sessions last for around 40 minutes, and are usually given three times a week [197]. Recently, a meta-analysis showed that FIR can positively influence fistula maturation with pooled unassisted patency rates significantly favouring the use of FIR therapy (1.23 [1.12-1.35], $p = 0.00001$); similarly, pooled secondary patency rates improved following FIR therapy (1.11 [1.04-1.19], $p = 0.003$) [97].

9.9 Brachio-Basilic AVFs:

An AVF formed by joining the basilic vein to the brachial artery is reserved for patients who cannot have a radio-cephalic or brachio-cephalic fistula. The basilic vein by nature of its deep anatomic position is often naturally preserved from repeated cannulation and as such less likely to suffer from stenotic lesions compared to other veins in the upper limb.

However once arterialised, it needs to be brought closer to the surface to allow for successful repeated cannulation; this can be achieved in either a one-stage or a two-stage procedure. A recent systematic review identified eight studies comparing one-stage to two-stage techniques [126]. There was no difference between the two groups in terms of the overall reported successful maturation (Pooled risk ratio = 0.95 [0.82, 1.11], 95% CI, P = 0.53).

9.10 Pharmacological manipulation:

Clopidogrel has been shown to significantly reduce the incidence of early AVF thrombosis; however it failed to increase the number of fistulae suitable for haemodialysis use in 3 to 4 months [219]. A randomised double-blind placebo controlled study of the effect of Clopidogrel on the early thrombosis of AVFs showed benefit, however both groups showed comparable maturation rates at the end of the study [220]. The use of Clopidogrel postoperatively in combination with an oral prostacyclin analogue (Iloprost) showed superior patency and maturation rates compared to placebo in a randomised controlled trial of 96 patients [221].

Antiplatelet therapy (Aspirin, Clopidogrel or Ticlopidine) when given for six months has been shown to reduce the risk of early thrombosis - within the first 6 months - of AVFs by nearly 50% in a meta-analysis [222]. There was also a reduction in the risk of early thrombosis even when antiplatelet therapy was given for six weeks.

One study showed that the use of a selective COX-2 inhibitor (Celecoxib) was associated with increased aortic blood flow and favourable vascular remodelling in rats with fistulae created between the abdominal aorta and the inferior vena-cava [223]. However, human studies are not yet available.

Statin therapy in patients with ESRD was associated with increased endothelial function and intimal hyperplasia, although patients with CVC who were on statin therapy had increased production and turnover of fibrin [224]. Another study did not find added benefits from statin therapy in terms of either improved patency rates or reduced rate of intervention [225].

9.11 Future Work:

9.11.1 Immunological manipulation:

Several agents have been suggested to modulate the formation of neo-intimal hyperplasia and favour fistula maturation. Nugent et al reported that veins treated with porcine aortic endothelial had a 2.8 fold increase in venous diameter and an 81% reduction in stenosis compared with controls after 28 days, by significantly reducing matrixmetalloproteinase-2 (MMP-2) in venous walls [226]. Gene therapy by means of Adenovirus-mediated vascular endothelial growth factor (VEGF-C) gene transfer has been shown to improve outcomes in post-angioplasty restenosis and reduction of vessel-wall thickening. This may be by activating pathways involved in increased production of nitric oxide (NO) and prostacyclin [227]. Similarly, Leppänen et al showed promising results in preventing intimal hyperplasia when the same gene therapy (VEGF-C gene) was coupled with an immunological treatment by means of platelet-derived growth factor (PDGF) antagonists [49].

In a double-blinded randomised placebo-controlled trial, the primary patency rate at one year was improved in the group that received a higher dose of PRT-201, whereas secondary patency rates were comparable across the groups [228]. Burke et al studied the effects of PRT-201 in the treatment of patients with atherosclerotic peripheral arterial disease; they found that it could increase arterial luminal area by increasing the arterial diameter through the degradation of elastin fibres. Conversely, Peden et al found no statistical difference between the placebo and the PRT-201 groups; furthermore, a subgroup analysis showed comparable patency rates between the different doses of PRT-201 in the study [229].

9.11.2 Markers of maturation:

AVF maturation is not completely understood. Inflammatory markers mediated through the release of Nitric Oxide play a role in vascular remodelling, which raises interest in the use of those inflammatory markers as predictors of fistula maturation, in particular the use of Matrix

Metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [6, 7, 230]. The release of MMPs in the patient serum at the time of fistula creation may serve as an important biomarker. Intervention aimed at controlling the release of NO pharmacologically or by use of short-term oxygen supplementation following creation of AVF can play a role in fistula maturation.

In summary, despite the magnitude of the clinical problem of primary and cumulative AVFs failure, there seems to be a lack of effective clinical, demographic and biological markers to predict the outcome of a newly formed AVF reliably [231, 232]. Vein diameter is a hugely important factor, arguably, the single most important predictor of maturation as fistulae created using veins of < 2 mm diameter are more likely to fail. Female gender, diabetes mellitus, age, arterial diameter, surgical technique and whether fistulae were created pre-emptively or after the start of HD can all be considered additional predictors of AVF maturation. Further studies are needed to evaluate emerging treatments, including molecular biological manipulation and FIR.

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APPENDICES

Appendix 1: Ethics Approval Form (Galway University Hospitals):



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive



Merlin Park University Hospital
Ospidéal na h-Ollscoile, Páirc Mheirlinne
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Main Administration Building
Merlin Park Hospital
Galway.

7th August, 2014.

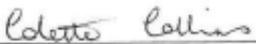
Professor Stewart Walsh
Consultant Vascular Surgeon
Department of Surgery
National University of Ireland
Galway.

*Ref: C.A. 1120 – An exploration of the relationship between serum metalloproteinases
MMP-2, MMP-9, metalloproteinase tissue inhibitors in patients and
arteriovenouse fistula maturation*

Dear Professor Walsh,

I have considered the above project, and I wish to confirm Chairman's approval to proceed.

Yours sincerely,

ff 
Dr. Shaun T. O'Keeffe
Chairman Clinical Research Ethics Committee.

c.c. Mr. Khalid Bashar, 24 The Swift Tassagard Greens, Garters Lane, Citywest, Co. Dublin.

Merlin Park University Hospital, OSPIDÉAL NA H-OLLSCOILE, PÁIRC MHEIRLINNE,
Galway, Ireland. Tel: 00 353 (0)91 757631

Appendix 2: Ethics Approval Form (University Hospitals Limerick):



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

HSE West,
Mid-Western Regional Hospital,
Dooradoyle,
Limerick, Ireland.

Tel: 00353 (0) 61 301111
Fax: 00353 (0) 61 301165
Website: www.hse.ie

21st October, 2013.

Mr. Khalid Bashar,
85 Lake Drive,
Kilminchy,
Portlaoise,
Co. Laois.

Re: Protocol Title
An exploration of the relationship between serum metalloproteinases MMP-2, MMP-9, metalloproteinase tissue inhibitors in patients and arteriovenous fistula maturation.

Dear Mr. Bashar,

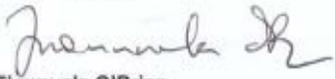
The Research Ethics Committee at the University Hospital Limerick has received a submission for ethical approval for the above study.

The following documents were reviewed and approved by the Research Ethics Committee:

| | |
|---|-----------------|
| <i>Application to the Research Ethics Committee</i> | <i>Approved</i> |
| <i>Patient Information Sheet</i> | <i>Approved</i> |
| <i>Research Participation Consent Form</i> | <i>Approved</i> |
| <i>Letter to GP</i> | <i>Approved</i> |

From an insurance perspective, please note that cover does not extend to those parties not employed by the Health Service Executive (HSE), or non-HSE Institutions.

Yours sincerely,



Fionnuala O'Brien,
Clinical Programmes Co-Ordinator,
(For and on behalf of the Research Ethics Committee & the Risk Management Department).

Appendix 3: Publication from the thesis “Pre-operative ultrasonography and arteriovenous fistulae maturation”:

JVasc Access 2014;15 (Suppl 7): S60-S63
DOI: 10.5301/jva.5000249

ORIGINAL ARTICLE

Pre-operative ultrasonography and arteriovenous fistulae maturation

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ABSTRACT

Background: Arteriovenous fistulae (AVF) are preferred for haemodialysis access, but maturation is unpredictable.

Results: Clinical examination alone is unreliable for AVF planning. Duplex ultrasonography may provide useful anatomical and physiological data to allow more accurate prediction of likely AVF success.

Conclusion: Selective use of duplex ultrasonography appears to enhance AVF success rates, but there are insufficient data to recommend routine duplex screening of AVF candidates. Agreed vessel criteria are needed.

Key words: Arteriovenous fistulae, Duplex ultrasonography, Haemodialysis

Accepted: March 5, 2014

INTRODUCTION

Arteriovenous fistulae (AVF) are the preferred mode of vascular access for dialysis. AVF formation is an operative vascular procedure, involving considerable resource utilization in terms of staff and theatre time. A considerable proportion of surgically created AVF fail to mature into usable dialysis access, with failure rates as high as 53% reported (1, 2). AVF maturation is a complex process. Formation of an AVF alters the biomechanical forces within the local vascular system, as flow is diverted from the artery and the venous limb is exposed to increased pressure. Maturation into a usable AVF depends upon obtaining sufficient flow within the AVF circuit. Flow is a function of the pressure gradient across the circuit and also the resistance within the circuit (3). Inadequate baseline flow in the arterial limb may thus impede fistula maturation due to an inadequate pressure gradient. Narrow diameter segments, stenoses and occlusions in the venous limb will result in an increased resistance within the circuit, also impeding AVF maturation. Duplex ultrasonography is a noninvasive and safe method of evaluating morphologic and functional vessel characteristics such as diameter, the presence of stenosis or occlusions or low arterial flow, which could identify proposed AVF circuits unlikely to successfully mature. Duplex is intuitively attractive for this role with several current guidelines recommending routine duplex mapping in advance of AVF formation (4).

CURRENT PRACTICE

Although recommended as a routine practice in some guidelines, there is no clear consensus regarding the role of pre-AVF duplex mapping. Traditionally, suitability for AVF formation was evaluated by clinical examination alone. Factors such as obesity and compromised vessels, for example previous cannulation or multiple previous access attempts, may render physical examination findings unreliable. Various imaging modalities have been evaluated as adjuncts to physical examination alone, with units developing selective imaging protocols for AVF candidates.

Patel et al initially screened patients by physical examination (5). If the examination findings did not identify any suitable vessels for haemodialysis access, the patients underwent duplex ultrasonography. If no suitable vessels were identified by ultrasound, or only a basilic vein was suitable, the patients underwent venography. They found that autogenous AVF formation in first-procedure patients increased from 66% to 83% using this protocol. Ultrasound was performed in two-thirds of the patients, while 32% underwent venography. The frequency with which imaging was used in this selective protocol underlines the limitations of clinical examination.

The reliability of clinical examination for AVF planning was evaluated in a recent prospective study (6). Patients attending a ‘one-stop’ AVF formation clinic were examined by a surgeon and a plan agreed for AVF formation. Each patient then underwent ultrasound examination

Bashar et al

by the surgeon using portable ultrasound equipment in the clinic. In total, the surgical plan was revised in 30% of patients following the ultrasound, with 10% of patients receiving a more distal AVF and 20% a more proximal one. Cumulative patency of 86% was achieved at 3 months post-procedure, although the study cohort was small (n=39 patients). Another small series (n=52 patients) also reported that ultrasound altered the surgical plan in 32% of patients planned on the basis of clinical examination alone (7). These findings further highlight the limitations of clinical examination alone and support the argument for routine imaging.

EVIDENCE FOR ROUTINE ULTRASONOGRAPHY

The effect of routine pre-AVF duplex mapping on subsequent AVF maturation rates was evaluated in a recent systematic review (8). The review included randomized trials of patients undergoing primary AVF formation who were assigned to either preoperative clinical examination as well as ultrasound or clinical examination alone. Pubmed and the Cochrane library were searched for relevant trials whilst conference proceedings from a number of relevant surgical conferences were manually searched for otherwise unpublished trials. The outcome for the review was successful use of the formed fistula for dialysis.

The systematic review identified three eligible trials, containing 402 patients (9-11). The results are summarized in Table I. Two hundred and fourteen patients randomized to ultrasound underwent surgery, of whom 174 successfully used their fistula for dialysis. Of the 188 patients assessed by clinical examination alone, 130 subsequently used their fistula for dialysis. Two trials reported that duplex improved successful AVF formation (9, 10) while the remaining trial reported no benefit (11). When the data were pooled for meta-analysis, there was no clear benefit for routine duplex (pooled odds ratio 1.96; 95% confidence interval 0.85-4.50; p=0.12) (8).

The review has a number of limitations. Random sequence generation and allocation concealment were

clearly reported in only one of the included trials (9), introducing a possibility of selection bias. It was also not possible to clearly establish that all outcome data had been collected and reported in most of the trials, leading to risks of attrition bias and reporting bias (8). The ultrasonographic criteria used to determine suitability for AVF formation differed between the trials, with a variety of arterial and venous criteria utilized (8). None of the trials included an economic analysis.

ULTRASONOGRAPHIC CRITERIA

The variability in ultrasound criteria found between the trials reflects clinical practice, with no clear consensus regarding minimal acceptable arterial or venous characteristics. Some of the criteria used in the literature are summarized in Table II. The optimal cut-off for arterial diameter with respect to AVF maturation and adequacy for dialysis is unknown and difficult to establish given the confounding influence of arterial disease elsewhere in the arterial tree. Using an arterial lumen diameter of at least 2 mm on ultrasound resulted in 92% of radiocephalic AVF maturing (12). Several studies suggest using a lower radial arterial diameter cut-off. Early failure has been reported in all AVF formed using radial arteries less than 1.6 mm diameter (13). Malovrh reported the results from 35 patients who underwent duplex mapping prior to AVF formation. Among patients with an internal arterial diameter less than 1.5 mm, immediate patency of the AVF was present in 45% (5/11) compared with 92% (22/24) for those with an internal diameter more than 1.5 mm (14). By 12 weeks, the AVF remained patent in only 36% of those with an initial arterial diameter less than 1.5 mm. Another study of 21 patients reported that 45% of those with an arterial diameter below 1.5 mm immediately thrombosed, while all patients with an initial diameter more than 1.5 mm had patent AVFs at 12 weeks (15). Other ultrasonographic criteria have been investigated, for example intimal medial thickness (16) and reactive hyperaemia (17), but are not routinely available in many centres.

There are no agreed minimum venous diameter values that predict radiocephalic AVF maturation. Silva et al reported good outcomes using a cut-off of 2.5 mm with a tourniquet, reporting 83% functional primary patency at 1 year (12). Wong et al reported that all AVF failed if the venous diameter was less than 1.6 mm. These investigators reported no difference in the average venous diameter at the wrist between failed and successful fistulae, although the sample size was small (13). Mendes et al evaluated 44 patients undergoing wrist AVF formation. In this cohort, only 16% of patients with a maximum venous diameter less than 2 mm developed a successful AVF compared with 76% among the remaining patients (18). Day-to-day variation in vein diameters combined with examination

TABLE I - OUTCOMES IN RANDOMIZED TRIALS OF PREOPERATIVE ULTRASONOGRAPHY

| Author | Year | Routine preoperative ultrasound | | Control | |
|---------------|------|---------------------------------|--------------|---------------------|--------------|
| | | Operation performed | Fistula used | Operation performed | Fistula used |
| Mihmanli (10) | 2001 | 72 | 68 (94%) | 52 | 39 (75%) |
| Nursal (11) | 2006 | 35 | 23 (66%) | 35 | 23 (66%) |
| Ferring (9) | 2010 | 107 | 83 (76%) | 101 | 68 (67%) |

Pre-operative ultrasound and AVF maturation

TABLE II - ULTRASOUND PARAMETERS ASSOCIATED WITH SUCCESSFUL MATURATION

| Author | Year | Study type | Fistula type | Venous criteria | Arterial criteria |
|---------------|------|--------------------|-----------------------------------|-------------------------|--------------------------------|
| Silva (12) | 1998 | Prospective cohort | Brachiocephalic | Venous diameter >2.5 mm | Lumen diameter >2 mm |
| Wong (13) | 1996 | Prospective cohort | Radiocephalic | Venous diameter >1.6 mm | Diameter >1.6 mm |
| Malovrh (14) | 1998 | Prospective cohort | Radiocephalic | Not evaluated | Arterial diameter >1.5 mm |
| Mihmanli (10) | 2001 | RCT | Radiocephalic and brachiocephalic | - | Radial artery flow >200 ml/min |
| Nursal (11) | 2006 | RCT | Radiocephalic and brachiocephalic | - | Diameter >2 mm |
| Ferring (9) | 2010 | RCT | Radiocephalic | Diameter >1.6 mm | Diameter >1.6 mm |

conditions (ambient temperature, patient position) render it essential that veins be evaluated under optimal conditions with distensibility testing for apparently small veins (19). These factors complicate efforts to identify an optimal vein diameter to predict success.

CONCLUSION

Accurate prediction of success is essential to optimize the use of scarce haemodialysis access resources. Clinical examination alone is not sufficiently reliable to allow accurate AVF planning and some form of adjunctive imaging is needed. Duplex ultrasonography is widely available and noninvasive, although operator-dependent. Current data are insufficient to justify a policy of routine duplex

ultrasound for all AVF candidates, although a selective policy appears justified. Consensus regarding ultrasonographic vessel criteria for AVF formation is needed.

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Bashar et al

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Appendix 4: Publication from the thesis “Predictive parameters of arteriovenous fistula functional maturation in a population of patients with end-stage renal disease”:



RESEARCH ARTICLE

Predictive Parameters of Arteriovenous Fistula Functional Maturation in a Population of Patients with End-Stage Renal Disease

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Abstract

Introduction

With increasing numbers of patients diagnosed with ESRD, arteriovenous fistula (AVF) maturation has become a major factor in improving both dialysis related outcomes and quality of life of those patients. Compared to other types of access it has been established that a functional AVF access is the least likely to be associated with thrombosis, infection, hospital admissions, secondary interventions to maintain patency and death.

Aim

Study of demographic factors implicated in the functional maturation of arteriovenous fistulas. Also, to explore any possible association between preoperative haematological investigations and functional maturation.

Methods

We performed a retrospective chart review of all patients with ESRD who were referred to the vascular service in the University Hospital of Limerick for creation of vascular access for HD. We included patients with primary AVFs; and excluded those who underwent secondary procedures.

Results

Overall AVF functional maturation rate in our study was 53.7% (52/97). Female gender showed significant association with nonmaturation ($P = 0.004$) and was the only predictor for non-maturation in a logistic regression model ($P = 0.011$). Patients who had history of renal transplant ($P = 0.036$), had relatively lower haemoglobin levels ($P = 0.01$) and were on calcium channel blockers ($P = 0.001$) showed better functional maturation rates.

Conclusion

Female gender was found to be associated with functional non-maturation, while a history kidney transplant, calcium channel-blocker agents and low haemoglobin levels were all associated with successful functional maturation. In view of the conflicting evidence in the literature, large prospective multi-centre registry-based studies with well-defined outcomes are needed.

Introduction

The number of patients with end stage renal disease (ESRD) has been increasing steadily, a trend which is expected to continue; as a result, more patients are expected to require vascular access placement for haemodialysis (HD) [1,2]. A mature and functional arteriovenous fistula (AVF) is considered the best modality for HD access when compared to arteriovenous grafts (AVG) and central venous catheters (CVC) [3–5], however it is expected that approximately one third (20%–50%) of AVFs will fail to mature into useful access [6–8]. Although the chances for an AVF to fail are high, they should still be considered first in all patients planned to start HD sessions, and for the ones who have already started HD. Mortality rate has been shown to be significantly higher in those who dialyse first by means of tunnelled catheters, and at the same time, they are at increased risk of failure of subsequent AVF [7,9,10]. Arteriovenous grafts tend to have better primary patency rates compared to AVF [6,11,12], however AVFs last longer, and with the exception of those fistulas which fail to mature primarily, the cumulative patency (from formation to permanent failure) is superior to grafts; moreover, AVFs—once they fully mature—are less likely to require secondary procedures for vascular access salvage to maintain patency, including angioplasty, stenting or thrombectomy [6,13–16]. The 2006 updated NKF-KDOQI Guidelines recommend AVF prevalence of $\geq 65\%$ for patients undergoing HD [17]. Currently, the prevalence of AVF in those patients is around 80% in Europe and around 60% in the United States [7,10,18].

Certain patients' characteristics have been associated historically with poor AVF maturation rates, in particular female gender, age and diabetes. Conte MS et al published study of 31 patients who had AVFs created as part of their V-HEALTH trial. They found that diabetic patients had significantly lower patency rates in the 24 weeks of the follow-up period [19]. Similarly, Salmela et al reported that diabetes, female sex and thrombophilia were all associated with decreased primary fistula patency rates [20]. Conversely, Sedlacek et al in study of 195 patients reported that diabetes was not associated with AVF maturation (67% matured in the diabetic group vs. 62% in non-diabetic group); also diabetes did not influence the prevalence of AVF creation as 66% in diabetic group underwent fistula placement compared to 60% in the non-diabetic group [21]. More recently Allon et al found that both age and diabetes were not associated with increased non-maturation rates, although they were both significantly linked to increased medial fibrosis [22].

Another factor thought to be associated with AVF maturation is age. Elderly patients are traditionally thought to have worse patency rates and more likely to suffer from AVF non-maturation [23,24]. However, this has been disputed by other authors [8,25].

With regards to the association between gender variation, and AVF non-maturation, there have been conflicting results reported in published literature. Several studies suggested a significant correlation between female gender and decreased patency rates in AVFs, as well as prolonged maturation time before the fistula can be used adequately to sustain HD sessions

[20,23,26]. A combination of female gender and increased age (> 65) has been shown to be significantly associated with non-maturation when compared to men of the same age group [22,24]. However, several other studies found no significant association between female gender and high risk of AVF non-maturation [22,25,27].

Certain haematological findings have been implicated in the maturation process of AVF. Khavanin Zadeh et al in a prospective study of HD patients who were referred for first time AVF formation reported higher risk of AVF failure in those with haemoglobin level < 8 g/dl (RR = 1.41; $p = 0.01$) [28]. More recently, Yilmaz et al looked into the relationship between late AVF stenosis and neutrophil-lymphocyte-ratio (NLR) based on blood results obtained from chronic haemodialysis patients. They hypothesised that increased level of inflammatory markers will lead to increased number of AVF stenosis cases. They suggested that the mechanisms responsible for AVF stenosis might be similar to those involved in atherosclerosis disease [29].

The objective of this paper was to report our own findings from the last 7 years in a regional hospital situated in the Mid-Western area of the Ireland in relation to patients' characteristics and comorbidities that might affect the process of AVF maturation according to predefined outcomes. We aimed to test the hypothesis that certain patients' characteristics (age, gender and medical co-morbidities—diabetes in particular) affect the maturation of AVF. We also aimed to test the association between specific inflammatory markers (white cell count and neutrophils) and haemoglobin's level preoperatively with AVF maturation.

Methods

Patients

We performed a retrospective chart review of all patients with ESRD who were referred to the vascular service in the University Hospital of Limerick for creation of vascular access for HD. Three surgeons performed the procedures. The data-analysis was performed according to a predefined set of outcomes based on extensive search of the literature.

Inclusion and exclusion criteria

We included all patients aged 18 years or older who underwent formation of AVF in the upper limb between 2006 and 2013. Patients with multiple episodes, each episode was considered separately and data from the corresponding episode was recorded on our data sheet. We excluded patients that underwent salvage procedures to improve maturation, i.e. secondary maturation, as we analysed data related to primary functional maturation rates only. All patients who had prosthetic graft and/or tunnelled catheters as the only means for HD were excluded.

Data collection

After obtaining an ethical approval for the study from the research ethics committee and the risk management department of the regional Health Service Executive (HSE West), data for all included patients were extracted from their medical records. Patients were not asked to provide consents (written/oral), as all records were anonymised and data were de-identified prior to analysis and reporting of findings. Baseline demographic information, site and type of the AV fistula were retrieved from the medical records, whereas results of blood investigations were obtained from electronic records. Functional maturation was recorded from dialysis records.

Study's primary and secondary endpoints

We aimed to evaluate patients' characteristics that have been reported to be associated with AVF non-maturation in the literature following an extensive review of published evidence. We

used functional maturation in this study which was defined as successful use of the arteriovenous fistula for 6 consecutive sessions of HD, and this was obtained from dialysis records. The use of functional maturation defined as sustained HD sessions ≥ 6 for the evaluation of AVF maturation has been validated in the literature in several previous studies [30–32]. While this method is acceptable, particularly in retrospective studies assessing AVF maturation before the regular use of preoperative venous mapping and postoperative US scans—as the case with this study as most of our patients did not have postoperative US scans—we should however point to its inferiority compared to the definition recommended in the updated NKF-KDOQI guidelines, famously known as the rule of (6s) (flow of approximately 600 mL/min, less than 0.6 cm below the skin surface and a minimal diameter of 0.6 cm) [17]. Also, in the absence of postoperative imaging scans, it will be difficult if not entirely impossible to differentiate between non-maturation and mis-cannulation due to less experienced staff. At our hospital, new fistulas are looked after by senior dialysis nurses who are well experienced in cannulation of those fistulas, however, it should be emphasised that the US based definition for AVF maturation adopted by the NKF-KDOQI is superior to the one we used.

We examined the relationship between age, gender, diabetes, smoking, hypertension, hyperlipidaemia, history of steroids use, history of Calcium channel blockers at the time of the access formation and the history of previous dialysis access (AVF, AVG or CVC). Secondary endpoints were perioperative blood investigations (Haemoglobin, White cells count and Neutrophils count). We also recorded the aetiology behind ESRD whenever available from medical records.

Statistical analysis

Data were extracted and recorded on spread sheet using IBM SPSS version 22.0 [33]. Categorical data are expressed in true value and as percentages and were compared using the Pearson Chi-Square (χ^2) test, whereas continuous data were reported as mean \pm SD and compared using the independent sample t-test for normally distributed data, and the Mann-Whitney U when indicated by normality tests. Levene's test for equality of variances was used to determine the *p* value in t-test regression analysis for continuous data [34]. Data distribution of various predictor variables were assessed by means of histograms, Q-Q plots and box plots. Finally, a prediction model was calculated by logistic regression analysis using data from variables that have been suggested to correlate to fistula in the literature, as well as variables from our study with a *p* value of < 0.1 in bivariate analysis with functional maturation being the dependent (outcome) measure of analysis. We also performed an overall logistic regression test with all of the included variables in our study without restrictions in terms of the *p* value.

Results

The study included a total of 86 patients (all diagnosed with ESRD by their attending consultant nephrologists and referred to the vascular department for access creation) with 97 arteriovenous fistulas formed to serve as vascular access for HD sessions. The most common cause leading to ESRD was diabetes ($n = 37/97$; 38.1%) followed by congenital renal agenesis (8/97; 8.2%), hypertension (7/97; 7.2%) and ischaemic injury (6/97; 6.2%). Other diagnosis included vasculitis, hypercalcaemia and a number of autoimmune diseases. From the 97 AVFs included in the study, 68 (70.1%) were constructed in men while 29 (29.9%) were constructed in female patients. Age did not follow a normal distribution with regards to gender variation in our patients [Figs. 1 and 2]. Age of all included patients was (mean \pm SD) 60.9 ± 16.9 ; men aged 63.7 ± 14.8 with a median of 67 (22–86) while women aged 54.5 ± 19.6 with a median of 55 (21–81); this difference was statistically significant ($P = 0.012$) [Fig. 3]. Demographic data of

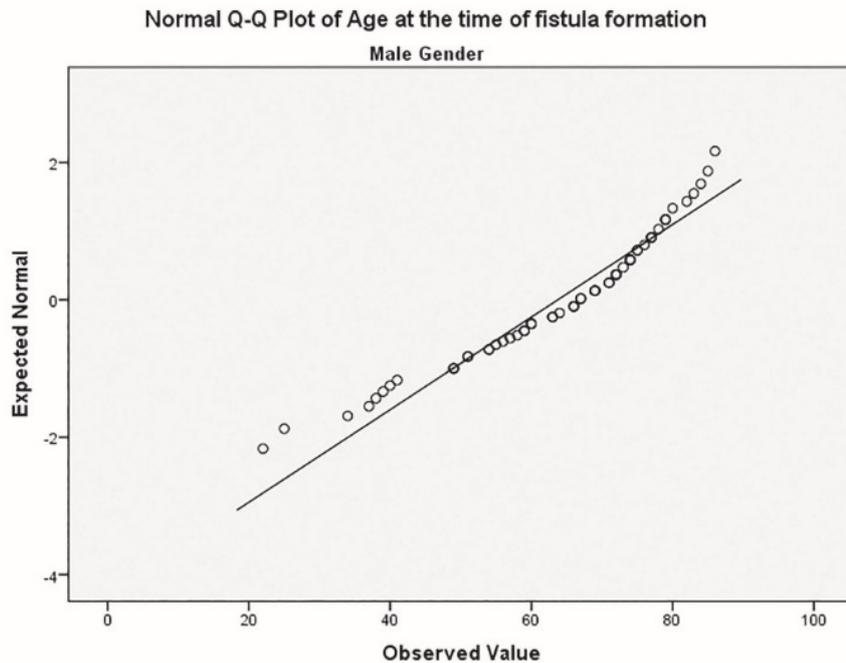


Fig 1. Age distribution among male patients.

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included patients along with comorbidities and drug therapy at the time of fistula formation are summarised in [Table 1], and summary of the continuous variables in our study can be found in [Table 2].

Patients' characteristics

Overall AVF functional maturation rate in our study was 53.6% (52/97). If we excluded the 9 patients that did not have sufficient information to confidently establish maturation according to the definition used from their medical records, the functional maturation rate was 57.6%.

We examined the relationship between different patients' characteristics, comorbidities and drug therapy and functional maturation in our patients using the appropriate statistical tests as outlined above; 40/59 (67.8%) fistulas matured in men while 9/26 (34.6%) matured in female patients; this difference was statistically significant ($P = 0.004$) suggesting female gender is associated with poor functional maturation. Age was not distributed equally among patients with a documented maturation outcome; however it was not found to be statistically associated with

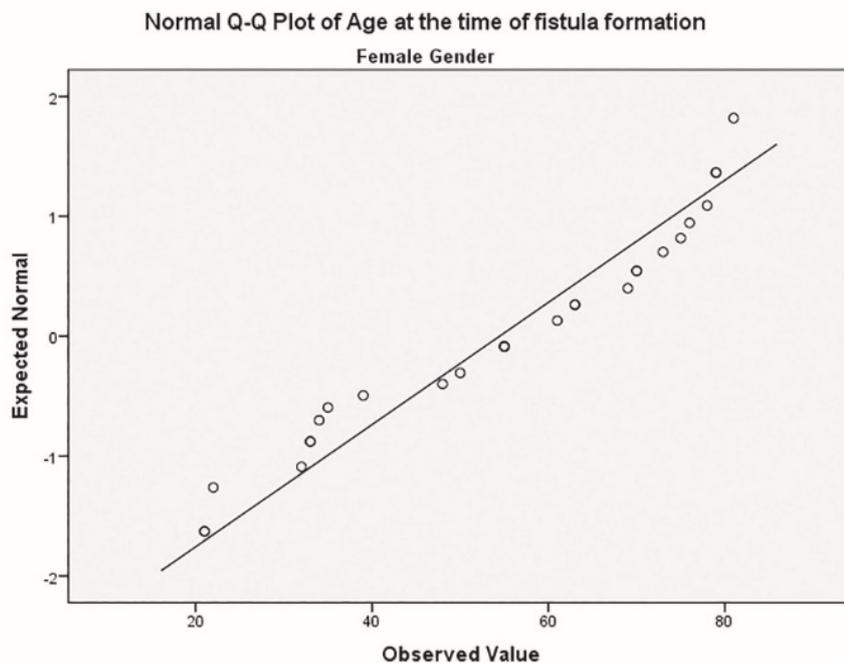


Fig 2. Age distribution among female patients.

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functional maturation as those who were found to have a functional access aged (62.4 ± 13.9) compared to (60 ± 20) in patients who could not dialyse from their AVFs ($P = 0.926$; Mann-Whitney U test) [Fig. 4]. Hypertension was diagnosed in 72 cases; 44 (61.1%) of those matured, whereas of the 13 cases who did not suffer from hypertension five (38.5%) fistulas matured ($P = 0.128$). Of the 34 fistulas with a positive diagnosis of diabetes 18 fistulas of those matured whereas 16 did not mature, compared to 31 and 20 respectively of the 51 patients who had a documented different aetiology for ESRD. The difference between the two groups of patients was not significant ($P = 0.473$). The use of Insulin for the treatment of diabetes also did not correlate significantly to functional maturation ($P = 0.839$).

Being on a calcium channel blocker at the time of fistula formation was significantly associated with a more favourable outcome as 21/25 patients on those medications had mature fistulas compared to 27/59 of patients who were not on calcium channel blockers ($P = 0.001$). There was no statistically significant difference in functional maturation if the patient was on Aspirin and/or Clopidogrel, or neither of the two drugs ($P = 0.617$). Previous history of HD was not found to be statistically related to functional maturation, as 37/60 functional AVFs

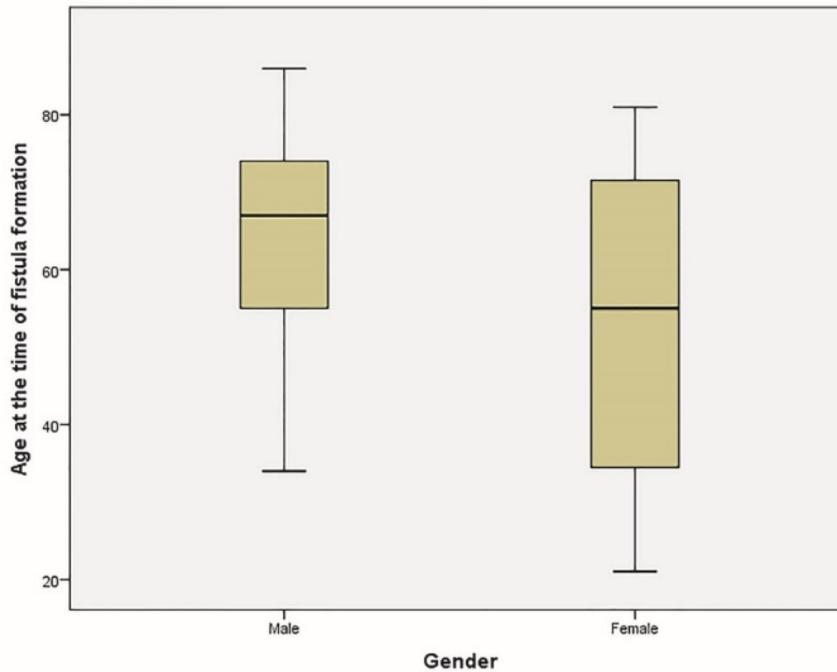


Fig 3. Variation in age between males and females groups.

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were created successfully in patients with previous access (AVF, AVG or CVC) whereas 12/25 non-mature fistulas were created in patients with previous access ($P = 0.245$), even when we performed separate analysis on those who only dialysed via tunnelled catheters, i.e. excluding AVF and AVG, the result remained insignificant ($P = 0.407$). Also, those who underwent a new fistula formation for a failed previous AVF did not do any worse or better in terms of functional maturation ($P = 0.530$). However, history of a previous kidney transplant surgery was found to be associated with better functional maturation ($P = 0.036$).

The site of the newly created AVF was not found to statistically influence the outcome of functional maturation in our study; of the 43 fistulas created around the wrist, 23 (53.5%) matured and 20 (46.5%) failed, compared to 26 (61.9%) and 18 (38.1%) of those placed in the forearm respectively ($P = 0.432$). The association between functional maturation and other categorical variables are shown in [Table 3].

Table 1. Characteristics of patients in study.

| Baseline characteristic | Frequency and percentage of the positive (yes) values | |
|-----------------------------------|---|-----------------|
| | Frequency (Observed %) | Valid %, N = 97 |
| Functional maturation | 52 (53.6) | 57.6 |
| Female gender | 29(29.9) | 29.9 |
| Male gender | 68 (70.1) | 70.1 |
| Diabetes | 40 (41.2) | 41.2 |
| Smoking | 30 (30.9) | 32.3 |
| Hypertension | 81 (83.5) | 85.3 |
| Hyperlipidaemia | 71 (73.2) | 74.7 |
| Coronary artery disease | 35 (36.1) | 36.8 |
| Atrial fibrillation | 15 (15.5) | 15.8 |
| Warfarin | 16 (15.5) | 15.8 |
| Congestive cardiac failure | 24 (24.7) | 25.3 |
| Insulin | 17 (17.5) | 18.1 |
| Calcium channel blockers | 30 (30.9) | 32.3 |
| Previous history of haemodialysis | 69 (71.4) | 73.4 |
| Dialysis through Venous Catheter | 64 (66) | 70.3 |
| Previous kidney transplant | 9 (9.3) | 10.1 |
| Previous Arteriovenous fistula | 21 (21.6) | 32.8 |
| Site of AVF: Wrist | 45 (46.4) | 50 |
| Site of AVF: Forearm | 45 (46.4) | 50 |

AVF = arteriovenous fistula.

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Preoperative blood tests

We also examined the relationship between functional maturation and a number of blood based investigations obtained within 24 hours prior to the time of access placement, we used (mean \pm SD) to report and compare our findings. Fistulas which were used successfully for HD had a haemoglobin level of (10.6 \pm 1.5 g/dl), platelets count (252.2 \pm 136.1 $10^9/L$), white cells count (7.6 \pm 2.2 $10^9/L$) and neutrophils count of (5.4 \pm 1.9 $10^9/L$) compared to (11.5 \pm 1.7 g/dl), (263 \pm 82.4 $10^9/L$), (8 \pm 2 $10^9/L$) and (5.5 \pm 1.8 $10^9/L$) in patients with non-mature fistulas respectively [Table 2].

Independent sample t-test analysis were performed to assess the relationship between each of the above blood investigations and AVF functional maturation in our study. We found that the most statistically significant predictor of functional maturation of laboratory variables was haemoglobin (P = 0.01) [Fig. 5]; with variances in both tests proven to be equally distributed in a Levene's test for equality of variances. Other blood investigations obtained preoperatively were not found to be independently associated with functional maturation [Table 4].

We performed two logistic regression analysis tests for study. The first test included all the variables in our study with a P value of < 0.1; this included gender variation, history of renal transplant prior to fistula construction, haemoglobin and a medical history of being on calcium channel blockers. The Omnibus test for model coefficients had a significant p value of < 0.001, the overall prediction accuracy of the model was 77.8% with the independent predictor for nonmaturation being a female gender (P = 0.04) and a history of calcium channel blockers (P = 0.034).

Table 2. Characteristics of continuous variables.

| | Age at creation of fistula | Urea (mg/dL) | Creatinine ($\mu\text{mol/L}$) | Haemoglobin (g/dl) | Platelets ($10^9/\text{L}$) | White Cells Count ($10^9/\text{L}$) | Neutrophils Count ($10^9/\text{L}$) |
|----------------|----------------------------|--------------|----------------------------------|--------------------|-------------------------------|---------------------------------------|---------------------------------------|
| Mean | 60.92 | 17.915 | 528.42 | 11.049 | 252.73 | 7.6639 | 5.3045 |
| Std. Deviation | 16.858 | 8.8747 | 260.563 | 1.6074 | 111.809 | 2.08253 | 1.82589 |
| Median | 66.00 | 16.800 | 448.00 | 11.000 | 234.00 | 7.2900 | 4.9400 |
| Minimum | 21 | 1.8 | 214 | 7.2 | 110 | 3.58 | 2.20 |
| Maximum | 86 | 45.4 | 1506 | 14.5 | 1007 | 14.04 | 12.11 |

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In addition to those variables, we performed a second multiple regression test and included variables that have been reported in the literature to be associated with fistula maturation, namely age, history of diabetes, smoking, hypertension, hyperlipidaemia, warfarin, congestive

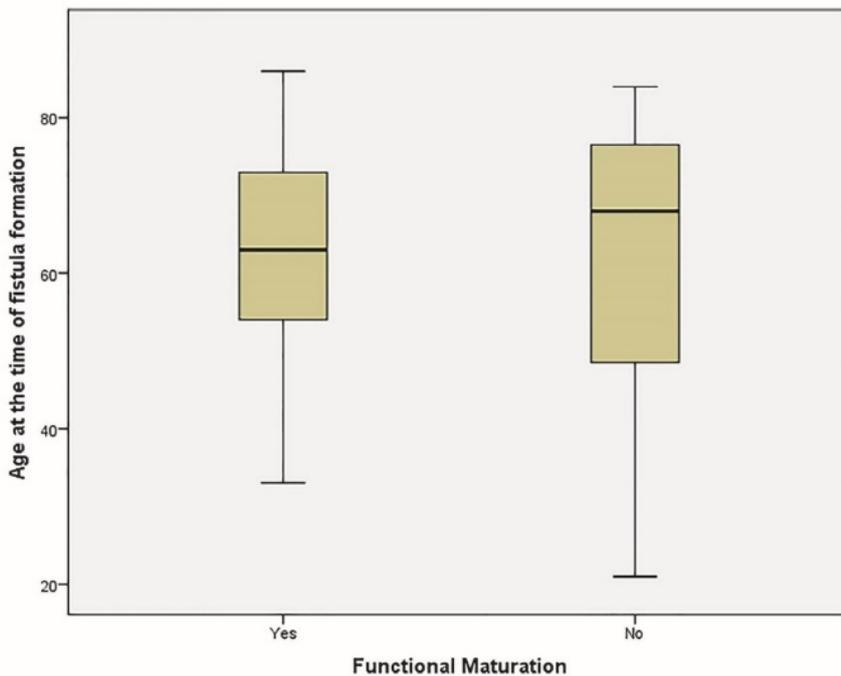


Fig 4. Variation in age between mature and non-mature AVF groups.

doi:10.1371/journal.pone.0119958.g004

Table 3. Categorical variables association with functional maturation.

| Variable | Functional maturation | N | % | P value |
|--------------------------------|-----------------------|----|------|--------------|
| Female gender | Yes | 9 | 34.6 | 0.004 |
| | No | 17 | 65.4 | |
| Male gender | Yes | 40 | 67.8 | |
| | No | 19 | 32.2 | |
| Diabetes | Yes | 18 | 52.9 | 0.473 |
| | No | 16 | 47.1 | |
| Smoking | Yes | 13 | 48.7 | 0.193 |
| | No | 14 | 51.9 | |
| Hypertension | Yes | 44 | 61.1 | 0.128 |
| | No | 28 | 38.9 | |
| Hyperlipidaemia | Yes | 38 | 57.6 | 0.980 |
| | No | 28 | 42.4 | |
| CAD | Yes | 17 | 54.8 | 0.691 |
| | No | 14 | 45.2 | |
| Atrial fibrillation | Yes | 8 | 66.7 | 0.495 |
| | No | 4 | 33.3 | |
| PVD | Yes | 10 | 58.8 | 0.913 |
| | No | 7 | 41.2 | |
| HD history | Yes | 37 | 61.7 | 0.245 |
| | No | 23 | 38.3 | |
| HD by central catheter | Yes | 35 | 61.4 | 0.407 |
| | No | 22 | 38.6 | |
| Previous AVF | Yes | 11 | 55 | 0.530 |
| | No | 9 | 45 | |
| Site of AVF: Wrist | Yes | 23 | 61.9 | 0.432 |
| | No | 20 | 38.1 | |
| Site of AVF: Forearm | Yes | 26 | 65.4 | |
| | No | 16 | 34.6 | |
| Renal transplant history | Yes | 8 | 88.9 | 0.036 |
| | No | 1 | 11.1 | |
| C ² channel blocker | Yes | 21 | 84 | 0.001 |
| | No | 4 | 16 | |
| Warfarin | Yes | 8 | 61.5 | 0.758 |
| | No | 5 | 38.5 | |
| Insulin | Yes | 9 | 60 | 0.839 |
| | No | 6 | 40 | |

CAD = coronary artery disease; PVD = peripheral vascular disease; HD = haemodialysis, AVF = arteriovenous fistula; AVF = arteriovenous fistula.

doi:10.1371/journal.pone.0119958.t003

cardiac failure, history of starting HD prior to AVF placement, history of dialysing through CVC, and history of an attempted AVF. Omnibus test for model coefficients had a significant p value of 0.016, the overall prediction accuracy of the model was 71.7%, and as in the first model, the only independent predictor for functional nonmaturation was a female gender ($P = 0.011$).

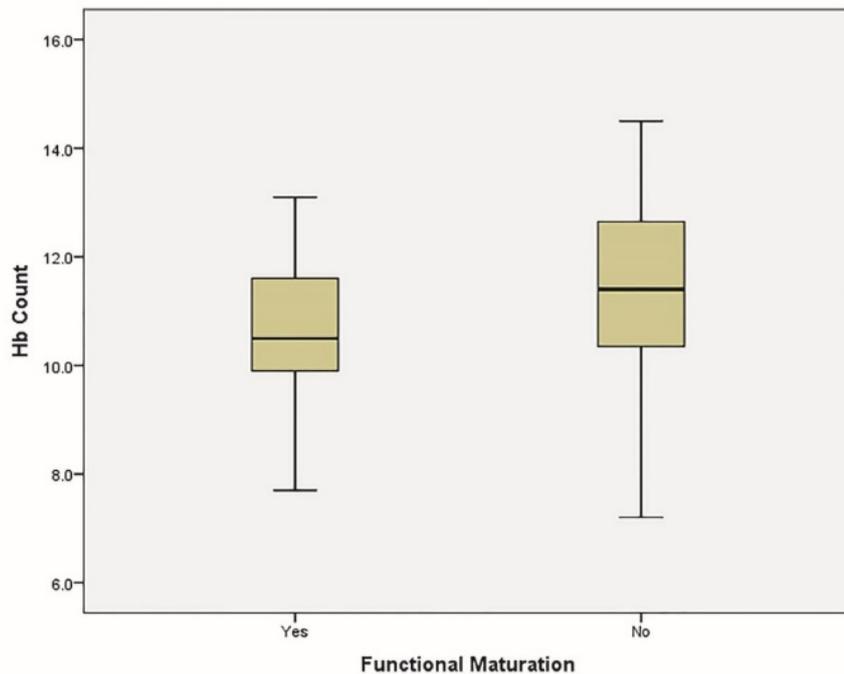


Fig 5. Variation in haemoglobin count between mature and non-mature AVF groups.

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Discussion

It has been established that a functional AVF access is the least likely to be associated with thrombosis, infection, hospital admissions, secondary interventions to maintain patency and death [15,16]. However, the process of AVF maturation is complex and remains poorly understood despite numerous studies looking into the pathophysiology of the process and bio-mechanical factors associated with maturation. Intimal hyperplasia (IH) has been identified as the main reason behind non-maturation in the newly formed arteriovenous conduit, it is the process of cellular proliferation within the inner most layer of the vessel resulting in remodeling of both the arterial and venous ends of the new fistula [35–37]; however factors influencing this process are yet to be fully elucidated.

Our study included a total of 86 who had a combined total of 97 fistulas. Functional maturation was achieved in 52/97 fistulas (53.6%), however we were unable to determine functional maturation from dialysis records in 9 patients, and as such, the observed maturation rate in

Table 4. Continuous variables (age and blood investigations) association with functional maturation.

| | Functional Maturation | N | Mean | Std. Deviation | P value |
|----------------------------|-----------------------|----|--------|----------------|--------------|
| Age at creation of fistula | Yes | 49 | 62.37 | 13.869 | 0.926 |
| | No | 36 | 59.97 | 20.029 | |
| Urea | Yes | 49 | 19.122 | 9.5929 | 0.243 |
| | No | 36 | 16.764 | 8.4825 | |
| Creatinine | Yes | 49 | 574.00 | 265.916 | 0.033 |
| | No | 36 | 458.31 | 209.047 | |
| Haemoglobin | Yes | 49 | 10.635 | 1.4720 | 0.010 |
| | No | 36 | 11.547 | 1.7039 | |
| Platelets | Yes | 49 | 252.24 | 136.058 | 0.676 |
| | No | 36 | 262.97 | 82.417 | |
| White cells count | Yes | 49 | 7.6110 | 2.21715 | 0.378 |
| | No | 36 | 8.0219 | 1.95970 | |
| Neutrophils | Yes | 49 | 5.3404 | 1.93037 | 0.899 |
| | No | 36 | 5.4625 | 1.80142 | |

doi:10.1371/journal.pone.0119958.t004

our study was 57.6%. Both percentages are in agreement with maturation rates reported in other studies [6–8]. Age did not follow a normal distribution in our study when explored against both gender and functional maturation using various normality tests provided by SPSS, however a Mann-Whitney U did not suggest an association between age and functional non-maturation. The functional maturation process in our study was statistically influenced by a female gender ($P = 0.004$), previous history of a kidney transplant ($P = 0.036$), patient on a calcium channel blocker at the time of AVF formation ($P = 0.01$) and haemoglobin levels. Out of those factors, functional non-maturation was associated with female gender and increased average of haemoglobin, while successful functional maturation was associated with a previous history of renal transplant and calcium channel blockers.

Logistic regression analysis test that included all the variables in our study that had a P value of < 0.1 ; (female gender, history of renal transplant, haemoglobin and being on a calcium channel blocker), showed that the only independent predictors for functional nonmaturation being female gender ($P = 0.04$) and a history of calcium channel blockers ($P = 0.034$), while the overall prediction accuracy of the model was 77.8%. Another model with the addition of other variables that have been reported elsewhere in the literature to be significantly associated with fistula functional maturation was performed; the overall prediction of this second model was 71.7%. The only independent predictor for functional nonmaturation was a female gender ($P = 0.011$).

Although old age (> 65) was shown to be significantly associated with non-maturation in previous studies [23,24], this however is by no means a consistent finding. Indeed many other authors found no association between age and maturation, including Renaud et al who reported similar maturation rates across all age groups in their study of 280 primary AVFs. In their study only female gender and a tunneled catheter were significantly associated with non-maturation [30]; we report similar findings with regards to age and gender, however, in our study a history of tunneled catheters was not associated with functional non-maturation. Also, Lok et al reported a comparable five years cumulative patency using 65 years as a cut-off point (64.7% in the ≥ 65 group and 71.4% in the < 65 group). They argued that age should not be a limiting factor when deciding which patients should have which vascular access procedure [8].

Those differences can be related to a different population, or confounding factors from other factors that might have influenced the maturation process.

We found that a lower haemoglobin level was associated with better functional maturation rates; we hypothesise that this might be explained by the up-regulation of endothelial Nitric Oxide Synthase (eNOS) in the newly formed conduit, leading to increased production of Nitric Oxide (NO) and Haeme Oxygenase-1 (HO-1) as a result of the relative hypoxia status caused by lower haemoglobin levels in the blood. NO is associated with vasodilation and decreased cellular proliferation [38], whereas HO-1 has been shown to inhibit proliferation of vascular smooth muscle cells, platelet aggregation, and vasospasm [3]. However, these are mere speculations and further studies aimed to specifically test the association of those markers and fistula maturation are needed. The significant association between calcium channel blockers and successful functional maturation is possibly mediated through the vasodilation effect commonly caused by most of those therapeutic agents.

Our findings contradict some of those reported by other authors. Nonmaturation in study by Feldman et al of 348 HD patients found was associated with a history of stroke, transient ischaemic attack, increasing age and dependence on dialysis when the fistula was created [39]. However, a study by Lee et al evaluated factors affecting cumulative access survival of AVF; they reported that age, race, diabetes, gender and peripheral vascular disease did not show significant association with access survival, with the only predictor of poor outcome being the number of salvage procedures; the higher number of secondary interventions required, the less likely for the fistula to last for a long period [25]. Those findings—with the exception of gender—were mirrored in our study.

Limitations of the study was the retrospective nature of data collection, missing data from medical records, certain continuous variables like age lacked a normal distribution pattern. It is important to mention that some of those fistulas deemed non-mature according to the criteria we used in our study—functional maturation—would have been patent on duplex scans and fistulograms, and certainly the variation in expertise among dialysis staff should be expected to have influenced our maturation rate.

Conclusion

While a retrospective study will inevitably suffer from inherent weaknesses in the methodology preventing it from sufficiently answering all questions concerning the association between demographic and haematological factors with AVF maturation, this paper would serve as a guide for future studies, as well as an up-to-date review of published evidence. Arteriovenous fistula maturation is a complex process with multiple factors involved (demographic, haematological and biomechanical). A female gender has been found to be associated with functional non-maturation, while a history of kidney transplant, calcium channel blocker agents and low haemoglobin levels were all associated with successful functional maturation. Logistic regression analysis showed that the only independent predictor of functional non-maturation was a female gender. In view of the conflicting evidence in the literature, large multi-centre registry-based studies with well-defined outcomes are required; however, other biomechanical factors that influence intimal hyperplasia should be considered as playing a leading role in AVF maturation.

Author Contributions

Conceived and designed the experiments: KB AZ DH MCM LC PB EK SRW. Performed the experiments: KB AZ DH MCM LC PB EK SRW. Analyzed the data: KB AZ SE DH SRW.

Contributed reagents/materials/analysis tools: KB AZ SE DH SRW. Wrote the paper: KB AZ SE DH PB EK SRW.

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Appendix 5: Publication from the thesis “The role of venous diameter in predicting arteriovenous fistula maturation: when not to expect an AVF to mature according to pre-operative vein diameter measurements? A best evidence topic”:

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Best evidence topic



The role of venous diameter in predicting arteriovenous fistula maturation: When not to expect an AVF to mature according to pre-operative vein diameter measurements? A best evidence topic

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ABSTRACT

This best evidence topic was investigated according to a described protocol. We asked the question: what is the minimal vein diameter that can successfully predict maturation of an arteriovenous fistula (AVF) in patients undergoing dialysis. Using the reported search 804 papers were found, of which five represented the best evidence to answer the clinical question. All studies assessed the association between successful AVF maturation and the size of vein used. The strongest evidence came from a nonrandomised controlled follow-up study in which 76% of fistulas created using >2 mm cephalic vein successfully matured compared to 16% when the vein measured ≤2 mm. Another prospective, multicentre study showed 65% successful maturation using veins >4 mm compared to 45% with veins <3 mm. Vein diameter was found to be an independent predictor of maturation in multivariate regression analysis in two retrospective observational studies. Another retrospective observational study found that using venous measurements of ≥2.5 mm following tourniquet application resulted in more fistulas being created that would have otherwise been denied based on venous ultrasound mapping. A large multicentre randomised clinical trial assessing the use of different vein sizes both with and without tourniquet application using proper statistical tools – such as receiver operating characteristic – is required to make a final recommendation. Until then, a vein diameter of <2.5 mm should be considered inadequate for formation of an AVF, particularly if those measurements remain unchanged following the use of tourniquet.

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1. Introduction

This best evidence topic was generated according to the structure outlined in the International Journal of Surgery [1].

2. Clinical scenario

In a regional hospital multidisciplinary team meeting, a patient with end stage renal disease (ESRD) is referred to the vascular service for formation of an arteriovenous fistula (AVF) before starting haemodialysis (HD). A preoperative venous mapping of the patient's left upper limb showed good measures for the arteries,

however the cephalic vein at the wrist is 2.5 mm, whereas it is 3 mm in the forearm. The operating surgeon feels an AVF at the wrist has a reasonable chance to mature, while another one argues a vein diameter <3 mm is highly predictive of maturation failure. You decide to review the literature for evidence.

3. Three-part question

In patients with [ESRD waiting to be started on HD], who are being [referred for AVF formation] with a preoperative venous mapping, what is [the minimum vein diameter] predictive of successful maturation?

4. Search strategy

We screened the Medline database and the Cochrane Central Register of Controlled Trials (up to June 2014) using the terms

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(([vein diameter] AND [arteriovenous fistula] AND ([maturation] OR [successful] OR [patent]) AND (OR [haemodialysis]) AND ([preoperative] OR [US] OR [Ultra Sound])). We restricted our search to English language and humans. No time restriction was applied. Studies that cross-matched preoperative vein diameter used to create AVF to successful maturation were included. Studies that did not correlate diameter of vein used to maturation were excluded.

5. Search outcome

Initial search produced 804 citations from Medline, and 11 trials from the Cochrane Central Register of Controlled Trials. Five studies provided the best evidence to answer the question (Fig. 1).

6. Results

3 retrospective observational studies, 1 non-randomised controlled follow-up study and 1 prospective multicentre cohort study were included in this BET article as shown in (Table 1).

7. Discussion

Arteriovenous fistula (AVF) has been established as the best modality for haemodialysis (HD) in patients with end stage renal disease (ESRD) [2–6]. AVFs has superior cumulative patency rates than arteriovenous grafts (AVGs) and lower incidence of thrombosis, stenosis, infection and hospital re-admissions compared to (AVGs) and central venous catheters (CVC) [7–10]. However, primary maturation failure remains the main disadvantage of AVF. Maturation of AVF depends on several biomechanical factors that

result in the formation of a low resistance conduit capable of dilation to accommodate increased blood flow required for successful HD sessions. One of the main predictors for maturation has been shown to be the diameter of the vein used in creation of the AVF.

Luavao et al. [11] assessed AVF maturation and functional maturation in 158 patients undergoing dialysis access formation. Only patients with first time fistulas were included, of those 88 patients had preoperative venous mapping assessing diameter, compressibility, depth and continuity. 111/158 fistulas matured (70%), with 71% maturation rate for those with preoperative US compared to 69% for those without preoperative US. In their univariate analysis, they found that fistula type and vein size significantly affected maturation ($P = 0.032$ and $P = 0.002$ respectively). Also, vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis ($p = 0.002$), a finding that was not affected when using the smallest or largest vein size for each anatomical region, however it was more significant with largest vein diameter (>4 mm). In their study, age, race, gender, body-mass index (BMI), diabetes, hypertension, smoking, time to referral, and dialysis through prior catheter placement had no effect on fistula maturation by univariate or multivariate analysis. The main limitation of this study is maturation in some cases was determined clinically by physical examination only, however 91% of clinically mature AVF achieved functional maturation.

Mendes et al. [12] performed a nonrandomised controlled follow-up study ($n = 44$) in patients undergoing formation of a wrist AVF who had preoperative venous mapping. They carried US venous assessment for diameter, compressibility, stenosis, anatomic variation, thickness and depth. They used the smallest cephalic vein diameter from the wrist to the proximal upper arm as a preoperative predictor of fistula maturation. They reported a successful maturation in 22 patients (50%), of those a cephalic vein ≤ 2 mm was used in 19 patients, with 3 (16%) showing functional maturation, whereas a cephalic vein >2 mm used in 25 patients with 19 (76%) showing successful maturation ($P = 0.0002$). Also, 3 AVFs with veins ≤ 2 mm matured successfully, while 6 AVFs had minimal vein measures >2 mm and failed to mature. The results did not include statistical tests for confounding factors such as age, gender, diabetes and obesity.

Feldman et al. [13] carried a prospective, multi-centre, cohort study in patients undergoing dialysis access formation ($n = 348$). They included adults (≥ 18) diagnosed with ESRD who were referred for having a first time AVF. Diameters of vessels at the anastomotic site was obtained by using a ruler after the vein had been collapsed or by US. Fistulas were performed by surgeons from the 12 participating hospitals, and only the first AVF was considered for analysis. Of their patients 228/348 had at least one use of their AVFs, and 193 patients met the definition for AVF maturation of the study. Maturation was associated with use of a large vein diameter ($P < 0.001$). Of note, thrill distance was significantly associated with maturation in the study (distance < 4 cm associated with 51% or less odds of maturation), and higher doses of heparin associated with higher rates of successful maturation. Also, Mean arterial pressure < 85 mmHg was associated with 48% reduction in odds of maturation. Main limitations of the study are having more than one surgeon performing procedures with expected variations in technique, equipment and experience. Also, they did not differentiate between non-maturation and thrombotic occlusion.

Lockhart et al. [14] retrospectively assessed access maturation in patients undergoing wrist RCAFV ($n = 73$) following recommendations by preoperative US. They had 2 groups in the study, Group (A), ($n = 28$) consisted of patients with pre-tourniquet

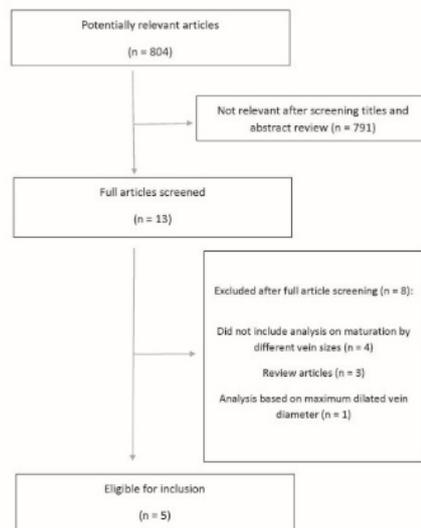


Fig. 1. A diagram summarising search results.

Table 1

| Author, date and country of research | Patient group | Study type and level of evidence | Outcomes | Key results | Comments |
|---|---|--|---|---|---|
| Luavao et al. [11], 2009 United States J Vasc Surg | Patients undergoing dialysis access formation between 2003 and 2007 (n = 158): PRAVF = 24 WRCAVF = 72 BCAVF = 62 Only patients with first time AVF were included. Preoperative venous mapping performed in 88 patients Patients with temporary dialysis catheter were not included | Retrospective, observational study, level IV evidence | Primary endpoints: - Fistula clinical maturation: adequate blood flow, ability of vein to dilate >6 mm, for a length of >10 cm and being <6 mm deep from surface - Fistula functional maturation: successful cannulation with ability to deliver 350–400 ml/min for 4 h session of HD | Vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis (p=0.002). This did not change when using mean, smallest or largest vein size for each region, although was more significant with largest (>4 mm) as follows: - PRAVF = 2/2 patients - WRCAVF = 15/18 - BCAVF = 29/28 Age, gender, diabetes and BMI had no significant effect on maturation. Fistula type (p = 0.032) and vein size on DUS (p = 0.002) significantly predicted maturation in univariate analysis. Patients with preoperative venous mapping had similar maturation rates to those who did not (71% vs 69%). | Maturation in some cases was determined clinically by physical examination only, however 91% of clinically mature AVF achieved functional maturation. Of the 9 that did not, 5 were never used due to death, transplant or renal preservation. Vein diameter was recorded using mean, smallest and largest for each anatomical region |
| Mendes et al. [12], 2002 United States J Vasc Surg | Consecutive Patients undergoing formation of a wrist AVF between 1999 and 2001 (n = 4448) Local or regional block Vein diameter obtained preoperatively using US Patients were removed from study for: Inadequate US mapping (n = 1) Died within 6 weeks of study (n = 1) Lost to follow-up (n = 2) | Nonrandomized controlled follow-up study, level III evidence | Primary outcome was fistula maturation defined as AVF used at 3 months from access formation Patients who were lost to follow-up or died within 3 months were excluded Smallest diameter of vein from the wrist to proximal upper arm was used as preoperative predictor for maturation | Successful maturation in 22 (50%) procedures Cephalic vein < 2 mm used in 19 patients, with 3 (16%) showing functional maturation Cephalic vein > 2 mm used in 25 patients with 19 (76%) showing successful maturation The difference between the 2 groups was significant (P = 0.0002, X ² test) 3 AVFs with veins < 2 mm matured (minimal vein diameter of 1.2 mm, 1.8 mm and 2.0 mm) 6 AVFs with minimal diameter > 2 mm failed to mature (vein diameter 2.1 mm–3.2 mm) | Small sample size First cannulation attempted by experienced dialysis nurse High failure rate for AVF maturation in this study Statistical analysis for possible confounding factors such as age, gender and diabetes were not included with the results. Cumulative patency rates following possible salvage procedures were not mentioned |
| Feldman et al. [13], 2003 United States Am J Kidney Dis | Patients undergoing dialysis access formation between 1994 and 1998 (n = 438) Inclusion criteria: Age > 18 with ESRD who underwent AVF formation. Only the first fistula was included Vein diameter obtained preoperatively using US or ruler after the vein has been collapsed | Prospective, multi-centre, cohort study, level III evidence | The main outcome was successful maturation defined as AVF used at least 6 successive times for HD. Patients followed for 3 months Did not differentiate between nonmaturation and thrombotic occlusion | 228/348 had at least one use of their AVF 29/23 patients met the definition for AVF maturation of the study Using a large vein diameter was associated with maturation (P = 0.001) Results by vein diameter (upstream): < 3 mm resulted in 45% matured AVF 3–4 mm resulted in 55% matured AVF 4–5 mm resulted in 58% matured AVF > 5 mm resulted in 65% matured AVF Thrift distance associated with maturation: distance < 4 cm associated with 51% or less odds of maturation Higher doses of heparin associated with higher rates of successful maturation Mean arterial pressure < 85% associated with 48% reduction in odds of maturation | Did not differentiate between nonmaturation and thrombotic occlusion Logistic regression analysis added to the rigor of this study as known confounding factors were considered |

(continued on next page)

Table 1 (continued)

| Author, date and country of research | Patient group | Study type and level of evidence | Outcomes | Key results | Comments |
|--|--|---|---|---|--|
| Lockhart et al. [14], 2006 United States J Ultrasound Med | Patients undergoing wrist RCAVF (n = 72), between 2003 and 2005 Group (A), (n = 28): patients with pre-tourniquet vein diameter > 0.25 cm Group (B), (n = 45): patients with pre-tourniquet vein diameter < 0.25 cm that increased to > 0.25 cm after tourniquet | Retrospective, observational study, level IV evidence | Primary outcome was fistula maturation: cannulated with >350 ml/min in at least 6 sessions in 1 month. Primary failure: early thrombosis if clotted within 12 weeks Failure to mature: patient, but not adequate for HD after 6 months | 26/71 (36%) AVFs were adequate for HD 27/64 (42%) could not be used for HD. Technical failure (n = 6) Early thrombosis (n = 23) Failure to mature (n = 18) 15/45 (33%) fistulas in group (B) [patients with pre-tourniquet vein diameter < 0.25 cm that increased to > 0.25 cm after tourniquet] used successfully for HD compared to 11/28 (39%) in group (A) [patients with pre-tourniquet vein diameter > 0.25 cm]. Difference between groups was not significant (P = 0.624), however, use of tourniquet resulted in more fistulas being created Men had higher overall fistula adequacy (50%) compared to women (39%), (P = 0.015) Arterial diameters were larger in those with adequate AVFs | Excluded 24 patients from the initial 97 patients from final analysis for not having a clear fistula outcome, which is a significant number and a concern for possible bias Only 36% of AVFs were deemed adequate for HD. This rate is lower than most studies. AVFs that were not adequate for HD were not analysed based on vein diameter measurements Assisted maturation rates for early thrombosis were not reported in the study |
| Maya et al. [15], 2009 United States Clin J Am Soc Nephrol | Patients who had Upper arm dialysis access (n = 678): BCAVF (n = 322) BBAVF (n = 67) Grafts (n = 289) Minimal vein diameter was >2.5 mm following application of tourniquet Fistulas cannulated after 6–8 weeks Immature fistulas underwent US assessment and appropriate salvage procedure Thrombectomy only attempted following successful cannulation for HD | Retrospective, observational study, level IV evidence | Primary outcome was fistula maturation defined as repeated successful cannulation with 2 needles for 1 month with blood flow > 300 ml/min Primary failure was defined as inability to use the fistula for dialysis due to early thrombosis or failure to mature Cumulative access survival calculated from access placement to complete failure | Primary access failure: 15%–18% in grafts and transposed BBAVF, whereas: 28% in BBAVF Multiple variable logistic regression analysis in patients with BCAVF showed only arterial and venous diameters predicted failure (P < 0.001) Mean venous diameter for BCAVF was (3.9 ± 1.0 mm) vs (4.6 ± 1.5 mm) for BBAVF Mean arterial diameter for BCAVF was (4.0 ± 0.9 mm) vs (5.1 ± 1.2 mm) for BBAVF The only predictors for primary failure in multiple variable logistic regression analysis were gender [Higher in females: (OR 0.54; 95% CI, 0.38 to 0.78, P = 0.001)] and access type [Higher for BCAVF vs BBAVF (HR 2.76; 95% CI, 1.41 to 5.38, P < 0.001)] BBAVFs had similar primary failure rates to grafts (HR 0.78; 95% CI 0.38 to 1.57, P = 0.48) Median cumulative access survival – including primary failures – was 1 year for grafts and BCAVF, and 2.7 years for BBAVF Excluding primary failures, cumulative survival was similar for BCAVF and BBAVF (3.4 and 4.1 years respectively), and 1.6 years for grafts. Gender and prior access were the only predictors for cumulative access failure when primary failures were included (P = 0.01), when primary failures were excluded, access type was the only predictor (P = 0.001) Access interventions among 3 groups: Angioplasty occurred at similar rates Thrombectomy similar between BCAVF and BBAVF, and much higher for grafts Surgical revisions were less common in BBAVF than BCAVF Annual rates of infection was <1% for BCAVF and BBAVF, and 10% for grafts. | Large number of patients Detailed logistic regression analysis Association between venous diameter and fistula maturation was provided as mean ± SD, but not broken into sub-groups according to different venous measurements (receiver operating characteristic analysis). |

AVF, arteriovenous fistula; PRAVF, posterior radiocephalic AVF; WRCAVF, wrist radiocephalic arteriovenous fistula; BCAVF, brachiocephalic arteriovenous fistula; BBAVF, brachio basilic arteriovenous fistula; HD, haemodialysis; DUS, duplex Ultra-Sound; BMI, body mass index.

vein diameter ≥ 0.25 cm, and Group (B), ($n = 45$) of patients with pre-tourniquet vein diameter < 0.25 cm that increased to ≥ 0.25 cm after application of tourniquet. Of the 73 patients who had known fistula outcome, 26/73 (36%) AVFs were adequate for HD, while 47/73 (64%) could not be used for HD. Group analysis showed there was no statistical difference in successful HD use of fistulas ($P = 0.624$), however, the use of tourniquet resulted in more fistulas being created, as those patients would have been denied the opportunity of AVF formation based on venous measurements without tourniquet. They also noted that men had higher overall fistula adequacy (50%) compared to women (19%), ($P = 0.015$), and arterial diameters in preoperative US scans were larger in those with adequate AVFs for HD. The study excluded 24 patients of the initial 97 from final analysis, and also lacked a separate analysis by vein size on AVFs that were not adequate for HD.

Maya et al. [15] retrospectively looked at patients who had Upper arm dialysis access ($n = 678$). Those included were brachiocephalic-AVF (BCAVF) ($n = 322$), brachiocephalic-AVF (BBAVF) ($n = 67$), Grafts ($n = 289$). Minimal inclusion criteria for AVFs were arterial diameter ≥ 2 mm and venous diameter ≥ 2.5 mm with absence of stenosis or thrombosis in the draining vein. Fistulas were performed by one of 5 surgeons, or by a trainee under supervision by staff surgeon. Brachiocephalic approach was considered first, if not suitable according to preoperative US, then a transposed brachiocephalic fistula was considered if suitable, otherwise, a graft. Multiple variable logistic regression analysis in patients with BCAVF showed only arterial and venous diameters predicted failure ($P < 0.001$), as the mean venous diameter for BCAVF was (3.9 ± 1.0 mm) vs (4.6 ± 1.5 mm) for BBAVF. Also, the only predictors for primary failure in multiple variable logistic regression analysis were gender [Higher in females (HR 0.54; 95% CI, 0.38 to 0.78, $P = 0.001$)] and access type [higher for BCAVF vs BBAVF (HR 2.76; 95% CI, 1.41 to 5.38, $P < 0.003$)]. The only predictors for cumulative access failure when primary failures were included in their study were gender and prior access ($P = 0.01$), when primary failures were excluded, access type was the only predictor ($P = 0.001$). This was a rigorously designed study however, it lacked a more detailed analysis (e.g.: receiver operating characteristic) on the association between vein size and AVF maturation, a test that was lacking in the rest of included studies as well.

8. Clinical bottom line

Improving maturation rates for AVF remains a challenging task due to the complex nature of the process and the multiple factors contributing to the maturation of those fistulas. However, the diameter of the vein used to create an AVF has been shown to be a consistent predictor for successful maturation. Having said that, there is still no agreement on the exact size of minimal venous diameter to confidently predict maturation, however evidence suggest it is between 2.5 mm and 4 mm. Also, routine use of tourniquet makes it possible to form AVFs in patients who otherwise would have been rejected. One study showed good results from using a transposed BBAVF when a BCAVF was deemed inappropriate following US [15]. A large multicentre randomised clinical trial assessing the use of different vein sizes both with and without tourniquet application using proper statistical tools - such as receiver operating characteristic - is required to make a final recommendation. Until then, a vein diameter of < 2.5 mm should be considered inadequate for formation of an AVF, particularly if those measurements remain unchanged following the use of tourniquet,

i.e. lack of venous distensibility.

Ethical approval

None.

Financial support

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Author contribution

K B, M C-M, M W, SR W: Study design.

K B, SR W: Data collection.

K B, M C-M, P B, E K, M W, SR W: Data analysis, writing and revision.

Conflicts of interest

None.

Guarantor

None.

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Appendix 6: Publication from the thesis “Can a Neutrophil-Lymphocyte Ratio derived from preoperative blood tests predict Arteriovenous Fistula Maturation?”



Can a Neutrophil–Lymphocyte Ratio Derived from Preoperative Blood Tests Predict Arteriovenous Fistula Maturation?

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Background: To evaluate the association between inflammatory markers expressed as neutrophil–lymphocyte ratio (NLR) and process of arteriovenous fistula (AVF) maturation.

Methods: A retrospective review of patients with end-stage renal disease referred for formation of a new AVF in one center. Patients referred to the vascular service in the University Hospital of Limerick for creation of vascular access between 2009 and 2013. The association between NLR, calculated from preoperative blood tests, and functional fistula maturation, as determined by successful use of the AVF for 6 consecutive hemodialysis sessions, was investigated using univariate and logistic regression analyses. A logistic regression analysis was carried out to assess potential influence from other factors related to AVF maturation. Stepwise regression test was performed including the NLR.

Results: Overall AVF functional maturation rate in our study was 53.7% (66/123). Patients with matured AVFs had an NLR of 4.850 (1.8–15.7) compared with 3.554 (1.7–15.0); this difference was found to be significant ($P = 0.024$). Female gender ($P = 0.008$) and a history of kidney transplant ($P = 0.004$) were the only independent factors of fistula maturation outcome in a logistic regression model.

Conclusion: Increased level of NLR was found to be associated with fistula maturation; however, more studies are needed to validate this finding.

INTRODUCTION

The increase in the incidence of patients diagnosed with end-stage renal disease (ESRD) is expected to strain the limited resources for hemodialysis (HD) in many hospitals.^{1,2} An arteriovenous fistula (AVF) is the best modality for HD; its superiority

has been shown and is well established in the literature.^{3–8} Therefore, it is important to give patients with ESRD the best chance of having a functioning AVF by the time they start HD. A well-functioning AVF capable of meeting the demands of repeated cannulation and maintaining enough blood flow through the formed conduit to successfully complete HD sessions is associated with less incidence of complications such as infections at the site of the fistula, sepsis, recurrent hospital admissions, and access-related deaths.^{3,9,10} The main disadvantage of an AVF is the high rate of primary failure—up to 50% in some studies.^{11–13}

An assessment of the relationship between AVF maturation and the inflammatory response at the time of creation of that fistula might provide a fast, cheap, and readily available tool to predict stenosis and therefore nonmaturation. This can help guide early intervention and preemptive angioplasty

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procedures to improve maturation rates. Fewer variables are required to calculate the neutrophil–lymphocyte ratio (NLR) compared with the use of more complex prediction models based on several factors with conflicted associations with maturation failure in the literature. Access failure secondary to stenosis and/or thrombosis is thought to be related to intimal hyperplasia (IH), a poorly understood phenomenon with several hematological and hemodynamic factors implicated in the pathophysiology of IH.^{14,15}

The systemic inflammatory response involves changes in the level of the circulating components measured in a full blood count test, namely neutrophils and lymphocytes. Neutrophilia has been shown to be associated with a relative lymphocytopenia.^{16–18} NLR has been suggested as a simple alternative to measure the systemic inflammatory response to surgical stress, systemic inflammation, or sepsis in critically ill patients.¹⁹ The utility of the NLR in predicting stenosis in AVFs has been previously tested in chronic HD patients.¹⁵ They found that their patients who were diagnosed as having AVF stenosis had a higher mean \pm SD (standard deviation) NLR (3.47 ± 0.46) compared with those with patent fistula (2.27 ± 0.22), this difference was significant ($P < 0.001$). Similarly, Yigit et al.²⁰ found that Pentraxin 3—a rapidly responsive acute phase protein—correlated moderately with NLR in patients with vascular access undergoing HD.

We hypothesized that inflammatory markers at the time of access formation are associated with the process of fistula maturation through increased production of hematological factors associated with increased levels of IH. Calculating the NLR at the time of AVF creation can predict the maturation outcome.

MATERIALS AND METHODS

Patients who were referred to the vascular unit in the University Hospital Limerick for formation of an upper limb AVF between 2009 and 2013 with a known fistula maturation outcome measured functionally in the HD unit were included in this study. Three surgeons performed the procedures. We included patients with a minimum age of 18 years. For those with multiple episodes of a new AVF formation, we considered each episode separately. All fistulae were created in the wrist or forearm.

Ethical approval for the study was obtained from the research ethics committee and the risk

management department of the regional Health Service Executive. We extracted all relevant data from the patients' medical records including electronic records for discharge notes and laboratory blood tests; all records were anonymized and data deidentified before processing.

Study Objectives and Definitions

We aimed to test the hypothesis that NLR—defined as the absolute neutrophils count divided by the absolute lymphocytes count—can predict fistula maturation. We calculated the NLR from blood tests obtained routinely on the morning of the fistula operation on all patients with the exception of inpatients who would have their routine blood tests done the evening before the procedure. We used functional maturation rate in this study, which was defined as the successful use of the AVF for 6 consecutive sessions of HD, and this was obtained from dialysis records. This method has been validated and extensively used in published literature.^{21–24}

We also aimed to evaluate the association between certain demographics (age, gender, diabetes, smoking, hypertension, hyperlipidemia, history of steroids use, history of calcium channel blockers at the time of the access formation, and the history of previous dialysis access) and functional AVF maturation as secondary end points. The etiology behind ESRD was also recorded whenever possible.

Statistical Analysis

Data were collected and recorded on spreadsheet; we used IBM SPSS version 22.0.²⁵ Categorical data are expressed in true value and as percentages and were compared using the Pearson chi-squared test. The independent sample *t*-test was used to compare normally distributed continuous data, which were reported as mean \pm SD; for abnormally distributed continuous data (reported as median and range), we used the Mann–Whitney *U*-test. Levene's test for equality of variances was used to determine the *P* value in the *t*-test regression analysis for continuous data.²⁶ Distribution of data was assessed by histograms, Q-Q plots, and box plots. The 5% level with a confidence interval of 95% was considered significant. A logistic regression test on the variables associated with fistula maturation was performed. In addition, stepwise regression test was performed on the same variables including the NLR.

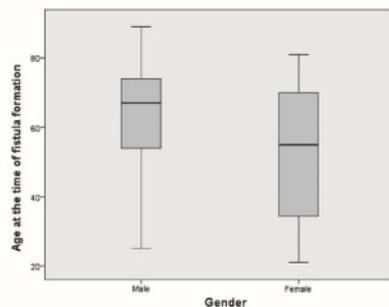


Fig. 1. A box plot showing age distribution per gender.

RESULTS

We included a total of 103 patients in this study with 123 AVFs, of which 88 were created in men (71.5%) and 35 in women (28.5%). Overall, 109 fistulae (66 in men and 43 in women) had known maturation outcome with 55/66 (84.8%) matured in men compared with 23/43 (53.5%) in women; this difference was significant ($P = 0.001$). The missing fistulae (14/123) belonged to patients who never started HD. The age of included patients (mean \pm SD) was 60 ± 17.6 and showed skewed distribution between men and women, as men aged 62.7 ± 16.3 with a median of 67 (20–89) while women aged 53.6 ± 19.3 with a median of 55 (21–81) (Fig. 1). The age difference between men and women was statistically significant ($P = 0.012$). The most frequent etiology behind ESRD was diabetes ($n = 42/123$; 37.4%) followed by congenital renal agenesis (11/123; 8.9%), hypertension (9/123; 7.3%), ischemic injury (8/123; 6.5%), polycystic kidney disease (7/123; 5.7%), and obstructive uropathy (7/123; 5.7%). The rest of the demographic data, comorbidities, and regular drug therapy at the time of fistula creation is shown in Table I. A summary of age and baseline blood results for all patients can be found in Table II.

The overall AVF functional maturation rate was found to be 53.7% (66/123); however, if we excluded the 14 patients who did not have a clearly identifiable maturation outcome in their medical records, the functional maturation rises to 60.6% (66/109).

Of our 123 fistulae, 55/78 (70.5%) matured in men compared with 11/31 (35.5%) in women; this difference was statistically significant ($P = 0.001$). Gender was the only demographic

Table I. Characteristics of patients in study

| Baseline characteristic | Frequency and percentage of the positive (yes) values | |
|--|---|---------|
| | Frequency (expected %) | Valid % |
| Functional maturation | 66 (53.7) | 60.6 |
| Female gender | 35 (28.5) | 85.5 |
| Male gender | 88 (71.5) | 71.5 |
| Diabetes | 46 (37.4) | 37.7 |
| Smoking | 40 (32.5) | 34.2 |
| Hypertension | 104 (84.6) | 86.7 |
| Hyperlipidemia | 89 (72.4) | 73.6 |
| Coronary artery disease | 46 (37.4) | 38 |
| Atrial fibrillation | 19 (15.4) | 15.7 |
| Warfarin | 19 (15.4) | 15.7 |
| Congestive cardiac failure | 29 (23.6) | 24 |
| Insulin | 22 (17.9) | 18.3 |
| Calcium channel blockers | 38 (30.9) | 31.9 |
| Previous history of hemodialysis | 84 (68.3) | 70.6 |
| Dialysis through venous catheter | 78 (63.4) | 67.2 |
| Previous kidney transplant | 18 (14.6) | 15.8 |
| Previous AVF | 26 (21.1) | 32.1 |
| Site of AVF: wrist | 60 (48.8) | 52.2 |
| Site of AVF: forearm | 55 (44.7) | 47.8 |
| Salvage procedures to maintain patency | 26 (21.1) | 30.2 |

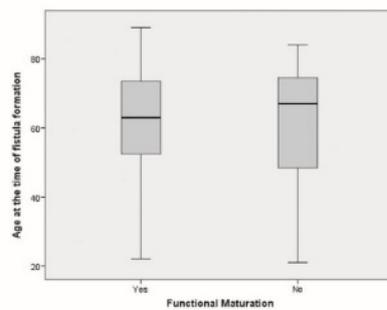
factor significantly associated with fistula outcome in this study. Age was not found to be significantly associated with maturation (patients with functional access had mean \pm SD age of 61.4 ± 16 compared with 59.1 ± 19.6 in patients with nonmature access; $P = 0.836$, Mann–Whitney U -test) (Fig. 2). Similarly, history of either diabetes or hypertension was not found to significantly influence fistula maturation (60% and 62% in patients with mature AVFs compared with 40% and 46% in those with failed access, $P = 0.976$ and $P = 0.249$, respectively). The rest of the association analysis between fistula maturation and patients' characteristics is shown in Table III.

Predictive Value of the NLR

The NLR (mean \pm SD) for all patients included in the study was 5.091 ± 3.091 , with a median of 4.263 and a range of 1.7–15.7. The NLR ratio was skewed when patients are grouped based on functional maturation (Figs. 3 and 4); therefore, we opted to report our findings as median (range) and used a

Table II. Characteristics of continuous variables

| | Age at creation of fistula | Hemoglobin (g/dL) | Platelets ($10^9/L$) | White cells count ($10^9/L$) | Neutrophils count ($10^9/L$) | Lymphocytes count ($10^9/L$) | NLR |
|--------------------|----------------------------|-------------------|------------------------|--------------------------------|--------------------------------|--------------------------------|--------|
| Mean | 60.19 | 11.085 | 244.77 | 7.6655 | 5.3478 | 1.270 | 5.091 |
| Standard deviation | 17.578 | 1.5575 | 105.092 | 2.08274 | 1.82714 | 0.5503 | 3.0709 |
| Median | 63.00 | 11.000 | 226.00 | 7.2850 | 4.9600 | 1.160 | 4.263 |
| Minimum | 20 | 7.2 | 96 | 3.58 | 2.20 | 0.4 | 1.7 |
| Maximum | 89 | 14.6 | 1,007 | 14.04 | 12.11 | 3.6 | 15.7 |

**Fig. 2.** A box plot showing age distribution per functional maturation.

nonparametric test (Mann–Whitney *U*) to calculate statistical significance. Patients with matured AVFs had an NLR of 4.850 (1.8–15.7) compared with 3.554 (1.7–15.0); this difference was found to be significant ($P = 0.024$). The NLR was calculated in patients who had clear maturation outcomes as per the functional maturation definition used in this study.

A logistic regression test that included all the variables found to be significantly associated with fistula maturation (age, gender, history of secondary intervention to maintain patency, history of taking a calcium channel blocker agent, hemoglobin level, and history of a previous kidney transplant) was performed. In this test, female gender ($P = 0.008$) and a history of previous renal transplant ($P = 0.004$) were found to significantly predict fistula maturation. When the NLR was added to the logistic regression model, female gender was the only significant predictor of outcome ($P = 0.006$). However, in stepwise regression analysis, the NLR was found to be the third predictor of maturation after female gender and a previous renal transplant ($P = 0.190$). A receiver operator curve for the NLR is shown in Figure 5.

DISCUSSION

Several studies have tried to establish a link between AVF nonmaturation and factors that will make it possible to predict the outcome of the newly created fistula. The process of fistula maturation is complex with several biomechanical factors involved to create a low resistance conduit capable of dilation to accommodate increased blood flow required for successful HD sessions.³ Prediction models based on patients' characteristics have been suggested^{27,28}; however, they tend to be complicated and are associated with both internal and external validity concerns considering the wide variations of independent measures used in those models. In addition, those models incorporate demographic data such as age, gender, and history of medical comorbidities, most commonly diabetes. The problem with that is the lack of universal evidence to associate fistula maturation with those factors. For instance, while many studies reported that a female gender was associated with fistula nonmaturation,^{29–31} others have disputed that association.^{32–34} Same can be said regarding age^{13,31,35} and the history of diabetes mellitus^{29,32,36,37} in pre-dialysis patients.

The use of vein diameter—and to a lesser degree, arterial diameter—has been tested as a predictor for fistula maturation with reasonable success. There is an increasing agreement that a minimal arterial diameter >2 mm and venous >2.5 mm should be considered as a cut-off point, as anything less than that is likely to be associated with nonmaturation.^{38–40} However, vein diameter will not predict nonmaturation in fistulae with adequate vessels based on preoperative venous mapping, but it remains a valuable predictive tool, in particular in choosing those who would require a basilic vein fistula.⁴¹ The results were not stratified by the size of vein diameter as most of our patients were done before we started using preoperative venous assessments routinely in our unit.

Functional maturation rate was 53.7% in our study, excluding 14 patients with unclear

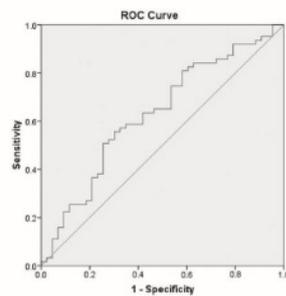


Fig. 5. Receiver operator curve for the utility of NLR in predicting maturation.

definition of functional maturation used in the study, compared with 55/66 and 23/43 in men, respectively; this difference was found to be significant ($P = 0.001$). Also, history of previous renal transplant ($P = 0.004$) was found to be associated with successful maturation ($P = 0.004$), whereas history of diabetes, hypertension, hyperlipidemia, smoking, steroids treatment, peripheral vascular disease, atrial fibrillation, warfarin, and history of a previous AVF were all not significantly associated with fistula maturation. Age also did not show a significant association with fistula outcome ($P = 0.836$; Mann–Whitney U -test).

NLR showed a significant value of $P = 0.024$ in a Mann–Whitney U -test because the distribution of NLR data in our patients when grouped based on the functional maturation outcome was abnormal. Patients with matured AVFs had an NLR of 4.850 (1.8–15.7) compared with 3.554 (1.7–15.0). Our findings suggest an association between proinflammatory markers and improved AVF maturation. We hypothesize that this finding could be explained by increased production of nitric oxide (NO) as part of a systemic response to inflammation. NO is a known vasodilator and is associated with decreased cellular proliferation³⁸; however, this remains speculative and more studies examining the relationship among inflammation, NO, and AVF maturation process are required. In addition, we need to highlight that our study was underpowered due to a relatively small sample size, and this could have affected our results.

The use of a simple, widely available test such as NLR has been shown to be beneficial in patients with other vascular abnormalities. Spark et al.

evaluated the use of the NLR to predict mortality in patients with chronic critical limb ischemia. They found that an elevated NLR along with a high troponin level (>0.1) was the only independent predictor of mortality in those patients.⁴² Also, in a study of 83 patients who underwent infrapopliteal percutaneous interventions for critical limb ischemia, Chan et al.¹⁵ reported that those with $NLR \geq 5.25$ had an increased risk of death (hazard ratio 1.97, 95% confidence interval 1.08–3.62, $P = 0.03$). Yilmaz et al.¹⁵ reported that in chronic HD patients with established AVF access, patients who developed late stenosis were found to have higher level of NLR. It is possible that the reversed NLR association seen in our study—successful AVF maturation more likely in patients with higher NLR—is due to differences in local response to proinflammatory markers between fistulae and bypass grafts in the lower limb. The NLR could be used to suggest those patients who are more likely to have poor outcomes from their newly created AVFs. Those patients may benefit from a follow-up ultrasound (US) test aimed to determine patency, possibly 6 weeks following postoperatively.

A logistic regression test that included all the variables found to be significantly associated with fistula maturation showed that only female gender ($P = 0.008$) and a history of previous renal transplant ($P = 0.004$) significantly predicted fistula maturation. NLR was not found to significantly predict fistula outcome when added to the regression model above, with female gender being the only predictor of outcome in the new logistic model ($P = 0.006$).

The main limitation of this article is the retrospective nature of the study and missing data from patients' medical records. Also, most of our old patients did not have routine postoperative US to determine patency and differentiate between primary failure and miscannulation. In addition, the lack of preoperative imaging makes it impossible to stratify our findings by vessel diameters as maturation failure could have been attributed to inadequate size of the vessels (artery and/or vein) used to create the fistula conduit. The site of the newly created fistula could also be a confounding factor as fistulae created more proximally around the elbow have better chances to mature than those created more distally at the wrist.

A maturation definition based on US measurements rather than functional maturation would have been better, and certainly prospective studies should opt for such definitions in particular the

one adopted by National Kidney Foundation - Disease Outcomes Quality Initiative.³⁹ In addition, a type 2 error due to the small sample size cannot be excluded.

CONCLUSION

NLR has not been found to independently predict AVF maturation in our study; however, the use of a functional maturation definition coupled with a relatively small size means more studies—particularly large prospective randomized controlled trials—are required to make a final recommendation on the utility of NLR in the prediction of AVF maturation.

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Appendix 7: Publication from the thesis “One-stage vs. two-stage brachio-basilic arteriovenous fistula for dialysis access: a systematic review and a meta-analysis”:



RESEARCH ARTICLE

One-Stage vs. Two-Stage Brachio-Basilic Arteriovenous Fistula for Dialysis Access: A Systematic Review and a Meta-Analysis

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Abstract

Introduction

A brachio-basilic arteriovenous fistula (BB-AVF) can provide access for haemodialysis in patients who are not eligible for a more superficial fistula. However, it is unclear whether one- or two-stage BB-AVF is the best option for patients.

Aim

To systematically assess the difference between both procedures in terms of access maturation, patency and postoperative complications.

Methods

Online search for randomised controlled trials (RCTs) and observational studies that compared the one-stage versus the two-stage technique for creating a BB-AVF.

Results

Eight studies were included (849 patients with 859 fistulas), 366 created using a one-stage technique, while 493 in a two-stage approach. There was no statistically significant difference between the two groups in the rate of successful maturation (Pooled risk ratio = 0.95 [0.82, 1.11], $P = 0.53$). Similarly, the incidence of postoperative haematoma (Pooled risk ratio = 0.73 [0.34, 1.58], $P = 0.43$), wound infection (Pooled risk ratio = 0.77 [0.35, 1.68], $P = 0.51$) and steal syndrome (Pooled risk ratio = 0.65 [0.27, 1.53], $P = 0.32$) were statistically comparable.

Conclusion

Although more studies seem to favour the two-stage BVT approach, evidence in the literature is not sufficient to draw a final conclusion as the difference between the one-stage and

the two-stage approaches for creation of a BB-AVF is not statistically significant in terms of the overall maturation rate and postoperative complications. Patency rates (primary, assisted primary and secondary) were comparable in the majority of studies. Large randomised properly conducted trials with superior methodology and adequate sub-group analysis are needed before making a final recommendation.

Introduction

The superiority of haemodialysis (HD) access created by means of an Arteriovenous Fistula (AVF) in patients with end stage renal disease (ESRD) has been shown before. Stenosis and thrombosis is less likely to occur in a well-functioning mature AVF when compared to arteriovenous grafts (AVG) and central venous catheters (CVC), resulting in prolonged patency rates for AVFs as has been described previously [1]. Also, AVFs carry a lower risk for infection [2,3]. However, around 20%–50% of all fistulas fail to mature into a useful HD access [4–7].

The preferred location for placing an AVF for the first time is distally at the radius, thus making it possible to place a second fistula proximally if the first one failed to mature. The order of preference for creating an AVF [8–10]:

1. Distal Radio-Cephalic
2. Proximal Radio-Cephalic
3. Brachio-Cephalic
4. Brachio-Basilic (transposed Basilic vein)

This order is in agreement with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines [11]. However, fistulas created distally at the wrist are less likely to mature compared to proximal AVF, at the same time proximal AVF require less intervention and are likely to last longer [12]. The decision of where to create the AVF can be helped by preoperative vascular mapping using ultrasound imaging which is expected to improve chances of creating an AVF that will likely mature into a useful dialysis access [13,14]. Placement of a primary forearm fistula is feasible in 40% to 50%, with an upper arm fistula possible in an additional 25% to 35% of patients [15]. An AVF prevalence of $\geq 65\%$ has been recommended in the KDOQI guidelines for patients undergoing HD [11], this prevalence is currently higher in Europe (67%–91%) compared to the US (24%–47%) [15–18]; however, the prevalence of AVFs in the US varies significantly among different dialysis units [15,19].

Dagher was the first to describe the use of basilic vein to create an AVF in the upper arm between the end of basilic vein and the side of the brachial artery to act as access for long term haemodialysis [20]. Since then, the procedure has seen several changes and modifications. Superficialisation of a brachio-basilic fistula to make it more susceptible to cannulation can be achieved either by an elevation technique without mobilisation to bring the vein superficial to the surgically reconstructed deep fascia and subcutaneous tissue in the anatomic location of the basilic vein [21], or by a transposition technique by mobilising the entire length of the basilic vein to position the vein anterolaterally through a subcutaneous flap [22].

Some of the debate surrounding brachio-basilic arteriovenous fistulas (BB-AVF) has been focused on the decision to choose between one-stage vs the two-stage techniques. The one-stage procedure aims to create a fistula between the basilic vein and the brachial artery in the upper arm in one procedure. This would require a long incision to gain access and mobilise the basilic

vein making sure the anastomosis is not placed under tension and no obvious stenosis is present proximally. The main advantage of this technique is the shorter waiting time required to cannulate the fistula. Also the one-stage will prevent the patient from having to undergo another procedure and is more cost effective as hospital resources will be used only once. One of the main disadvantages of this technique is the long incision which will require a longer time to heal and also carries a higher risk for wound-related complications. Also the procedure takes longer and is more demanding [23–25]. Moreover, in a study by Anaya-Ayala et al assessing the anatomy of basilic vein found that only 66% of patients are expected to have a “normal” basilic vein entering one of two paired brachial veins close to the axilla, while up to 34% will have an “abnormal” variant that would negatively influence the newly created fistula maturation [26].

The two-stage procedure allows the basilic vein to become arteriased and as such, more resistant to torque and will become easier to mobilise in the second procedure as it gets transformed into a bigger and stronger structure. The hope is that operative difficulty and complications would be reduced with improved patency rates [27].

This review was designed to systematically assess the difference between both procedures in terms of access maturation and survival, as well as complications and interventions required to maintain patency for haemodialysis.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [28]. No published protocol exists for this review.

Eligibility criteria

We searched for randomised controlled trials (RCTs) and observational studies that compared the one-stage technique with the two-stage technique for creating a brachiobasilic arteriovenous fistula (BBAVF) for haemodialysis access. Case series and review articles were excluded from this review.

Search strategy

A search of the literature for relevant studies was conducted in August 2014 using the following terms: (“Basilic Vein” OR “Basilic”) AND (“Fistula” OR “Arteriovenous” OR “Access”) AND “dialysis”. We searched the online databases of Medline, CINAHL, EMBASE, the Cochrane library and Google Scholar. We did not restrict our search by publication date or status, however, we only included studies published in English language and those conducted on humans. We also searched the bibliographies of included trials for additional studies. A summary of the study selection process can be found in the PRISMA flow diagram below [Fig. 1]. Studies were not restricted based on the duration of follow-up.

The main outcome measures for this review were successful maturation and development of postoperative complications, namely wound haematoma, wound infection and steal syndrome. Secondary outcomes were primary and secondary patency rates. Definitions for “maturation”, “primary patency” and “secondary patency” were those specified in individual studies.

Data collection

KB and DH independently extracted the data from included studies on a Microsoft Excel spreadsheet. Any differences in recording the outcomes of interest were discussed between two

Fig 1: PRISMA 2009 Flow Diagram

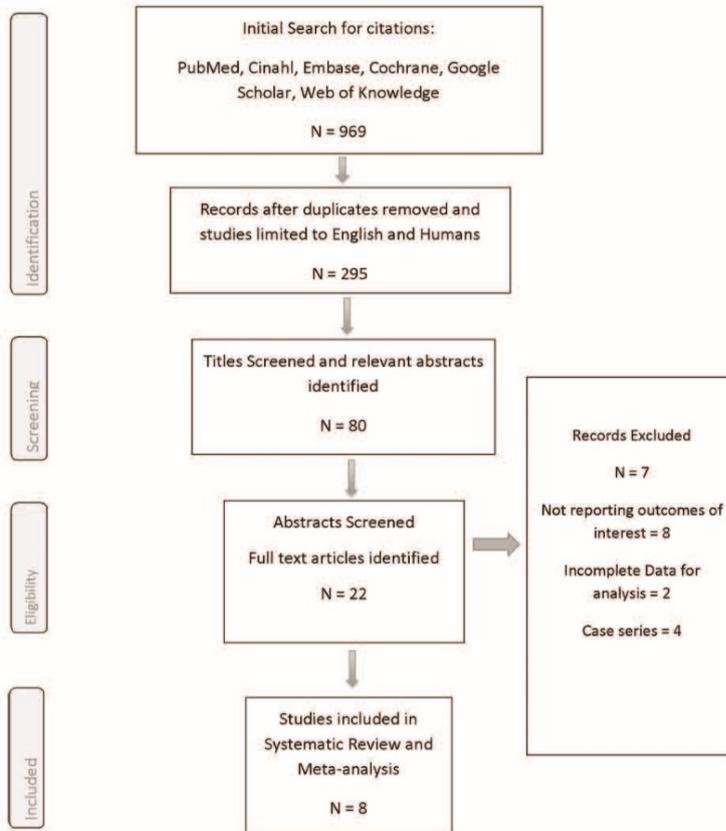


Fig 1. Prisma Flow Diagram. Eligibility for inclusion was determined by two researchers separately (KB, DH) by going through the abstracts of the relevant citations. Differences were settled by examining the full article by both authors, and then any remaining uncertainties regarding eligibility of studies were settled following a discussion with a third author (SRW).

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authors (KB, DH), and if remained unsettled, a third author was consulted to resolve the issue (SRW). The following characteristics regarding participants were recorded: age, sex, presence of co-morbidities, primary patency rate, secondary patency rate, maturation rate and postoperative complications (Haematoma, wound infection and steal syndrome). Usability of fistula for Haemodialysis, time to first use for HD and interventions needed to maintain patency were recorded when possible. We also extracted data on compliance with the Society for Vascular Surgery (SVS) recommended standards for reports dealing with arteriovenous haemodialysis accesses [29]. To this end, we assessed whether studies provided SVS standard-based grading of factors that affect outcomes and whether studies provided SVS standard-based grading of severity of arteriovenous access complications. The studies' inclusion and exclusion criteria were also recorded [Table 1].

Quality assessment for risk of bias

The Downs and Black Tool was used for quality assessment [36]. This tool consists of a total of 27 questions assessing the quality of reporting, external validity and internal validity generating scores between 0 to 32 which includes a score of 0–5 for sample size justification, however, this has been modified by awarding one point for studies that reported on sample size calculations, and zero for those that did not report a methods of sample size calculation. Hence, the modified score ranged from 0 to 27, with higher scores reflecting higher quality. Details of the quality assessment can be found in a separate supplemental table [S1 Table].

Data analysis

Statistical analyses were performed using Review Manager version 5.3 [27]. We used the random effects model of DerSimonian and Laird [38] to calculate pooled risk ratios for categorical outcomes measures. The Cochran's Q test was used to determine statistical heterogeneity among studies. 95% confidence interval and P-values < 5% were used to determine statistical significance. We compared between the fixed and random effects modelling to produce a sensitivity analysis aimed at detection of the influence of publication bias of small-study effects [39]. Regarding the meta-analysis we additionally, performed a sensitivity analysis limited to published articles only.

Results

Study selection

The results of the study selection process are summarised in the PRISMA flow diagram [Fig. 1]. We started with a total of 969 citations. Following the removal of duplicates and limiting the search criteria to studies conducted on humans and in English language, we were left with 295 citations. We then screened the titles of those papers, and found 80 potentially relevant citations. The abstracts of those titles were examined for relevant outcomes, and 22 papers were evaluated for eligibility criteria, of those 8 citations met our criteria and were included in the systematic review [21,22,30–35]. Of those 8 studies, 1 was a randomised controlled studies (RCT). Five were retrospective cohort studies [22,30,31,33,34] and 2 studies were cohort studies but it was unclear whether they were retrospective or prospective [21,35]. This last citation was a conference presentation which we included in the review, however we also ran a group of sensitivity tests excluding the data from this citation and including data extracted from published papers only [35].

Six of the included studies compared outcomes between 1-stage versus 2-stage BB-AVF formation techniques, while Hossny et al compared 3 different groups, first group of patients had

Table 1. Characteristics of individual studies.

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics 1 stage | Number 2 stage | Characteristics 2 stage |
|-------------------|----------------|---|---|----------------|---|--|---|--|--|--|---|---|
| Wales [24] | 2013 | Retrospective cohort study at Kings College Hospital London. BBAVF patients was 559 days (SD33). Median interval between first and second operation was 200 days. Two stage group was 80 days. Allocation to groups was based on preference of patients of either of the two surgeons. Patients with small veins who would not undergo two stage procedure. | Consecutive patients who underwent BBAVF between January 1st 2009 and December 31st 2011. | None specified | Basilic vein dissected and mobilised with preservation of the medial cutaneous nerve. Side anastomosis in the anastomotic fossa. | First BBAVF created at the cubital fossa, then 4–6 weeks later a second procedure carried following US assessment to determine if a second stage is needed. Mobilisation and superinfalisation of the fistula. | Primary, secondary and functional outcomes. Complications such as thrombosis, steal syndrome, hypertension, venous stasis, hypernatremia, anaemia, mortality. | Two stage patients had better functional outcomes than BBAVF as assessed by the number of patients requiring secondary intervention at 1 and 2 years. Complication rates were similar. | Data were provided using the number of patients who were included in the analysis. | Mean age was 58 years (SD 15). 32/85 were female. Mean BMI was 29.965 (SD 5.915). Hypertension, hypernatremia, steal syndrome, venous stasis were complications. Mean BMI was 29 (SD 6). 29/85 were black. Mean age was 4.0mm (1.8SD). The difference was in patients with a history of stroke (0.041). Patients that were not described in accordance with guidelines. | 84 two stage procedures were performed. Number of patients was unclear. | Mean age was 58 years (SD 15). 32/85 were female. Mean BMI was 29.965 (SD 5.915). Hypertension, hypernatremia, steal syndrome, venous stasis were complications. Mean BMI was 27 (SD 7). 30/84 were black. Mean age was 4.0mm (1.8SD). The difference was in patients with a history of stroke (0.041). Patients that were not described in accordance with guidelines. |
| Ozcan [25] | 2019 | Retrospective cohort study at the authors' institution. Allocation to groups was based on surgeon preference and other patients with basilic vein diameter < 3mm had the 2 stage procedure. The second stage of the two stage procedure took place 30 days. Mean follow up was for 38 months. | Patients who underwent BVT in the authors' institution(s) between January and January 2012. | None specified | Basilic vein dissected and mobilised with preservation of the medial cutaneous nerve. End to side anastomosis in the anastomotic fossa. HD was allowed after one month. | First BBAVF created at the cubital fossa, then 4 weeks later a second procedure carried following mobilisation and superinfalisation of the fistula. | Primary and secondary patency rates, postoperative complications such as thrombosis, haemorrhage, haematoma, infection, venous stasis, steal syndrome, mortality. Rate of fistula maturation and time to fistula maturation. Auditory interventional for patency. | Two stage procedure patients had a higher rate of maturation but 1 stage BVT's denominated as 'break-fist'. Thrombosis, haematoma, infection, venous stasis, steal syndrome, mortality were included and intervention for patency within 30 days but after had some interventional for patency. Primary and secondary patency were better in the two stage group but no statistical analysis was performed for this outcome. | Data were provided using the number of patients who were included in the analysis. | Mean age was 43.1 years (SD 16) for men and 42.5 years (SD 19) for women. 28/47 were male. Mean duration of dialysis was 63.1 months (SD 17) for men and 63.2 (SD 21) for women. 4/59 had hypertension, 9/47 had DM, 4/47 had heart failure, 4/47 were smokers. Mean basilic vein diameter was 2.7mm (SD 0.1). The difference between groups was in vein size (p<0.001). Reasons that affect outcome were not described in accordance with the SVS guidelines. | 59 two stage procedures on 59 patients were included. | Mean age was 43.1 years (SD 16) for men and 42.5 years (SD 19) for women. 28/47 were male. Mean duration of dialysis was 61.7 months (SD 20) for men and 63.2 (SD 21) for women. 4/59 had hypertension, 11/59 had DM, 3/59 had heart disease, 3/59 were smokers. Mean basilic vein diameter was 2.7mm (SD 0.1). The difference between groups was in vein size (p<0.001). Reasons that affect outcome were not described in accordance with the SVS guidelines. |

(Continued)

Table 1. (Continued)

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics Number 2 stage | Characteristics Number 2 stage |
|-------------|----------------|---|---|----------------|--|--|---|---|--|--|--------------------------------|
| Kakkos [31] | 2010 | Retrospective cohort study at Henry Ford Hospital, Detroit, USA on 173 patients who were scheduled for BVT. Allocation to groups was based on surgeon's preference. The length of follow up was not described although the report suggests that follow ended when fistulas were used in dialysis. | Patients who underwent BVT at the institution during a 1 year period between xx and xx. | None specified | Basilio vein dissected and mobilised with preservation of the medial cutaneous nerve of the forearm. Anastomosis in the antecubital fossa via the mobilisation and brachial or proximal radial or ulnar artery. HD was allowed only after least 6 weeks. | First BS-AVF created at the cubital fossa, then 4-6 weeks later a second anastomosis was created for mobilisation and superinfoculation of the fistula | Maturation rates and complications such as haematomas, infection, steal syndrome, hypertension, 30 day mortality. | One stage procedures had significantly higher complication rates. Haematomas and venous hypertension occurred significantly more often in one stage procedures. Maturation rates were similar although time to anastomosis was longer in the two stage group. | Data were provided using number of BVTs as the number of patients. 76 one stage procedures performed. One patient had two distal BVT anastomosis and was thus included twice but it was not clear which patients in one stage group had a history of previous anastomosis and they also were more likely to have a history of previous anastomosis. Notably there were no data on baseline vein diameter. Venous hypertension affected outcome were not described in accordance with the SVS guidelines. | Mean age was 59 years (SD 15), 49/76 were male, 8/76 were black, 257 were black, 577 were black, 88 had previous dialysis access. One patient in the study had two anastomosis and was included twice but it was not clear which anastomosis was the included one. There were no data on baseline vein diameter. Factors that affected outcome were not described in accordance with the SVS guidelines. | |

(Continued)

Table 1. (Continued)

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics 1 stage | Number 2 stage | Characteristics 2 stage |
|----------------------|----------------|--|--|----------------|---|--|--|--|---|--|---|--|
| EI Mallah [33] | 1998 | Prospective randomised controlled trial at El Manoufia University Hospital, Alexandria, Egypt. Allocation concealment was performed randomly and groups were blinded to allocation details on the randomisation process. Follow up was 10–24 months. | Involves 40 patients who were admitted for secondary vascular disease between June 1992 and December 1995. | None specified | BBAVFs were made using the traditional one stage technique. | First BBAVF created at cubital fossa by anastomosing a mobilised basilic vein to the brachial artery. Then 2–4 weeks later a second BBAVF was created for mobilisation and superinfoculation of the fistula. | Patency at 4 weeks and patency at end of follow up period. | Early patency was achieved in 12/20 in the one stage group versus 18/20 in the two stage group. Patency at end of follow up was 10/20 versus 16/20. The authors did not perform an intention to treat analysis. When an intention to treat analysis was used, the difference in patency rates was not significant. There was no significant difference in infection or aneurysm rates. | 20 patients who underwent 20 one stage procedures | Mean age was 32.5 years (SD 9), 12/20 were male. Mean period of follow up was 14.8 (SD 5) months (SD 3.5). Factors that affect outcome were not described in the SVS guidelines. | 20 patients who underwent 20 two stage procedures | Mean age was 33.5 years (SD 7.5), 11/20 were male. Mean period of follow up was 14.8 (SD 5) months (SD 3.5). Factors that affect outcome were not described in the SVS guidelines. |

(Continued)

Table 1. (Continued)

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics 1 stage | Number 2 stage | Characteristics 2 stage |
|-----------|----------------|--|---|----------------|---|--|---|---|-------------------------------------|--|--|--|
| Sved [33] | 2012 | Retrospective cohort study on 105 patients who underwent BVT at the Methodist Hospital, Baylor College of Medicine, and the University of Texas, Dallas, Texas, USA. It is unclear whether this was based upon patient preference. Data came from a computerised database. | Involved 105 patients who underwent BVT between 1998 and 2008. Inclusion criteria were: age > 18 years, atherosclerotic disease, and a history of dialysis. | None specified | Brachial artery to brachial vein anastomosis along with the superficial transposition of the arm procedures | The anastomosis was created in the first stage and, subsequently, was transposed in the second stage | Primary, primary assisted and secondary patency up to three years, mortality, major complications, fistula maturation and complications | Primary patency and assisted primary patency were better in the one stage procedure. Mortality, major complications, not significantly different. | 29 patients underwent one stage BVT | Mean age was 54 years (SD 14), 29/77 were male. 19/29 had current catheter in place at the time of the surgery. 16/29 had prior ipsilateral aortic, 30/77 had prior failure of anastomosis, 29/77 had atherosclerosis, 28/29 had hypertension, 5/29 had coronary artery disease, 29 had congestive heart failure, 13/29 had GA and the others had regional arm differences in significant differences in baseline characteristics were noted. In regard to history of catheter use and prior ipsilateral aortic disease, factors that affect outcome were not described in accordance with the SVS guidelines. | 77 patients underwent two stage procedure. | Mean age was 54 years (SD 14), 29/77 were male. 67/77 had current catheter in place at the time of the surgery. 16/77 had prior ipsilateral aortic, 30/77 had prior failure of anastomosis, 29/77 had atherosclerosis, 28/29 had hypertension, 5/29 had coronary artery disease, 29 had congestive heart failure, 13/29 had GA and the others had regional arm differences in significant differences in baseline characteristics were noted. In regard to history of catheter use and prior ipsilateral aortic disease, factors that affect outcome were not described in accordance with the SVS guidelines. |

(Continued)

Table 1. (Continued)

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics Number 2 stage | Characteristics Number 2 stage | |
|------------------------------|----------------|--|---|--|---|---|---|--|--|---|--|---|
| Agarwal, 2014 [34] | | Retrospective cohort study involving 144 consecutive patients who underwent BVT creation at a US hospital. Patients with basilic vein diameter of 2.0 cm were included in the two stage procedure. Mean follow up duration was unclear. Some patients were lost to follow up for a number greater than 4 years. | Involves consecutive patients who underwent BVT creation at a US hospital. Patients with basilic vein diameter of 2.0 cm were included in the two stage procedure. Mean follow up duration was unclear. Some patients were lost to follow up for a number greater than 4 years. | Patients were excluded if interventions had taken place at an institution. | Not specified | Not specified | Maturational rates, mean time to initiation of fistula use, intensity of interventions per patient, year primary patency, secondary patency and secondary patency annually. | Moderate reduction in primary and secondary patency rates in the two stages compared to the one stage group | 61 patients underwent BVTs | Mean age was 59.1 years. No other data were provided on baseline characteristics. Factors that affect outcome were not described in accordance with guidelines. | 83 patients underwent 83 two stage BVTs. | Mean age was 61.5 years. No other data were provided on baseline characteristics. Factors that affect outcome were not described in accordance with guidelines. |
| Hosery, 2009 [21] | | Cohort study involving 70 brachioabulic fistulas in 70 patients at Menofia University, Egypt. It is unclear whether it was prospective or retrospective although it seems to be prospective. The study compared basilic vein transposition stage selection procedure versus a two stage elevation procedure. It is unclear on what grounds patients were selected for different procedures. Mean follow up time was 25.8 months. | Involved 70 brachioabulic fistulas that were included in the study. 70 patients over an unspecified 2 year period at the author's institution. | None specified | 30 fistulas created using a traditional one stage BVT to create a BB-AP20 fistula. In addition, 40 fistulas were brought into the study using a superficial to the deep fascial and subcutaneous tissue rather than thrombolysis, subcutaneous tunnel | 20 fistulas created in a two stage elevation technique. In this study, the basilic vein was brought superficial to the deep fascial and subcutaneous tissue rather than thrombolysis, subcutaneous tunnel | Ability to access dialysis, cumulative primary patency, complications (edema, haematoma, hypertension, lymphoedema), perioperative mortality. | The one stage BVT had a lower complication rate and was by the dialysis staff compared to the one stage basilic vein anastomosis and 10/20 had complications (edema, haematoma, hypertension, lymphoedema, mortality). | 20 patients underwent BVTs, while 20 one stage BVTs were performed by the dialysis staff | For the one stage BVT: Mean Age = 45.7 (16–89). Factors that affect outcome were not described in accordance with guidelines. | 20 patients underwent two stage basilic vein anastomosis procedure. Mean Age = 42.0 (15–70). Factors that affect outcome were not described in accordance with guidelines. | Mean Age = 54 (25–71), 8 were created in male patients. Mean Age = 42.0 (15–70). Factors that affect outcome were not described in accordance with guidelines. |

(Continued)

Table 1. (Continued)

| Study | Date published | Key aspects of design | Inclusion | Exclusion | Nature of the one stage procedure | Nature of the two stage procedure | Outcomes assessed | Main findings | Number 1 stage | Characteristics 1 stage | Number 2 stage | Characteristics 2 stage |
|-------------|----------------|---|--|---|---|---|---|---|--|---|--|-------------------------|
| Effect [33] | 2013 | Cohort study involving 104 patients who underwent 106 Brachioabulic fistulas at Zubeidat University Hospital from October 2010 to December 2011. Whether it was retrospective or prospective comparison between one stage BVT, two stage BVT, two superinfatation. Allocation to groups was surgeons' or patients' preference. The period of follow up was not specified. | Scheduled for fistula with a ballio vein >2.5mm diameter and a brachial artery >3mm. | Patients were excluded if vein diameter <2.5mm, failure of fistula to mature in staged groups, stial varicos after creation of the brachioabulic shunt and failed to be mature in patients who refused the second stage or who were lost to follow up between stages. | All fistulas created using a traditional one stage BVT to create BB-AVF | 38 fistulas were created using a two stage BVT technique. One involved AVF, the second stage involved mobilization and superinfatation of the fistula. In addition, they carried two stages superinfatation procedures without mobilizing the ballio vein | functional patency (ability to access the fistula for haemodialysis), use of the second stage as a complication such as haematoma requiring reoperation, wound dehiscence or infection, thrombosis, steal syndrome, hypertension requiring intervention, failure to mature. | Lower patency rates for the one stage technique and increased chance of postoperative complications compared to the two stage technique | 28 one stage BVTs performed. Number of patients unclear. | Mean age = 43.6 ± 11.9, 13/29 were male, 13/29 had diabetes and 10/28 had hypertension. Factors that affect outcome were not described in accordance with guidelines. | 38 two stage BVTs performed. Main age = 48.4 ± 10.2, 20/38 were male, 19/38 had diabetes and 22/38 had hypertension. Factors that affect outcome were not described in accordance with the SVS guidelines. | |

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traditional 1-stage basilic vein transposition (BVT), while the second group had 1-stage basilic vein elevation, and the third group underwent a 2-stage BB-AVF. For the sake of this meta-analysis, we pooled the first 2 groups from this particular study together [21]. Similarly, Effat had 3 groups of patients in his conference paper, the first group had standard 1-stage BVT, whereas the second group had a 2-stage BVT and the last group consisted of patients who had 2-stage superficialization of the basilic vein to create BB-AVF. We pooled the data from the 1-stage procedures in this last study together in the meta-analysis [35].

Participants

The studies included a total of 849 patients who had 859 fistulas, of those 366 fistulas were formed using a 1-stage technique, while the remaining 493 fistulas were created in a 2-stage technique. Overall, 432 were male patients versus 417 female patients. Kakkos et al [31] did not specify the male to female ratio in the 72 patients who underwent a 2-stage procedure in their study, however, in the remaining studies, 181 men had 1-stage fistula procedure compared to 164 in the 2-stage group. Similarly, 226 in the 1-stage group were female patients compared to 150 in the 2-stage group. Of the 6 [21,22,30,31,33,35] studies that reported past history of diabetes, 143/295 patients were in the 1-stage group while 202/390 were in the 2-stage group. History of hypertension was reported in 5 studies [21,22,30,33,35], with 123/219 patients in the 1-stage group and 202/390 in the 2-stage group having the diagnosis. All studies reported on findings in adult patients with end stage renal disease (ESRD), El-Mallah [32] had the youngest patients (23.5 ± 5.8 years for the 1-stage group, and 35.8 ± 7.3 years for patients in the 2-stage group), while the remaining studies included patients in their fifties and sixties [Table 1]. Inclusion and exclusion criteria of studies among other characteristics are outlined in [Table 1]. Main outcomes reported in studies are summarised in [Table 2].

Successful maturation rate

Successful maturation rates were reported in 6 of included studies [21,22,31–34]; the criteria used for reporting maturation are found in [Table 3]. Those studies had a combined total of 683 fistulas, 301 of those were created in the one stage group, whereas 382 were created in the two stage group. The difference between the two groups was not significant in pooled analysis (Pooled risk ratio = 0.95 [0.82, 1.11], 95% CI, $P = 0.53$) [Fig. 2]. Heterogeneity was detected statistically (Cochran's $Q = 14.48$; degree of freedom (DF) = 5; $P = 0.001$; $I_2 = 65\%$). The significance of the results was not altered when using the fixed effects analysis model as a sensitivity test to detect publication bias (Pooled risk ratio = 0.92 [0.84, 1.01], 95% CI, $P = 0.07$).

Postoperative complications

Haematoma. The incidence of postoperative wound haematoma was reported in 6 of the included studies [21,22,30,31,33,35] with a total of 711 fistulas, of those, 295 fistulas were created in the 1-stage group and 416 fistulas in the 2-stage group. Analysis of pooled data showed the difference was not significant (Pooled risk ratio = 0.73 [0.34, 1.58], 95% CI, $P = 0.43$) [Fig. 3]. Heterogeneity was not detected statistically (Cochran's $Q = 9.76$; degree of freedom (DF) = 5; $P = 0.08$; $I_2 = 49\%$). The results were not changed significantly when using the fixed effects analysis model as a sensitivity test to detect publication bias (Pooled risk ratio = 0.67 [0.41, 1.11], 95% CI, $P = 0.12$). A sensitivity test by excluding the data from the conference paper by Effat [35] was carried out, and no significant difference was found in the incidence of postoperative haematoma between the two groups (Pooled risk ratio = 0.67 [0.27, 1.64], 95% CI, $P = 0.38$).

Table 2. Main outcomes from included studies.

| Study | 1-stage procedure | | | | 2-stage procedure | | | | | |
|-----------------------|--|---|--|---|--|--|---|---|--|--|
| | Number of fistulas | Patency | Haematoma | Wound infection | Stent | Number of 2-stage fistulas | Patency | Haematoma | Wound infection | Stent |
| Vrakas [21] | 85 one stage procedures were performed. Number of patients was unclear. | Primary functional patency at 1 and 2 years was 71% and 55%. Assisted patency at 1 and 2 years was 77% and 67%. Secondary functional patency at 1 and 2 years was 79% and 57%. The definitions for patency outcomes were based upon the SVS guidelines. | 3 / 65 No SWS grading was provided | 3 / 65 | 2 / 65 No SWS grading was provided | 84 two stage procedures were performed. Number of patients was unclear. | Primary functional patency at 1 and 2 years 67% and 75%. Assisted patency at 1 and 2 years was 77%. Secondary functional patency at 1 and 2 years was 95% and 77% | 3 / 84 No SWS grading was provided. | 2 / 84 | 3 / 84 |
| Ozcan [30] | 47 one stage on 47 patients were included and Total number of patients was 96 therefore some patients were included twice. | Primary patency at 1, 2 and 3 years was 53/47 (70%), 39/47 (64%), and 27/47 (64%) respectively. Secondary patency was 38/47 (76%), 43/47 (72%), and 49/47 (69%). The definitions for patency outcomes were unclear. | 8 / 47 No SWS grading was provided | 6 / 47 No SWS grading was provided | 4 / 47 No SWS grading was provided required surgical management | 69 two stage procedures performed. Number of patients was unclear. | Primary patency at 1, 2 and 3 years was 41/69 (59%), 36/69 (52%), and 34/69 (49%). Secondary patency at 1, 2 and 3 years was 44/69 (64%), 49/69 (71%), and 58/69 (84%). | 3 / 69 No SWS grading was provided | 5 / 69 No SWS grading was provided but all require surgical treatment | 3 / 69 No SWS grading was provided but all require surgical treatment |
| Kakkos [31] | 76 one stage procedures were performed. One patient in the study had two distinct BVT procedures but it was not clear which procedure the patient underwent. | Not reported | 10 / 76 No SWS grading was provided. Across the whole study, most were grade 1 or 2 and 3 were grade 3 | 6 / 76 No SWS grading was provided. Across the whole study, most were grade 1 or 2 and 3 were grade 3 | 3 / 76 No SWS grading was provided but all were managed conservatively | 96 patients underwent two stage procedures. 96 had the first stage and 72 subsequently underwent the second stage. One patient in the study had two distinct BVT procedures but it was not clear which procedure this patient underwent. | Not reported | 3 / 72 No SWS grading was provided. Across the whole study, most were grade 1 or 2 and 3 were grade 3 | 0 / 72 No SWS grading was provided but all were managed conservatively | 2 / 72 No SWS grading was provided but all were managed conservatively |
| El Mallah [32] | 20 patients who underwent 20 one stage procedures were included. | Early patency (4 weeks) = 12/20 (60%). Overall patency (at the end of follow-up) = 19/20 (95%). The definitions for patency outcomes were unclear. | 3 / 20 No SWS grading was provided but they were described as patency outcomes | 3 / 20 No SWS grading was provided but they were described as patency outcomes | 0 / 20 | 20 patients who underwent 20 two stage procedures were included. One fistula occurred in the interval between stages and this was excluded. | Early patency (4 weeks) 2-stages = 18/20 (90%). Overall patency at the end of this study = 16/20 (80%) | 1 / 20 No SWS grading was provided but they were described as patency outcomes | 0 / 20 | 0 / 20 |

(Continued)

Table 2. (Continued)

| Study | 1-stage procedure | | | | 2-stage procedure | | | |
|---------------------|---|--|------------------------------------|-----------------|--|--|------------------------------------|------------------------------------|
| | Number of fistulas | Patency | Haematoma | Wound infection | Number of fistulas | Patency | Haematoma | Wound infection |
| Syed [33] | 29 patients underwent 20 one-stage BVT | Primary patency at 1, 2 and 3 years was 82%, 81%, and 51%. Assisted patency at 1, 2 and 3 years was 91%, 77%, and 48%. Secondary patency at 1, 2 and 3 years was 91%, 89%, and 89%. The definitions are in the SVS guidelines. | 2 / 20No SVS grading was provided. | 0 / 29 | 77 patients underwent two stage procedure. | Primary patency at 1, 2 and 3 years was 67%, 27%, and 15%. Assisted patency at 1, 2 and 3 years was 77%, 41%, and 24%. Secondary patency at 1, 2 and 3 years was 81%, 61%, and 46% | 6 / 77No SVS grading was provided. | 3 / 77No SVS grading was provided. |
| Agarwal [34] | 61 patients underwent 61 one-stage BVTs | Primary patency at 1, 2, 3 and 4 years was 67%, 39%, 21%, and 15%. Secondary patency at 1, 2, 3 and 4 years was 86%, 75%, 69%, and 57%. The definitions are similar to those in the SVS guidelines. | 0 / 61 | 0 / 29 | 83 patients underwent two stage BVTs. | Primary patency at 1, 2, 3 and 4 years was 15% and 0%. Primary assisted patency at 1, 2, 3 and 4 years was 66%, 39%, 7%, and 0%. Secondary patency at 1, 2, 3 and 4 years was 76%, 71%, 49%, and 25%. | 6 / 83No SVS grading was provided. | 0 / 83 |
| Hosany [21] | 20 patients underwent 20 one-stage BVTs, while 20 patients underwent one-stage basic vein elevation procedure | The study reported 67% cumulative secondary patency rate at 1 year for the 1-stage elevation group, with 88.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the 2-stage elevation group. 1 death was excluded from final analysis. | 6 / 50No SVS grading was provided. | 0 / 50 | 20 patients underwent two stage basic vein procedure | The study reported 97% cumulative secondary patency rate at 1 year for the 1-stage elevation group, with 88.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the 2-stage elevation group. 1 death was excluded from final analysis. | 6 / 20No SVS grading was provided. | 0 / 20 |

(Continued)

Table 2. (Continued)

| Study | 1-stage procedure | | | | 2-stage procedure | | | | |
|-----------------------------|--|--------------|------------------------------------|------------------------------------|--|--------------|------------------------------------|-------------------------------------|------------------------------------|
| | Number of fistulas | Patency | Haematoma | Wound Infection | Number of 2-stage fistulas | Patency | Haematoma | Wound Infection | Stool |
| Erft conference [35] | 28 one stage BVTs performed. Number of patients unclear. | Not reported | 2 / 28No SVS grading was provided. | 2 / 28No SVS grading was provided. | 36 two stage BVTs and 40 two stage superficialization. Number of patients unclear. | Not reported | 7 / 78No SVS grading was provided. | 12 / 78No SVS grading was provided. | 0 / 78No SVS grading was provided. |

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Table 3. Maturation.

| Study | One stage | Two stage | Source of data | comments |
|----------------|-----------|-----------|---|--|
| Vrakas [22] | 36 / 65 | 49 / 84 | Primary failure rates were reported. This was defined as an AVF that was never used for dialysis. Primary failure may have resulted from inadequate maturation, early thrombosis, failure of first cannulation, and other complications which made AVF unusable. Successful maturation rates were derived from these data. | The number of AVFs that required intervention to assist maturation is unclear. |
| Kakkos [31] | 67 / 76 | 69 / 98 | Maturation rates were reported. Maturation was based upon clinical judgement (development of basilic vein dilatation and thrill for a sufficient length). | Includes fistulas that required intervention to assist maturation for dialysis. 7 one stage fistulas required such intervention and 3 two stage fistulas required such intervention. |
| El-Mallah [32] | 12 / 20 | 18 / 20 | Patency at 4 weeks was reported and we used this figure to determine successful maturation. The authors did not provide a definition for patency. | The number of AVFs that required intervention to assist maturation is unclear. |
| Syed [33] | 6 / 29 | 14 / 77 | Maturation rates were reported. Fistula maturation was defined as dilation of the vein to allow cannulation and support dialysis at a minimum flow rate of 350ml/min for at least 3 sessions. | The number of AVFs that required intervention to assist maturation is unclear. |
| Agarwal [34] | 55 / 61 | 62 / 83 | Maturation rates were reported. Maturation was defined as the use of the fistula for haemodialysis for any amount of time or, if it was not used, documentation in surgical or renal records that the fistula was mature and ready for use based upon successful cannulation and/or physical examination by vascular surgery. | Includes an unspecified number of fistulae that needed percutaneous intervention to assist maturation. |
| Hosny [21] | 47 / 50 | 19 / 20 | Numbers of fistulas that were successfully used for dialysis at 6 weeks were reported. | No patients needed reintervention to assist achievement of successful dialysis at 6 weeks. |

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Wound infection. Six of the included studies [30–33,35] reported on the incidence of postoperative wound infection with a total number of 681 fistulas, 265 of those belonged to the 1-stage group, while 416 consisted of 2-stage fistulas. Meta-analysis of the pooled data showed the difference between groups not to be significant (Pooled risk ratio = 0.77 [0.35, 1.68], 95% CI, $P = 0.51$) [Fig. 4]. There was no evidence of statistical heterogeneity (Cochran's $Q = 5.76$; degree of freedom (DF) = 5; $P = 0.51$; $I^2 = 13\%$). The results were not changed significantly when using the fixed effects analysis model (Pooled risk ratio = 0.73 [0.39, 1.37], 95% CI, $P = 0.32$). A sensitivity test by excluding the data from the conference paper by Effat [35] was carried out, and no significant difference was found in the incidence of postoperative wound infection between the two groups (Pooled risk ratio = 0.57 [0.25, 1.27], 95% CI, $P = 0.17$).

Steal syndrome. Six of the studies [22,30–33,35] reported on the risk of developing significant postoperative ischaemia (steal syndrome). Those studies had a combined total of 681

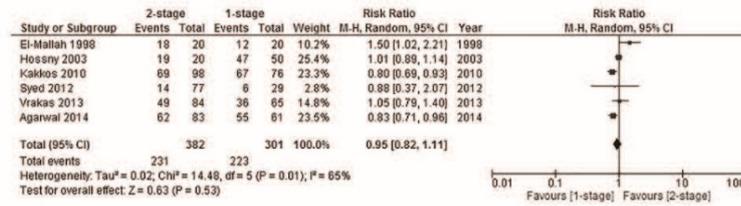


Fig 2. Successful maturation rate.

doi:10.1371/journal.pone.0120154.g002

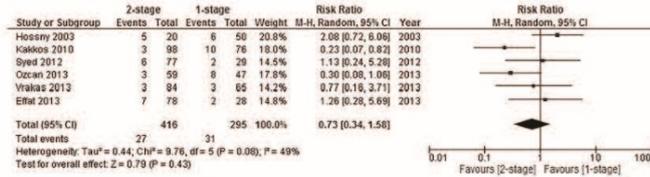


Fig 3. Postoperative Haematoma.

doi:10.1371/journal.pone.0120154.g003

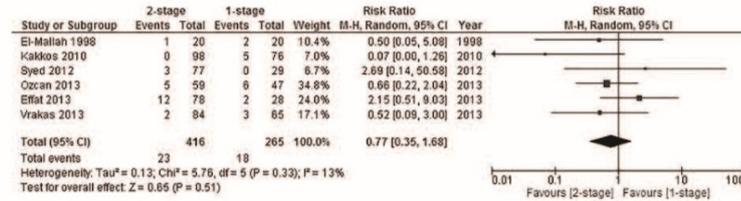


Fig 4. Postoperative wound infection.

doi:10.1371/journal.pone.0120154.g004

patients, of those, 265 belonged in the 1-stage group, while 416 belonged in the 2-stage group. Analysis of pooled data showed the difference was not significant (Pooled risk ratio = 0.65 [0.27, 1.53], 95% CI, P = 0.32) [Fig 5]. Heterogeneity was not detected statistically (Cochran's Q = 3.42; degree of freedom (DF) = 4; P = 0.49; I₂ = 0%). The results were not changed significantly when using the fixed effects analysis model (Pooled risk ratio = 0.64 [0.29, 1.40], 95% CI, P = 0.26). A sensitivity test by excluding the data from the conference paper by Eftat [35] was carried out, and no significant difference was found in the incidence of postoperative haematoma between the two groups (Pooled risk ratio = 0.79 [0.32, 1.94], 95% CI, P = 0.60).

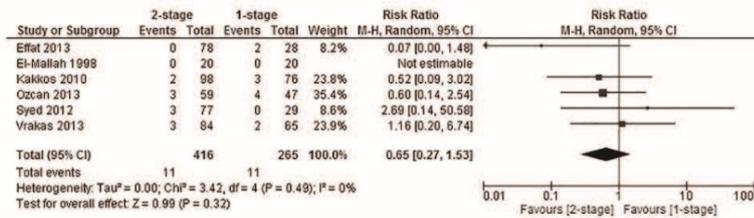


Fig 5. Steal syndrome.

doi:10.1371/journal.pone.0120154.g005

Systematic Review

El-Mallah in his paper titled “Staged basilic vein transposition for dialysis angioaccess” published in 1998 [32] compared outcomes in two groups randomly allocated to receive either 1-stage BVT or 2-stage BVT. The difference in early patency rates was significant and favoured the 2-stage approach (60% of 1-stage vs 90% of 2-stage, $P < 0.05$), as well as overall patency rates at the end of follow-up (50% of 1-stage vs 80% of 2-stage, $P < 0.05$) [32]. Postoperative wound infection rate also favoured the 2-stage approach with one case compared to 3 in the 1-stage group. There was no difference in postoperative aneurysmal dilatation, and there was no significant ischaemia (steal syndrome) reported in either of the two groups [32].

Hossny looked at the different surgical techniques used in creation of a BB-AVF in 2003 [21]. He compared patency rates and dialysis related complications in 70 patients divided in 3 groups, 30 of those patients had traditional BVT whereas 20 patients had 1-stage BB-AVF with elevation and the remaining 20 patients had 2-stage fistula with elevation of the vein [21]. Cumulative secondary patency rates were comparable among the 3 groups at 1 year and 2 years; at 1 year (86.7% for the BVT group, 90% for the 1-stage elevation group and 84.2% for the last group), while at 2 years (82.8%, 70%, and 68.4%, respectively) [21]. Similarly, no significant difference was found in his study in postoperative early thrombosis across the groups. Postoperative arm oedema occurred in a total of 14 patients, all of whom had temporary subclavian access catheters sited on the same arm on which the new fistula was created. All 14 cases were managed conservatively with success. The difference in developing postoperative haematoma significantly favoured the traditional BVT approach compared to the two elevation methods with fewer haematomas reported in the first group. Interestingly, the dialysis staff were more satisfied with the 1-stage BVT technique, whereas only 53.3% reported satisfaction with the elevation technique (1-stage and 2-stage techniques) ($P < .001$) [21].

Kakkos et al also tried to answer the question of “What is the Optimal Technique” for performing a BVT in a retrospective study of 173 patients published in 2010 [31]. They found that the incidence of venous hypertension (17% vs 4%, $P = 0.004$), wound infection (13% vs 3%, $P = 0.012$) and all complications (43% vs 11%, $P < 0.001$) were significantly higher in patients who had 1-stage BVT when compared to those who had a 2-stage BVT [31]. Time to fistula use in HD was—expectedly—shorter in the 1-stage group (Median = 68 (49–103) days) compared to the 2-stage group (Median = 132 (102–166) days). This difference was significant ($P < 0.001$) [31]. However maturation rates were similar (85% for the 1-stage groups versus 82% for the 2-stage group, $P = 0.49$). Median time to use the fistulas for HD in the 2-stage group was 66 in patients who developed postoperative complications, compared to 50 days in those who did not

($P = 0.019$). They also found that wound infection occurred more in patients who were operated under general anaesthetic compared to those who had their procedures done under local anaesthetic (OR 38, $P < 0.001$). Also, venous hypertension was found to occur more frequently in patients who developed postoperative wound haematoma, but the difference was not statistically significant (18% vs 6%, $P = 0.12$) [31]. A trend was noted towards steal being more common in patients with previous vascular access than in those who did not have such access (4.9% vs 1.1%, $P = 0.19$) [31].

Syed et al carried out a similar study comparing the outcomes of 1-stage (29 patients) and 2-stage (77 patients) BVT and published their findings in 2012 [33]. 79% of patients in the 1-stage group had a history of a previously failed access for HD compared to 51% of the 2-stage group. They found that the rate of primary failure was comparable between both groups (21% vs 18%) [33]. In their study, patients who had 1-stage BVT had better patency rates when compared to those who had 2-stage procedures at 1 year (82% vs 67%), 2 years (81% vs 27%) and 3 years (51% vs 18%) respectively. The same finding was reported for secondary patency (91%, 80% and 58% for 1-stage BVT compared to 81%, 61% and 45% for the 2-stage group at 1, 2 and 3 years respectively) [33]. Reintervention rate in this study was 62% for the 1-stage vs 66% for the 2-stage group. It is worth noting that 87% of the patients in the 2-stage group were using catheters for dialysis, whereas 55% of the 1-stage group were dialysing through a catheter at the time of access formation [33].

Ozcan et al published a paper in 2013 with preliminary results from their study comparing 1-stage and 2-stage BVT to create AVF access in HD patients [30]. They retrospectively divided their patients to those with a basilic vein > 3 mm and who had a 1-stage BVT procedure, and those with a basilic vein < 3 mm who had a 2-stage procedure. Although the diameter of the basilic vein was statistically higher in the first group (3.46 ± 0.2 mm) compared to the second group (2.79 ± 0.1 mm) ($P < 0.005$), the rate of fistula maturation was significantly lower in the first group (66% vs 77%, $P < 0.005$) [30]. Also, postoperative complications were significantly higher among the first group of patients who had 1-stage BVT. Thrombosis occurred in 34% compared to 23% of patients who had a 2-stage procedure, haemorrhage in (36% vs 14%) and haematoma in (17% vs 6%) respectively. Time required for the fistula to mature was significantly shorter in the first group (Mean 41 ± 14 days) compared to the second group (Mean 64 ± 28 days) ($P < 0.05$) [30]. Early interventions (≤ 10 days) for fistula thrombosis occurred more frequently in the first group (21% vs 12%, $P < 0.05$), although there was no significant difference in terms of late interventions (≥ 10 days) required to deal with access thrombosis (20% in the first group vs 22% in the second) [30]. Also they reported superior primary patency rates at 6, 12, 18, 24, 30 and 36 months for those who had 2-stage BVT fistulas compared to the first group of patients (1-stage 83%, 70%, 68%, 64%, 60% and 57% versus 88%, 84%, 80, 73%, 71% and 69% for the 2-stage respectively). Similarly, the 1-stage had lower secondary patency rates at 6, 12, 18, 24, 30 and 36 months when compared to the 2-stage group (85%, 76%, 74%, 72%, 70% and 66% versus 94%, 90%, 84%, 82%, 80% and 77% respectively) [30].

Similarly, Vrakas et al evaluated the difference in outcomes between 1-stage (65 fistulas) and 2-stage (84 fistulas) BB-AVFs performed in 141 patients [22]. They performed ultrasound scans 4–6 weeks after the first stage procedure to determine if a second stage was required. Patients who had their fistulas created in a 1-stage approach had a bigger preoperative basilic vein diameter (4.0 ± 1.1 mm vs 3.6 ± 1.3 mm, $P = 0.041$) [22]. There was no difference in primary failure between the groups (45% vs 42%, $P = 0.718$), however the 1-stage BB-AVF had significantly lower primary (71% vs 87%; $P = 0.034$), assisted primary (77% vs 95%; $P = 0.017$), and secondary (79% vs 95%; $P = 0.026$) functional patency rates compared to the 2-stage BB-AVF [22]. Multivariate Cox regression analysis showed that the 1-stage procedure was 3.2 times more likely to fail ($P = 0.028$), and male gender was associated with loss of access ($P = 0.054$).

66% of the fistulas in the first group were used successfully for HD compared to 60% in the 2-stage group ($P = 0.407$), and intervention before first successful HD session was equivalent between both groups (21% vs 11%, $P = 0.201$) [22]. Overall, 93 (62%) fistulas were successfully used for HD (66% 1-stage vs 60% 2-stage; $P = 0.407$), of the remaining 56 (38%), 19 fistulas (34%) failed before needling, 2 (4%) received a renal transplant, 7 (13%) died, and 28 (50%) BBAVFs remain patent in patients awaiting to start HD [22].

Agarwal et al examined the outcomes of 1-stage vs 2-stage BVT AVF. They included patients who underwent percutaneous angioplasty (assisted maturation) in calculating the overall maturation rate which was 90% for the 1-stage group (55/61 patients) compared to 75% of the 2-stage group (62/83 patients) ($P = 0.02$). Subgroup analysis showed that both men (54/66 patients) and women (64/78) in this study had a maturation rate of 82% ($P = 0.97$) [34]. Primary unassisted patency rates were comparable between the groups (69%, 52%, 26%, and 7% for the 1-stage BVT at 3 months, 6 months, 1 and 2 years; compared to 58%, 35%, 13%, and 0% of the 2-stage group, respectively ($p = 0.12$) [34]. Similarly, no significant difference was found in secondary patency on an intent-to-treat basis (86%, 75%, 69%, and 57% at 1, 2, 3, and 4 years for 1-stage group; compared to 76%, 71%, 49%, and 25% of the 2-stage group, respectively; ($p = 0.12$) [34]. The intensity of percutaneous interventions in their study was 1.84/patient-year of dialysis (PYD) for the 1-stage group versus 2.15/PYD for the 2-stage group ($P = 0.57$) [34]. They suggested that although the 2-stage BB-AVF technique resulted in modest reduction in maturation and patency rates, it should still be favoured to the use of synthetic grafts in patients who would not be suitable for a 1-stage BB-AVF procedure [34].

The number of AVFs that failed to progress from the first stage to the second stage in the two-staged BVT approach were unclear in four studies [22,30,34,35]. In the remaining four, El-Mallah [32] reported 1/20 patient which had an occluded shunt, while Hossny [21] also had 1/20 patient failing to progress due to spontaneous thrombosis within the first 4 weeks postoperatively. Syed [33] had 2/77 patients that never progressed to the second stage of the procedure. Kakkos [31] reported that 26/98 of his patients never had a second stage procedure (thrombosed ($n = 4$), failed to mature and was abandoned during the re-exploration ($n = 12$), patient refused the procedure ($n = 3$), lost to follow-up ($n = 1$), died ($n = 2$), venous hypertension ($n = 2$), venous monomelic neuropathy ($n = 1$) requiring ligation, moved out of state ($n = 1$)).

Number of interventions required to maintain patency or to improve the fistula maturation rates were not reported clearly in all studies. Hossny reported that in the one-stage group one patient underwent ligation and another had a surgical revision, same numbers occurred in the two-stage group. All ligations were done to treat venous hypertension, whereas all revisions were performed to improve poor flow [21]. Kakkos reported that in the two-stage group 6 patients had endovenous angioplasty interventions, 3 had surgical revisions compared to 3 patients and 1 patient in the one-stage group respectively [31]. Syed et al performed 37 angioplasty interventions, 9 surgical revisions and 5 thrombectomy procedures in their two-stage group, compared to 14, 2 and 2 patients respectively [33]. The remaining studies either did not report data related to fistula salvage procedures or it was reported in poor details making it difficult to quantify those interventions.

With the exception of the studies by El-Mallah et al [32] and the one by Vrakas et al [22] which both reported significantly superior patency rates in the two-stage groups, and the paper by Syed [33] which conversely reported a significantly better patency rates in the one-stage BVT group, the remaining studies all reported comparable patency rates [21,30,31,34,35] [Table 2]. However it is important to point out that patency rate data were reported as percentages with the lack of clearly identifiable denominators in the majority of those studies, thus making pooling those data in a meta-analysis not feasible. Also, definitions used in individual studies included in this review for patency rates (primary, assisted primary and secondary) differed significantly.

Discussion

The number of patients with end stage renal disease (ESRD) requiring haemodialysis (HD) is steadily rising, a trend that is expected to continue [2]. A well-functioning AVF is superior to grafts and central catheters in providing access for haemodialysis efficiently and at the same time with the least rate of access related complications. This has lead vascular surgeons to resort to the basilic vein which by virtue of its anatomical position is less likely to be damaged by repeated cannulation as with the more superficial veins of the arm and forearm. However, a consensus on how to form a brachiobasilic AVF does not exist as some surgeons choose to do this in a one-stage operation, while others prefer a two-stage procedure with the first procedure usually involving making the anastomosis between the basilic vein and the brachial artery, while in the second stage the arterialised vein is mobilised and brought closer to the skin surface to facilitate cannulation for HD sessions.

This review identified eight studies [21,22,30–35], including data from a conference paper [35] in order to increase the rigour of the review. The pooled data referred to 849 patients with a total of 859 fistulas, 366 of those fistulas belonged to patients who underwent a 1-stage BB-AVF, while 493 fistulas were performed using a 2-stage technique to create the access. The data from 6 of the included studies [21,22,30,31,33,35] were used to compare the difference between the two groups in developing postoperative haematoma which was not significant (Pooled risk ratio = 0.69 [0.30, 1.56], 95% CI, $P = 0.37$). Excluding the data from the conference paper by Effat [35] in a sensitivity test did not alter the result (Pooled risk ratio = 0.61 [0.23, 1.60], 95% CI, $P = 0.31$).

Incidence of postoperative wound infection was reported in five studies [30–33,35], and the difference between the 1-stage group and the 2-stage group was not found to be significant (Pooled risk ratio = 0.82 [0.31, 2.18], 95% CI, $P = 0.69$). This remained unchanged when excluding the data by Effat [35] in a sensitivity test (Pooled risk ratio = 0.57 [0.21, 1.51], 95% CI, $P = 0.27$).

Similarly, the difference between the two groups was not found to be significant when it came to postoperative ischaemia (steal syndrome) in the 6 studies which reported this complication [22,30–33,35] (Pooled risk ratio = 0.51 [0.20, 1.30], 95% CI, $P = 0.16$). We performed a sensitivity test by excluding the data by Effat [35] from the pooled data, and the result was not altered (Pooled risk ratio = 0.63 [0.23, 1.69], 95% CI, $P = 0.35$).

Ozcan et al [30] allocated patients to groups based on vein diameter, with those with basilic vein > 3 mm receiving a 1-stage BVT, while patients with basilic vein < 3 mm received a 2-stage BVT. Even with this seemingly advantageous difference in favour of the 1-stage approach, they reported superior patency rates and maturation rates in patients who had a 2-stage procedure with primary patency at 1, 2 and 3 years for the 1-stage group of (70%), (64%), and (54%) versus (84%), (73%), and (69%) in the 2-stage group. Secondary patency rates at 1, 2 and 3 years for the 1-stage group were (76%), (72%), and (66%) versus (90%), (82%), and (77%) in the 2-stage group.

Similarly, Vrakas et al reported a smaller mean vein diameter of (3.6 ± 1.3 mm) for the 2-stage, versus (4.0 ± 1.1 mm) fistulas created in the 1-stage group, yet their results favoured the 2-stage approach with primary functional patency at 1 and 2 years for the 1-stage group of 71% and 53% versus 87% and 75% in the 2-stage group. Assisted Primary functional patency at 1 and 2 years for the 1-stage group was 77% and 57% versus 95% and 77% in the 2-stage group, while secondary functional patency at 1 and 2 years for the 1-stage group was 79% and 57% versus 95% and 77% in the 2-stage group.

Conversely, in study by Agarwal et al [34], their patients in the 1-stage group achieved better maturation rate than those who had a 2-stage BVT fistulas (90% vs 75%, $P = 0.02$). They did

not include any analysis between the two groups based on vein diameter. Vein diameter has been shown to negatively influence maturation and patency rates in AVFs, and is one of the main predictors of those outcomes in fistulas [40,41], and indeed has been shown to be the only independent predictor of maturation in some studies [42,43]. Syed et al reported similar findings with better primary and cumulative patencies in the 1-stage group with primary patency at 1, 2 and 3 years (82% vs 67%), (81% vs 27%) and (51% vs 18%), while (secondary patency at 1, 2 and 3 years (91%, 80% and 58% for 1-stage BVT and 81%, 61% and 45% for the 2-stage group. Variations in vein diameter between the two groups were not reported in this study.

Kakkos et al [31] did not find a significant difference in maturation between the two groups, as 15% of fistulas in the 1-stage group did not mature, compared to 18% in the second group ($P = 0.49$). They did however find significant difference in developing postoperative haematoma (13% vs 3%, $P = 0.012$), venous hypertension (17% vs 4%, $P = 0.004$) and overall complications (43% vs 11%, $P < 0.001$), all in favour of the 2-stage BVT technique.

Kim et al compared the 2-stage approach to all other AVF procedures including 1-stage BVT, radiocephalic and brachiocephalic fistulas. All of the 2-stage BB-AVFs in their study successfully matured compared to a pool consisting of all different types that showed a combined maturation rate of 52% ($P = 0.001$). Fistula failure occurred in 7% of the 2-stage BVT compared to 59% of other fistulas ($P = 0.001$), and more 2-stage BVT fistulas were used successfully for HD compared to all other fistula types (87% vs 48%, $P = 0.024$). Also, the patency rate at 1 year was superior in the 2-stage group compared to other AVFs (91% vs 47%, $P = 0.003$).

One of the limitations of this review is the low number of randomised trials included—1 study was randomised—while the remaining 7 were cohort studies. Most of these studies were retrospective. Another limitation is the variation in surgical approaches, those variations include technical differences in performing the procedure, as well as differences in equipment used and expertise among participating surgeons. Those limitations can be addressed by conducting a large randomised multi-centre trial that would adhere to a rigid protocol in patients' selection process and performing the procedures. Another limiting factor is the lack of sufficient sub-group analysis among included studies, particularly analysis taking into account factors that are known to be associated with fistula maturation such as vein diameter. Finally, we highlight that included studies were not compliant with SVS reporting recommendations regarding baseline factors that affect outcomes or severity of complications.

Conclusion

Although more studies seem to favour the 2-stage BVT approach, evidence in the literature is not sufficient to draw a final conclusion as the difference between the 1-stage and the 2-stage approaches for creation of a BB-AVF is not statistically significant in terms of the overall maturation rate and postoperative complications. Patency rates (primary, assisted primary and secondary) were comparable in the majority of studies. Large randomised properly conducted trials with adequate sub-group analysis are needed before making a final recommendation. Future studies should aim for compliance with established reporting standards.

Supporting Information

S1 PRISMA Checklist. PRISMA 2009 Checklist.
(DOCX)

S1 Table. Quality assessment score of individual studies.
(DOCX)

Author Contributions

Conceived and designed the experiments: KB DH LB MW MCM EK PB SRW. Performed the experiments: KB DH SE LB MW MCM EK PB SRW. Analyzed the data: KB DH SRW. Wrote the paper: KB DH SE SRW.

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Appendix 8: Publication from the thesis “Role of far infra-red therapy in dialysis arterio-venous fistula maturation and survival: systematic review and meta-analysis”:

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PLOS ONE

Role of Far Infra-Red Therapy in Dialysis Arterio-Venous Fistula Maturation and Survival: Systematic Review and Meta-Analysis



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Abstract

Introduction: A well-functioning arteriovenous fistula (AVF) is the best modality for vascular access in patients with end-stage renal disease (ESRD) requiring haemodialysis (HD). However, AVFs' main disadvantage is the high rate of maturation failure, with approximately one third (20%–50%) not maturing into useful access. This review examines the use of Far-Infra Red therapy in an attempt to enhance both primary (unassisted) and secondary (assisted) patency rates for AVF in dialysis and pre-dialysis patients.

Method: We performed an online search for observational studies and randomised controlled trials (RCTs) that evaluated FIR in patients with AVF. Eligible studies compared FIR with control treatment and reported at least one outcome measure relating to access survival. Primary patency and secondary patency rates were the main outcomes of interest.

Results: Four RCTs (666 patients) were included. Unassisted patency assessed in 610 patients, and was significantly better among those who received FIR (228/311) compared to (185/299) controls (pooled risk ratio of 1.23 [1.12–1.35], $p=0.00001$). In addition, the two studies which reported secondary patency rates showed significant difference in favour of FIR therapy-160/168 patients - compared to 140/163 controls (pooled risk ratio of 1.11 [1.04–1.19], $p=0.003$).

Conclusion: FIR therapy may positively influence the complex process of AVF maturation improving both primary and secondary patency rates. However blinded RCTs performed by investigators with no commercial ties to FIR therapy technologies are needed.

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Introduction

The number of patients with end stage renal disease (ESRD) requiring haemodialysis (HD) is steadily rising, a trend that is expected to continue [1]. Vascular access is a critical component in successful HD. A well-functioning arteriovenous fistula (AVF) is the best modality for HD vascular access [2–6]. AVF maturation is a complex process of remodelling. The newly formed fistula has to form a low resistance circuit capable of dilation to accommodate the increased blood flow required for HD. The AVF also has to be cannulated repeatedly with ease. The need for re-intervention to maintain patency should be minimal [2–4,6,7].

AVFs' main disadvantage is the high rate of maturation failure, with approximately one third (20%–50%) not maturing into useful access [8–10]. AVFs have higher primary failure rates to mature compared to grafts [8,11,12]. However they last longer, and with exclusion of fistulas that fail to mature primarily, the cumulative

patency from formation to permanent failure is superior to grafts. AVFs also require fewer secondary interventions in the form of angioplasty, stenting or thrombectomy [8,13–16]. AVFs are associated with fewer complications compared to AVG and CVC in terms of infection, death, vascular access salvage procedures and hospitalizations [15,16]. Also, a mature AVF has a lower incidence of thrombosis and stenosis. This translates into prolonged patency rates and lower risk for infection [1,17–20].

Maturation of AVF depends on variable biomechanical forces. Remodelling of the arterial limb is characterised by vessel dilatation and outward hypertrophic remodelling of the intimal layer. Remodelling at the venous end can be accompanied by aggressive intimal thickening resulting in inward hypertrophic remodelling. Intimal hyperplasia (IH) is defined as the abnormal migration and proliferation of vascular smooth muscle cells provoked by injury, inflammation or stretch with associated

Table 1. Results of the study quality assessment.

| Included study | Domain | Support for judgement | DH's judgement |
|------------------------------------|--|---|-------------------|
| Lai 2013 ESVS [37] | Random sequence generation | The method of generating the random sequence was not described. | Unclear |
| | Allocation concealment | No description of methods for maintaining allocation concealment. | Unclear |
| | Blinding of participants and personnel | Participants and personnel were not blinded. Dysfunctional access signs and other referral criteria could have a subjective component. | High risk of bias |
| | Blinding of outcome assessment | Outcome assessors were not blinded. Dysfunctional access signs and other referral criteria could have a subjective component. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was minimal. Analysis was not by intention to treat. 9/59 control group patients crossed over to the intervention group potentially leading to bias in favour of the intervention | Unclear |
| | Selective reporting | No link to the protocol was given | Unclear |
| Lin 2007 J Am Soc Neph [35] | Other sources of bias | None | Not available |
| | Random sequence generation | A computerised minimisation algorithm was used | Low risk of bias |
| | Allocation concealment | Allocation sequence was kept by a study nurse who would not disclose allocations until time of intervention. Diagnosing malfunction in a fistula could have had a subjective element. | Unclear |
| | Blinding of participants and personnel | Participants and personnel were not blinded. | High risk of bias |
| | Blinding of outcome assessment | Outcome assessors were not blinded. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was minimal and was similar between groups and was unlikely to influence results | Low risk of bias |
| Lin 2013 AJKD [38] | Selective reporting | Protocol was not available. | Unclear |
| | Other sources of bias | None | Not available |
| | Random sequence generation | A computer generated sequence was used | Low risk of bias |
| | Allocation concealment | Sealed opaque envelope were used to conceal allocation. There was no information in the manuscript or protocol on who had access to the envelopes and whether they were opened sequentially | Unclear |
| | Blinding of participants and personnel | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Blinding of outcome assessment | Ultrasonographers were blinded however patients were not blinded. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| Lin 2013 Neph Dial Transplant [36] | Incomplete outcome data | Loss to follow up was similar between groups and unlikely to influence results | Low risk of bias |
| | Selective reporting | Link to protocol was provided (NCT01138254). Trial was not prospectively registered and there were several changes made including changes to outcomes. | High risk of bias |
| | Other sources of bias | None | Not available |
| | Random sequence generation | A computer generated sequence was used | Low risk of bias |

Table 1. Cont.

| Included study | Domain | Support for judgement | DH's judgement |
|----------------|--|--|-------------------|
| | Allocation concealment | Sealed opaque envelope were used to conceal allocation. Two study nurses had access to the envelopes and there was no information in the manuscript or protocol on whether they were opened sequentially | Unclear |
| | Blinding of participants and personnel | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Blinding of outcome assessment | No blinding. Diagnosing malfunction in a fistula could have had a subjective element. | High risk of bias |
| | Incomplete outcome data | Loss to follow up was similar between groups and unlikely to influence results | Low risk of bias. |
| | Selective reporting | All outcomes that were mentioned in the protocol were reported. The subgrouping based on polymorphisms of heme oxygenase-1 was not prespecified | Low risk of bias |
| | Other sources of bias | None | Not available |

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deposition of extracellular matrix in the intimal layer of the vein [21–23].

Far infra-red FIR therapy, which is a form of heat therapy, has been implicated in improvement of endothelial function and haemodynamics in coronary arteries, probably through up-regulating endothelial nitric oxide synthase (eNOS) expression in arterial endothelium leading to improved cardiac function in patients with chronic heart diseases [24]. Repeated leg hyperthermia using FIR has been shown to reduce oxidative stress in bed ridden type II diabetics [25].

FIR has also been reported to show encouraging results in phantom limb pain control [26], stimulation of the secretion of TGF-beta1 and activation of fibroblasts which may promote better wound healing independent of skin blood flow and skin temperature [27,28], reduction of both stress and fatigue levels of patients with end stage renal disease (ESRD) and stimulates the autonomic nervous system in those who are receiving regular haemodialysis (HD) [29].

This review was designed to examine the effect of FIR on AVF maturation using primary and secondary patency rates as the main outcomes of interest.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [30].

Eligibility Criteria

We included observational studies or randomised controlled trials (RCTs) that examined FIR therapy in patients with AVFs and ESRD. Eligible studies reported on AVF patency rates in FIR and non-FIR groups at one year or more following initiation of FIR therapy. Cases series and case reports were excluded. There was no restriction with regard to publication status or language.

Search strategy

A search of the literature for relevant studies was conducted in March 2014. We searched Medline without date restriction using

the free text “far infra-red”. Additionally we used the strategy (“far infra-red” OR “far infrared” OR “post conditioning”) AND [“arteriovenous fistula” OR “dialysis” OR “end stage renal disease” OR “dialysis access” OR “access survival” OR “primary patency” OR “secondary patency” OR “fistula maturation”]) to search CINAHL, EMBASE, the Cochrane library and Google Scholar. Bibliographies of included studies were searched for additional studies.

Abstracts of the relevant titles were subsequently obtained and evaluated for eligibility (KB, DH). Any remaining uncertainty was resolved by examination of the full article (KB, DH). Discussion with a third author (SRW) resolved discrepancies in cases of disagreement regarding eligibility.

The relevant outcomes for this review were primary patency defined as unassisted AVF patency rates after at least 12 months of follow up - and secondary patency defined as assisted patency rates after at least 12 months of follow up. The incidence of salvage procedures (endoluminal procedures or surgical procedures) for dysfunctional fistulas during follow up was a secondary outcome.

Data Collection

Data were extracted and checked for accuracy by two reviewers (KB, DH) independently and recorded on a Microsoft Excel spreadsheet. Any disagreements in extracting data were discussed between two reviewers (KB, DH), and if not settled this was resolved by consulting with a third reviewer (SRW). The following information regarding participant characteristics were recorded: age, sex, presence of co-morbidities, start of HD, primary and secondary patency rates, AVF salvage procedures, underlying cause of ESRD, definition of first AVF malfunction and overall access survival. The trials' inclusion and exclusion criteria were also recorded.

Quality assessment for risk of bias

The risk of bias for each study was assessed according to the criteria outlined in the in the Cochrane Handbook for Systematic Reviews of Interventions [31]. For each included study; the method used to perform random sequence generation, allocation concealment and blinding was described. The study was then

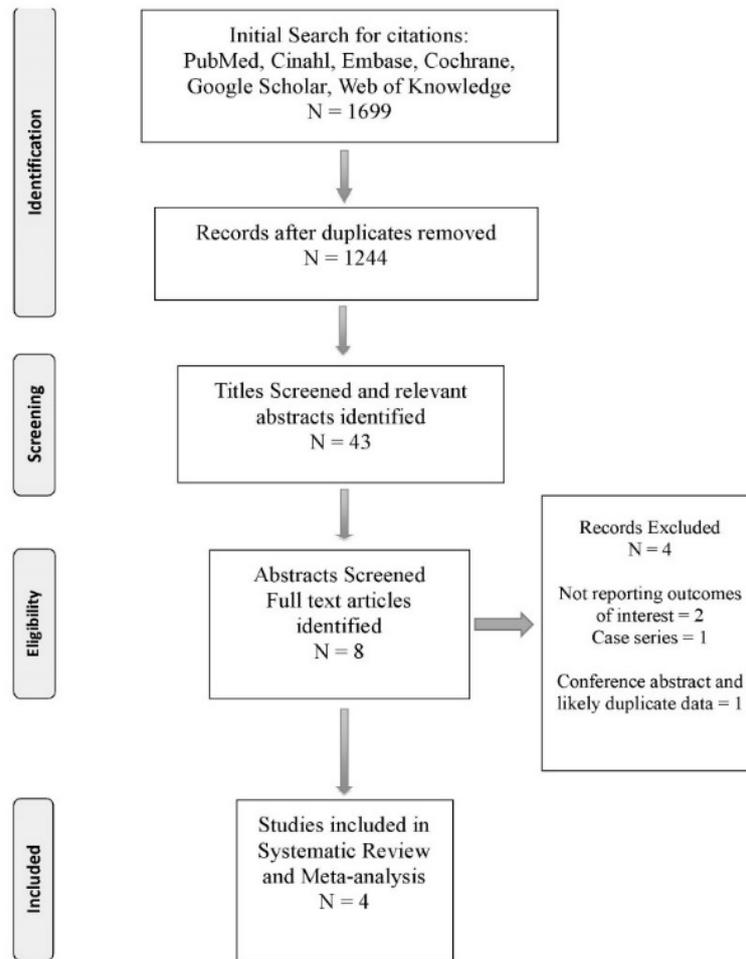


Figure 1. PRISMA 2009 Flow Diagram.
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scrutinised for incomplete data outcomes, selective reporting and other potential sources of bias. Where possible, study protocols were obtained from trial registries to ascertain whether there was selective reporting within studies [Table 1].

Data analysis

Statistical analyses were performed using Review Manager version 5.2.8 [32]. Pooled risk ratios were calculated using the random effects model of DerSimonian and Laird [33]. For

Table 2. Inclusion & exclusion criteria and definition of AVF malfunction for included studies.

| Study | Inclusion criteria | Exclusion criteria | Definition of AVF malfunction |
|--------------------|---|---|---|
| Lin 2007 [35] | (1) Receiving 4 h of maintenance HD therapy three times weekly for at least 6 months at Taipei Veterans General Hospital, (2) Using a native AVF as the current vascular access for more than 6 months, without interventions within the last 3 months, and (3) Creation of AVF by cardiovascular surgeons in our hospital with the standardized surgical procedures of venous end-to-arterial side anastomosis in the upper extremity. | During the 1-yr follow-up, patients would be excluded from the study because of the following censoring criterion: (1) Renal transplantation, (2) Death with a functioning access, (3) Shifting to peritoneal dialysis, and (4) Loss of follow-up. | The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning AVF that cannot sustain an extracorporeal blood flow >200 ml/min during HD after exclusion of the following stenosis-unrelated events: Infectious complication, progressive aneurysmal formation, or steal syndrome. |
| Lin 2013_AJKD [38] | (1) Aged 18–80 years, (2) Had CKD with estimated glomerular filtration rate (eGFR) of 5–20 mL/min/1.73 m ² , (3) Were not anticipated to receive dialysis or kidney transplantation within the next 3 months, and (4) Were undergoing AVF creation with venous end-to-arterial side anastomosis in the upper extremity. | (1) Those receiving an arteriovenous graft or cuffed tunneled double-lumen catheter as the type of permanent vascular access, (2) Heart failure of New York Heart Association functional class III or IV, and (3) Episode of cardio- or cerebrovascular event or receiving interventional therapy within 3 months prior to screening. | The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning fistula which could not sustain an extracorporeal blood flow >200 ml/min during HD after excluding the following stenosis-unrelated events, such as infectious complication, progressive aneurysmal formation or steal syndrome. |
| Lai 2013 [37] | (1) Received two or more PTA on the target lesions at upper extremities, with the last PTA successfully performed within the week before patient enrolment, and (2) After successful completion of at least 1 week of HD treatment, the patients with AVF or AVG were consecutively enrolled and randomly assigned to either a post-PTA FIR radiation group or a control group receiving the usual form radiation therapy at a 1:1 ratio. | (1) Received HD treatments other than three times a week, (2) Had previously received FIR radiation therapy, (3) Received implantation of an endovascular stent, (4) Had multiple lesions that a single radiation field did not cover or the central lesion was considered too deep to be irradiated, (5) Missed FIR radiation treatments exceeding 10%, (6) Underwent renal transplantation, (7) Switched to peritoneal dialysis treatments, and (8) Had any severe disease with an estimated life expectancy of less than 1 year. | A significant lesion was defined as a lumen loss of 50% or more compared with adjacent normal vessel on angiography following dysfunctional diagnosis based on clinical signs suggestive of stenosis. |
| Lin 2013_NDT [36] | (1) Receiving 4 h of maintenance HD therapy three times weekly for at least 6 months at Taipei Veterans General Hospital, (2) Using a native AVF as the present vascular access for >6 months, without interventions within the last 3 months, and (3) Creation of AVF by cardiovascular surgeons in our hospital with the standardized surgical procedures of venous end-to-arterial side anastomosis in the upper extremity. | Received an AV graft as the first vascular access. | The need for any interventional procedure (surgery or angioplasty) to correct an occlusive or malfunctioning fistula which could not sustain an extracorporeal blood flow >200 ml/min during HD after excluding the following stenosis-unrelated events, such as infectious complication, progressive aneurysmal formation or steal syndrome. |

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continuous outcome variables the weighted mean difference (WMD) was calculated. The presence of statistical heterogeneity between studies was evaluated using the Cochran's Q statistic. P-values less than 5% were considered as statistically significant. Publication bias was assessed visually using a funnel plot, and additionally by comparing fixed and random effects modelling in a sensitivity analysis this is a recognised method that can detect the influence of small-study effects [34].

Results

Study Selection

The results of the study selection process are summarized in the PRISMA flow diagram (Figure 1). The initial search yielded a total of 1669 citations, with 1244 citations remaining following removal of duplicates. The titles of these citations were screened with a total of 43 titles deemed potentially relevant. The abstracts of those titles were examined and eight full text articles were subsequently retrieved and examined. After assessing for eligibility

Table 3. Patients' Characteristics across included studies.

| Study | Patients | | Age | | Gender (M:F) | | Diabetes | | Hypertension | | Hx of AVF failure | | Time on HD | | Withdrawals |
|--------------------|----------|---------|-----------|-----------|--------------|---------|----------|---------|--------------|---------|-------------------|---------|--------------|--------------|---|
| | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | FIR | Control | |
| Lin 2007 [35] | 63/72 | 64/73 | 61.9±1.44 | 59.2±1.90 | 37/35 | 38/35 | 25 | 24 | 40 | 39 | 33 | 34 | 85.2±4.11 | 79.2±42.2 | Creation of another vascular access because of the poor response to angioplasty in 3 patients and 4 patients in control group. Patients were censored in case of: Renal transplantation (n=3), death with a functioning access (n=5), shifting to peritoneal dialysis (n=4) or loss of follow-up (n=1). |
| Lin 2013_AIRD [38] | 60 | 62 | 63.2±18.5 | 63.0±14.4 | 32/28 | 35/27 | 28 | 23 | 18 | 20 | - | - | Pre-dialysis | Pre-dialysis | Lost to FU: FIR = 1; Control = 1. Shifting to PD: FIR = 1; Control = 1. Death eAVF: FIR = 2; Control = 3. Renal transplantation: FIR = 1; New AVF: FIR = 1; Control = 1. CVC intervention: FIR = 2; Control = 1. |
| Lin 2013_MDT [36] | 119/139 | 120/141 | 61.3±14.1 | 62.8±15.9 | 79/60 | 71/70 | 45 | 47 | 80 | 90 | 47 | 45 | 66.0±59.1 | 75.9±58.0 | Underwent creation of another vascular access: 3 patients receiving FIR therapy and 2 patients in the control group. Patients were censored in case of: Renal transplantation (n=5), death with a functioning access (n=5), shift to peritoneal dialysis (n=5) or loss of follow-up (n=9). |
| Uhl 2013 [37] | 69 | 50 | 62.7±10.9 | 63.1±12.5 | 32/37 | 24/26 | 47 | 28 | 48 | 38 | All | All | 50.4±42.0 | 58.8±56.4 | Crossover patients: 9 from Control to FIR. |

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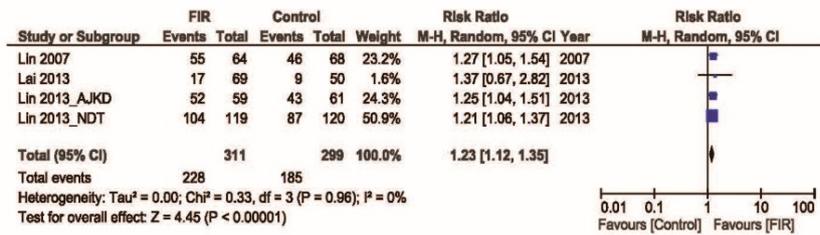


Figure 2. Forest Plot showing Primary AVFs patency at 12 months.
doi:10.1371/journal.pone.0104931.g002

criteria, four RCT's were included in the review [35–38]. Three of those studies reported on patients with history of previous AVF who had been on HD prior to FIR therapy [35–37], while one study reported on patients with newly formed AVF not on HD [38]. We were not able to include another study by Lin et al [39] with a follow up of 3 months for primary patency rates as it was a conference abstract only, also we had concerns that the data in this study was used in another study by the same author [36] that has

already been included in this review. Three studies were excluded from the final analysis after going through the full articles. Shipley et al followed their patients for six months in a case series of 20 patients – no control group – and reported maturation in 10 of those patients [40]. Two studies did not report on the outcomes of interest to the author of this systematic review [29,41].

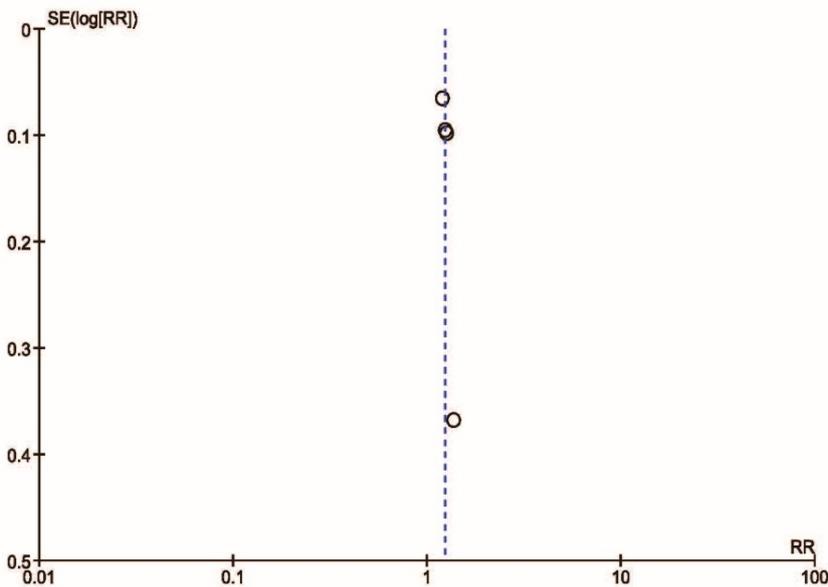


Figure 3. Funnel plot for Primary AVFs patency at 12 months.
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Far Infra-Red Therapy Role in Maturation of AVF

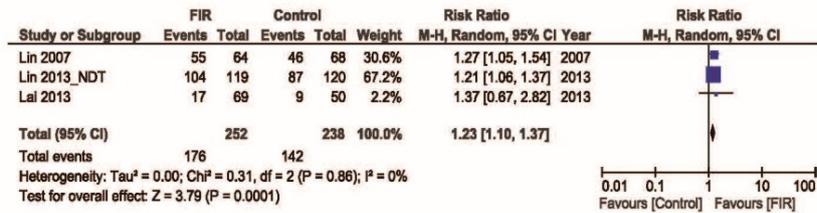


Figure 4. Forest Plot showing Primary AVFs patency at 12 months, Lin et al RCT on new AVFs excluded.
doi:10.1371/journal.pone.0104931.g004

Characteristics of included studies

Far Infrared (FIR) technique. All studies included used the same technique for delivering of FIR therapy. WS TY101 FIR emitter (WS Far Infrared Medical Technology Co., Ltd., Taipei, Taiwan) was used in all studies which generates electromagnetic waves with wavelengths in the range between 5 and 25 (peak at 5.8.2 μm). The top radiator was set at a height of 20–30 cm above the surface of the AVF with the treatment time set at 40 min during HD three times per week.

Participants

The four studies included 666 patients, with 340 patients randomised to receive FIR therapy (median age 62.3±14.5 SD), while 326 were randomised to the control group (median age 62.0±14.5 SD). 348 patients were males (180 in FIR group and 168 in the control group), while females were 318, of those 160 received FIR therapy and 158 were controls.

Inclusion and exclusion criteria of studies are outlined in [Table 2], along with the definition of AVF malfunction for each of the included studies.

Apart from Lin et al who evaluated the effects of FIR in pre-dialysis patients with newly formed AVFs [38], the remaining RCTs included patients who already started HD. Mean time on HD in months for Lin et al [35] was 85.2±41.1 for FIR group and 79.2±42.2 for the control group, for Lai et al [37] FIR = 50.4±42 and control = 58.8±56.4 and for Lin et al in 2013 [36] FIR = 66.0±59.1 and control = 75.9±58.0. All patients in included trials received FIR therapy for 40 minutes per session three times a week for the duration of the study.

Lai et al studied patients with history of dysfunctional AVFs and repeated angioplasty. The mean life of the AVFs for their patients was 21.8±23.0 months for FIR group and 23.5±22.6 months for

the controls [37]. 33 patients from 72 had history of AVF malfunction and 14 patients required surgical intervention, while 20 patients had a total of 49 angioplasty procedures in the FIR group compared to 34 patients from 73 with history of AVF malfunction, 13 of those required surgical intervention and 20 patients with total of 46 angioplasty procedures in the control group, in the RCT by Lin et al in 2007 [35]. Similarly, 47 patients had history of AVF malfunction with 12 patients requiring surgery from 139 and 35 patients underwent 79 angioplasty procedures in the FIR group, compared to 45 patients with history of malfunction, 13 patients of those required surgery and 32 patients underwent angioplasty as a salvage procedure in the control group in the study by Lin et al in 2013 [36]. All patients in both FIR and control groups had angioplasty procedures prior to recruitment in the study by Lai et al [37], while none of the patients included by Lin et al had a history of either surgical or angioplasty salvage procedures since they were all first time AVFs [38]. Lai et al had 9 of their patients who were initially randomised to the control group crossing over to the FIR group based on their request [37]. Clinical maturation was reported in 49 (81.7%) patients of 60 who received FIR therapy by Lin et al, compared to 37 (59.7%) from the 62 control subjects [38]. Sub group analysis by age, gender and diagnosis of hypertension was not possible as this was not included in studies, and we did not have access to the raw data used by the authors. Other patients' characteristics are detailed in [Table 3].

Primary - unassisted - patency rates at 1 year

All of the 4 included studies (610 patients) reported on unassisted primary patency rate after 12 months of follow-up on the FIR therapy. 228/311 patients in FIR group had primarily patent AVFs at 12 months compared to 185/299 patients in the

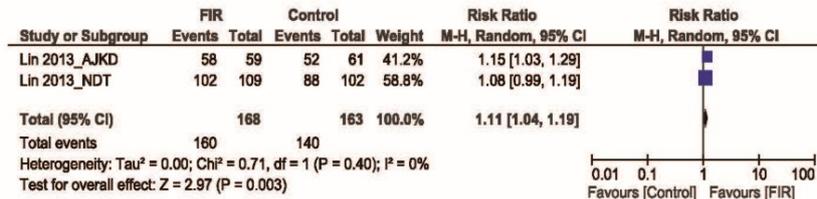


Figure 5. Forest plot showing assisted patency rates at 12 months.
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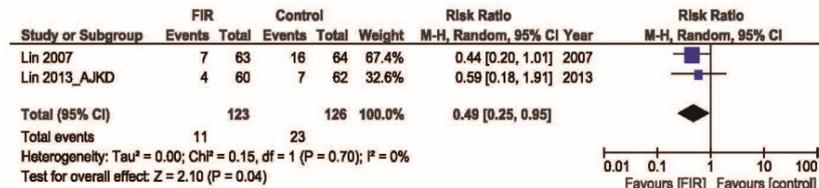


Figure 6. Forest plot showing surgical intervention for AVF malfunction.
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control group. Pooled results showed significant difference between the two groups, with those who received FIR showing better primary patency rates compared to control (Pooled risk ratio = 1.23 [1.12, 1.35], 95% CI, $p = 0.00001$) [Figure 2]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.33$; degree of freedom (DF) = 3; $p = 0.96$; $I^2 = 0\%$). The funnel plot did not suggest bias [Figure 3], and the result was unchanged when fixed effects modelling was used (pooled risk ratio 1.24 [1.13, 1.37], 95% CI, $p < 0.0001$).

Excluding the RCT by Lin et al on newly formed AVFs in pre-dialysis patients [38] from the analysis for primary patency after 12 months, the remaining studies (490 patients) showed better results in the FIR group with 176/252 AVFs being patent at 12 months compared to 142/238 in the control group [35–37]. This was statistically significant (Pooled risk ratio = 1.23 [1.10, 1.37], 95% CI, $p = 0.0001$) [Figure 4]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.31$; degree of freedom (DF) = 2; $p = 0.86$; $I^2 = 0\%$).

Secondary - assisted - patency rates

Data could be retrieved from 2 studies (331 patients) for analysis of assisted secondary patency rates at 12 months following salvage procedures [36,38]. 160/168 patients in the FIR group had patent AVFs following intervention for dysfunctional fistulas, compared to 140/163 patients in the control arm. Pooled results showed statistically significant difference favouring FIR therapy (Pooled risk ratio = 1.11 [1.04, 1.19]; 95% CI, $p = 0.003$) [Figure 5]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.71$; degree of freedom (DF) = 1; $p = 0.40$; $I^2 = 0\%$).

Intervention

Two studies [35,38] (249 patients) reported the need for intervention to salvage a dysfunctional AVF. Patients who received FIR therapy required less interventions, 11/123 patients compared to 23/126 patients in the control group. The difference was significant (Pooled risk ratio = 0.49 [0.25, 0.985; 95% CI; $p = 0.04$) [Figure 6]. There was no evidence of statistical heterogeneity (Cochran's $Q = 0.15$; degree of freedom (DF) = 1; $p = 0.70$; $I^2 = 0\%$).

Discussion

This review identified four studies (666 patients) which evaluated the use of FIR therapy to improve primary and secondary patency rates for AVFs in patients with ESRD. They all reported significant improvement in the outcome measures assessed in this review in favour of FIR therapy. Three of those studies (490 patients) were carried out on patients already started

HD sessions, and one study (122 patients) focused on pre-dialysis first time AVF maturation. All four trials following some form of randomisation, and the demographics of patients in included studies did not differ significantly. Pooled analysis showed that primary - unassisted - patency was significantly better in the FIR group (pooled risk ratio of 1.23 [1.12, 1.35], p value of 0.0001). Secondary - assisted - patency was reported in two studies (279 patients) and was found to be significantly better in those who received FIR therapy (pooled risk ratio of 1.19 [1.07, 1.31], p value of 0.0008).

Post-conditioning using Far Infra-Red therapy has been shown to increase the level of heme oxygenase-1 (HO-1) expression which protects against Ischaemia/reperfusion injury in study by Tu et al [42]. HO-1 is a known vasodilator and at the same time inhibits proliferation of vascular smooth muscle cells, platelet aggregation, and vasospasm leading to favourable conditions for maturation of AVFs. Also, Ikeda et al repeated thermal therapy was shown to up-regulate endothelial nitric oxide synthase expression in Syrian hamsters [24], a finding that was validated by Akasaki et al, who also reported increased angiogenesis via (eNOS) following repeated thermal therapy in mice with hindlimb ischemia. [43]. Kipshidze et al irradiated cultures of rabbit endothelial cells and smooth muscle cells with different doses of non-ablative infrared. They found that non-ablative infrared laser inhibited neointimal hyperplasia after coronary arteries angioplasty in cholesterol-fed rabbits for up to 60 days [44]. FIR therapy is still considered a novel treatment for AVF although the technique has been described since 2007 by Lin et al [35]. This review demonstrated a beneficial use of FIR therapy that improved both primary and secondary patency rates across all studies included. This statistically significant difference was consistent even when one excluded study for having only 3 months of follow-up was added to the sensitivity analysis [39]. Also, excluding the only RCT found by the authors on newly formed AVF did not alter the outcome of the pooled analysis in terms of significance.

FIR therapy was also shown to improve access flow (Q_a). The study by Lin et al which was one of the RCTs included in the review - showed that 40 min of FIR therapy in a single HD session could increase access flow of AVF by about 50 mL/min with a 1-year effect of improving Q_a by up to 150 mL/min and increasing unassisted patency of AVF by about 18% in comparison with controls [35].

A serious limiting factor of this systematic review is that the four RCTs came from the same institution (Yang-Ming University in Taiwan), and three of the four were authored by the same two authors (Lin-cc and Yang-wc) [35,36,38]. Dr Lin-cc reported that he was receiving lecture fees from WS Far Infrared Medical Technology, the company that makes the infrared machines used in the studies raising the potential of bias.

Also, all the RCTs were performed in an unblinded fashion, which can impact outcomes as demonstrated by the fact that in one study nine patients opted to join the FIR group despite initially being allocated as controls. Blinding in clinical trials involving FIR therapy would involve additional costs in making machines that resemble the ones used to deliver FIR therapy. These machines should be convincing to both staff and patients if effective double blinding is to be considered. However, blinding can be attempted by placing a screen between the FIR device and the patient. Also, double-blinding can be achieved by placing a box over the device and then creating simple mock devices that also appear as boxes. This review provides a thorough examination of published evidence supporting the use of FIR therapy to promote AVF access maturation in patients with ESRD in HD, and also for those who are likely to require dialysis in the near future. The meta-analysis showed overwhelming support for regular use of FIR therapy, however there were limitations that need to be considered. Finally, this review may serve to guide future advances in using repeated thermal therapy in postconditioning of AVFs.

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Conclusion

Results from four RCTs suggest that regular use of FIR therapy in haemodialysis and pre-haemodialysis patients, in particular those with AVFs, can positively influence AVF function. However, more blinded randomised controlled, multicentre and international clinical trials are required. We also hope to see sub-group analysis in those studies, particularly by age (e.g. using 65 as cut-off), gender and diagnosis of hypertension.

Supporting Information

Checklist S1 PRISMA 2009 Checklist.

(DOC)

Author Contributions

Conceived and designed the experiments: KB DH EK SRW MCM PB EK MW LB. Performed the experiments: KB DH EK SRW MCM PB EK MW LB. Analyzed the data: KB DH EK SRW MCM PB EK MW. Contributed reagents/materials/analysis tools: KB DH. Contributed to the writing of the manuscript: KB DH EK SRW MCM PB EK MW LB.

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Appendix 9: Publication from the thesis “Arteriovenous Fistula in dialysis patients: Factors implicated in early and late AVF maturation failure”:

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Arteriovenous fistula in dialysis patients: Factors implicated in early and late AVF maturation failure

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| <p>Article history: Received 17 October 2015 Received in revised form 9 February 2016 Accepted 12 February 2016 Available online xxx</p> <p>Keywords: Arteriovenous fistula AVF Dialysis End stage renal disease Dialysis access Access survival Primary AVF patency Fistula maturation AVF failure AVF non-maturation Brachio basilic arteriovenous fistula Far-Infra Red</p> | <p>Increasing numbers of patients are being diagnosed with end-stage renal disease (ESRD), and the demand for on haemodialysis (HD) is rising. Arteriovenous fistulae (AVFs) remain the best conduit for adequate HD, with fewer complications associated with long-term use compared to bypass grafts and central venous catheters. However, it is known that many newly formed fistulae do not mature to provide useful HD access. The paper provides a narrative overview of factors influencing the process of AVF maturation failure. © 2016 Royal College of Surgeons of Edinburgh (Scottish charity number SC005317) and Royal College of Surgeons in Ireland. Published by Elsevier Ltd. All rights reserved.</p> |

Introduction

The number of patients with end-stage renal disease (ESRD) has been growing steadily, thus increasing the demand for haemodialysis (HD).^{1,2} Arteriovenous fistula (AVF) has been

shown to be the best route for delivering HD.^{3–5} The main disadvantage of AVF is the rate of non-maturation (failure to use the new fistula for successful haemodialysis sessions); as the newly formed conduit needs to mature into a low resistance circuit, allowing frequent cannulation with increased flow rates. There is no universal definition for a mature AVF;

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2

THE SURGEON XXX (2016) 1–7

the one adopted in the updated NKF-KDOQI guidelines has been widely in use. KDOQI introduced the role of 6s to define maturation (Flow of 600 ml/min, an AVF located less than 6 millimetres from the skin surface to facilitate successful repeated cannulation by HD staff and finally a minimal diameter of 6 millimetres).⁶ A mature fistula should be consistently cannulatable, and should allow blood flow of at least 300–400 ml per minute. This review summarises current knowledge about why so many fistulae fail to mature.^{7,8} Additionally, it provides an overview of the current practice and understanding of the complex nature of the process of AVF maturation by the authors of this review.

Methods

Pubmed and Embase were searched using a number of search terms (maturation, arteriovenous fistula, AVF, non-maturation, prediction, failure, end-stage renal disease and haemodialysis) in different combinations. Retrieved articles were included based on relevance to the subject of the narrative overview after assessing all abstracts. Although we agree that a detailed assessment of the quality of the individual studies included would increase the rigour of the review, however, we feel it can be addressed in a future systematic review, as this article is intended as a narrative review.

Patient characteristics: sex, age and diabetes mellitus

Various patient factors have been suggested to be associated with poor AVF maturation, including diabetes mellitus (DM), female sex and age. However, those factors are less important when preoperative ultrasound mappings show adequate size vessels. Preoperative US venous mapping has been proven to significantly aid the decision of placing an AVF that will have better odds of successful maturation.^{9–11}

Salmela et al., found that diabetes mellitus, female sex and thrombophilia were associated with decreased primary fistula patency rates.¹² Conversely, Sedlacek et al. reported that diabetes was not an independent risk factor for AVF non-maturation, and furthermore presence of diabetes had no effect on the prevalence of AVF creation.¹³ Recently, Allon et al. reported that both diabetes and age did not influence AVF maturation outcomes, although both were significantly linked to increased intimal hyperplasia.¹⁴ Similarly, Farber et al. found that diabetes was not associated with early thrombosis.¹⁵

Diabetes potentially exerts its influence on AVF maturation by affecting the bioavailability of Nitric Oxide (NO) as most of the metabolic abnormalities that take place in diabetic patients can disrupt the balance between production of NO and its degradation.¹⁶ In addition, diabetes is a known risk factor for atherosclerosis, which can also limit blood flow through a newly created AVF. Overall, the evidence that diabetes alone can predict non-maturation is controversial, as the rate of AVF maturation in diabetics is similar to non-diabetics in some published series.

Elderly patients (e.g. above 65 years) are thought to have worse patency rates.^{17,18} Lok et al. argued that age should not be a limiting factor when considering vascular access options for HD as their study showed equal survival and procedural rates in patients above or under 65 years of age.⁸ This suggests that in those fistulae that mature successfully, age is less relevant in determining cumulative patency.

A study of cumulative access survival in AVF found that age, race, diabetes, gender and peripheral vascular disease did not show significant association with access survival.¹⁹ The number of salvage procedures was the only significant factor associated with cumulative access survival in this study, as more interventions were required in elderly patients to maintain patency.¹⁹ Tordoir et al. argued that elderly patients are more likely to have calcified arteries and small veins, therefore suggested the use of early stick catheters and central vein catheters.²⁰ In the very elderly with multiple comorbidities, the authors believe that consideration should be given to dialysis via central venous catheters (CVCs) as the primary access choice to reduce the surgical burden from repeated salvage procedures usually required to maintain patency.

Some studies suggested a significant negative association between female gender and fistula patency rates and prolonged maturation.^{12,17,21} Also, others have suggested that elderly female patients (65+) are at higher risk of fistula non-maturation than men are of the same age group.^{14,18} However, several studies disputed the association between female sex and high risk of AVF non-maturation.^{14,19,22} Recently, Bashar et al. found that female gender, history of a kidney transplant and calcium channel blocker agents at the time of fistula creation all influenced AVF maturation, with non-maturation associated with a female gender in their series ($P = 0.004$).²³

Lee et al. studied factors implicated in AVFs maturation. They found that race, diabetes, age, gender and peripheral vascular disease did not statistically influence the outcome; however, the sole predictor of access cumulative failure in their study was the number of secondary procedures required to maintain patency.¹⁹ Feldman et al. in a series of 348 HD patients found that non-maturation was associated with a previous history of stroke, transient ischaemic attack, increasing age and dependence on dialysis when the fistula was created.²⁴

In summary, there are papers suggesting that diabetes mellitus, female sex and increasing age among other factors can decrease fistula maturation and increase failure, however other papers dispute this. Certainly none of these factors should influence the decision to proceed to AVF formation in these groups.

Pathophysiology of AVF non-maturation

Maturation of AVF depends on variable biomechanical forces induced in the vascular system following AVF formation. Remodelling of the arterial limb is characterised by outward hypertrophic remodelling of the intimal layer leading to vessel dilatation; while at the venous side, the process can result in excessive intimal thickening resulting in narrowing of the venous limb.²⁵ The outward remodelling of the arteries assist

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in accommodating more blood flow through the conduit, whereas the inward remodelling at the venous limb can lead to stenosis and access failure. This can lead to stenosis and early thrombosis, and eventually, in non-maturation. The degree of intimal hyperplasia developing in a vessel depends on the length and depth of any (surgical) injury. It increases in proportion to direct injury to the smooth muscle layer.²⁶ In the absence of significant injury, wall stretch can lead to less marked smooth muscle cells proliferation.^{26,27} Intimal hyperplasia usually causes failure of fistulae in the long-term; however, it can also cause failure of primary maturation.²⁸

Vein diameter

Venous diameter is an independent predictor of maturation. A diameter <2.5 mm is usually associated with non-maturation, particularly if the vein lacks distensibility following the application of a tourniquet, whereas successful maturation can be expected if the vein measures ≥ 4 mm in preoperative US assessment.²⁹ Lauvaio et al. reported in a series of 158 patients that vein diameter was the main independent predictor of functional maturation; also, vein diameter was the only independent predictor of maturation in multivariate logistic regression analysis.³⁰ Mendes et al. used the smallest cephalic vein diameter distally at the wrist to predict AVF maturation. Of the 22 fistulae that were created using a cephalic vein ≤ 2 mm, 19 failed to mature, whereas 19/25 (76%) fistulae successfully matured of those created using a cephalic vein diameter of >2 mm ($P = 0.0002$).³¹

In the older patients where conservation of venous real estate is not such a priority, it is our practice not to use a cephalic vein at the wrist that measures <2.5 mm; instead, we aim to create a fistula at the elbow, or utilise a PTFE graft for brachio-axillary bypass. On the other hand, in younger patients using veins >2 mm seems reasonable.

Timing of initial cannulation and previous access

The NKF-KDOQI guidelines recommend allowing fistulae to mature for at least one month before cannulation.³² Cannulation within 14 days of creation reduces long-term fistula survival, with a 2.1-fold increased risk of subsequent fistula failure compared to fistulae cannulated beyond 14 days.⁷ No significant difference in non-maturation rates was observed in fistulae cannulated between 15 and 28 days compared to those used after 43–84 days.⁷

Several studies have suggested that the use of a previous ipsilateral CVC to initiate HD is associated with higher primary failure rates for subsequent AVF. Pisoni et al. showed that both AVFs and grafts displayed better survival if used when initiating HD compared with being used after patients began dialysis with a catheter.³³ Rayner et al. in a prospective observational study of 3674 patients found that the risk of AVF failure was increased for patients with a prior ipsilateral temporary access.⁷ A review in 2004 of vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that tunnelled catheters pose a higher mortality risk than permanent access and are associated with

increased risk of failure of a subsequent fistula.³⁴ CVCs can also result in central vein stenosis, which will reduce the chances of AVF maturation if placed on the same side of a previous catheter. The authors believe that contrast venography or other imaging should be performed preoperatively to evaluate the patency of central veins in patients with previous CVCs.

In general, AVFs created before patients start HD (pre-emptive) have higher primary patency rates (time from access creation to the first surgical intervention required to restore adequate fistula flow) compared with those created after the start of HD. Baldrati et al. showed that AVF created prior to starting HD had 94.6% patency rate immediately and 72.2% in 2 years, compared to 85.5% immediately and 54.8% in 2 years in patients with AVF created after starting HD.³⁵

Surgical technique, site and ultrasound mapping

Study by Saran et al. looked into prospective data from 12 countries in the DOPPS. They found that primary failure rate was 34% lower when the fistula was created by a surgeon who performed ≥ 25 AVFs in training, underlining the impact of surgical experience on fistula maturation.³⁶ This has been validated by other studies; therefore, AVFs should be performed by surgeons with sufficient experience in the field.^{37,38}

In the interest of preserving “venous real estate” AVFs are usually created distally at the wrist, however distally created fistulae have a greater risk of non-maturation, are likely to require more interventions and are associated with inferior cumulative rates compared to those placed proximally.^{39,40} The siting of a new AVF should be based on preoperative vascular mapping. Preoperative ultrasound venous mapping has been proven to significantly improve maturation.^{9–13} A Forearm fistula can be placed in 40%–50%, while 25%–35% more fistulae can be placed in the upper arm in patients referred initially for AVF formation.⁴¹ However, although the use of routine preoperative ultrasound in venous mapping has been recommended, its superiority to physical examination alone remains debatable, as it has been challenged in at least one randomised study.⁴²

Anatomic lesions within vessels

Focal stenosis either at the anastomosis (juxta-anastomotic) or in the draining vein, presence of a large accessory vein and very deep fistulae are the three most common observed anatomic variations, with juxta-anastomotic stenosis being the most common.^{41,43} Lesions peripheral to the arterial cannulation site are classified as inflow stenoses, whereas those central to the venous cannulation site are classified as outflow stenoses. The KDOQI guidelines recommend that all fistulae should be monitored, and advised referral for a contrast fistulogram if flow was <400–500 ml/min, or the ratio of venous access pressure to mean arterial pressure (VAPR) was >0.55.³ It needs to be highlighted that measuring the VAPR is intrinsically limited by design in detecting inflow stenosis as the pressure drops distal to the stenosis.

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THE SURGEON XXX (2016) 1–7

Venoplasty or surgical revision can assist maturation or salvage stenosed fistulae; accessory veins can be ligated and deep fistulae can be superficialised for better access.^{41,44} Planken et al. in 2007 in small series of 15 patients found that accessory veins with a diameter >70% of the cephalic vein diameter had a sensitivity of 80% and specificity of 100% of predicting non-maturation of AVFs, and they advised routine identification and surgical management of accessory veins.⁴⁵ Most anatomical causes of failure can be managed effectively with endovascular intervention, although this may be associated with higher restenosis rate which is thought to be due to intimal hyperplasia (IH) and remodelling of the AVF.⁴⁶

Far-Infra Red therapy

Heat application by means of Far Infra-Red (FIR) therapy may enhance AVF maturation, improving both primary and secondary patency rates, as well as overall cumulative rates.^{47,48} FIR is a form of post-conditioning, which has been shown to increase the levels of Haeme Oxygenase-1 (HO-1) expression, a potent vasodilator and inhibitor of vascular smooth muscle cells proliferation as well as platelet aggregation and vasospasm.⁴⁹ This is delivered by a radiator that generates electromagnetic waves (5–12 µm); the device is placed 25 cm above the fistula site, and each treatment session lasts for around 40 min, and is usually given three times a week.⁵⁰ Recently, a meta-analysis showed that FIR can positively influence fistula maturation with pooled unassisted patency rates significantly favouring the use of FIR therapy (1.23 [1.12–1.35], $p = 0.00001$); similarly, pooled secondary patency rates improved following FIR therapy (1.11 [1.04–1.19], $p = 0.003$).²⁵ In addition, fewer interventions were required to maintain patency in patients who received FIR therapy (Pooled risk ratio = 0.49 [0.25–0.985]; 95% CI, $p = 0.04$).²⁵

Immunological and pharmacological manipulation

Clopidogrel has been shown to significantly reduce the incidence of early AVF thrombosis; however it failed to increase the number of fistulae suitable for haemodialysis use in 3–4 months.⁵¹ A randomised double-blind placebo controlled study of the effect of Clopidogrel on the early thrombosis of AVFs showed benefit, however both groups showed comparable maturation rates at the end of the study.⁵² The use of Clopidogrel postoperatively in combination with an oral prostacyclin analogue (Iloprost) showed superior patency and maturation rates compared to placebo in a randomised controlled trial of 96 patients.⁵³

Antiplatelet therapy (Aspirin, Clopidogrel or Ticlopidine) when given for six months has been shown to reduce the risk of early thrombosis – within the first 6 months – of AVFs by nearly 50% in a meta-analysis.⁵⁴ There was also a reduction in the risk of early thrombosis even when antiplatelet therapy was given for 6 weeks.

One study showed that the use of a selective COX-2 inhibitor (Celecoxib) was associated with increased aortic blood flow and favourable vascular remodelling in rats with fistulae

created between the abdominal aorta and the inferior vena-cava.⁵⁵ However, human studies are not yet available.

Statin therapy in patients with ESRD was associated with increased endothelial function and intimal hyperplasia, although patients with CVC who were on statin therapy had increased production and turnover of fibrin.⁵⁶ Another study did not find added benefits from statin therapy in terms of either improved patency rates or reduced rate of intervention.⁵⁷

Several agents have been suggested to modulate the formation of neo-intimal hyperplasia and favour fistula maturation. Nugent et al. reported that veins treated with porcine aortic endothelial had a 2.8 fold increase in venous diameter and an 81% reduction in stenosis compared with controls after 28 days, by significantly reducing matrixmetalloproteinase-2 (MMP-2) in venous walls.⁵⁸ Gene therapy by means of Adenovirus-mediated vascular endothelial growth factor (VEGF-C) gene transfer has been shown to improve outcomes in post-angioplasty restenosis and reduction of vessel-wall thickening. This may be by activating pathways involved in increased production of nitric oxide (NO) and prostacyclin.⁵⁹ Similarly, Leppänen et al. showed promising results in preventing intimal hyperplasia when the same gene therapy (VEGF-C gene) was coupled with an immunological treatment by means of platelet-derived growth factor (PDGF) antagonists.⁶⁰

In a double-blinded randomised placebo-controlled trial, the primary patency rate at one year was improved in the group that received a higher dose of PRT-201 (a recombinant human elastase); secondary patency rates were comparable across the groups.⁶¹ Burke et al. studied the effects of PRT-201 in the treatment of patients with atherosclerotic peripheral arterial disease; they found that it could increase arterial luminal area by increasing the arterial diameter through the degradation of elastin fibres. Conversely, Peden et al. found no statistical difference between the placebo and the PRT-201 groups; furthermore, a sub-group analysis showed comparable patency rates between the different doses of PRT-201 in the study.⁶²

Recently, the use of drug eluting balloons has been suggested to improve AVF outcomes. In a retrospective study, Massmann et al. reported that the use of paclitaxel-coated balloon angioplasty in patients with central vein stenosis resulted in longer freedom from revascularisation for target lesions when compared to standard angioplasty ($P = 0.029$).⁶³ In addition, Patane et al. found the use of drug eluting balloons in juxta-anastomotic lesions improved primary patency and reintervention rates.⁶⁴ However, those studies were inadequately powered to draw a final conclusion.

Brachio-basilic AVFs

An AVF formed by joining the basilic vein to the brachial artery is reserved for patients who cannot have a radio-cephalic or brachio-cephalic fistula. The basilic vein by nature of its deep anatomic position is usually naturally preserved from repeated cannulation and as such less likely to suffer from stenotic lesions compared to other veins in the upper limb. However once arterialised, it needs to be brought closer to the

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surface to allow for successful repeated cannulation; this can be achieved in either a one-stage or a two-stage procedure.

A recent systematic review identified eight studies comparing one-stage to two-stage techniques.⁶⁵ There was no difference between the two groups in terms of overall reported successful maturation (Pooled risk ratio = 0.95 [0.82, 1.11], 95% CI, P = 0.53).

Markers of maturation

AVF maturation is not completely understood. Inflammatory markers mediated through the release of Nitric Oxide play a role in vascular remodelling, which raises interest in the use of those inflammatory markers as predictors of fistula maturation, in particular the use of Matrix Metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).^{66,67} The release of MMPs in the patient serum at the time of fistula creation may serve as an important biomarker. Intervention aimed at controlling the release of NO pharmacologically or by use of short-term oxygen supplementation following creation of AVF can play a role in fistula maturation.

In summary, despite the magnitude of the clinical problem of primary and cumulative AVFs failure, there seems to be a lack of effective clinical, demographic and biological markers to reliably predict the outcome of a newly formed AVF.^{68,69} Vein diameter is a hugely important factor, arguably, the single most important predictor of maturation as fistulae created using veins of <2 mm diameter are more likely to fail. Female gender, diabetes mellitus, age, arterial diameter, surgical technique and whether fistulae were created pre-emptively or after the start of HD can be considered additional predictors of AVF maturation. Further studies are needed to evaluate emerging treatments, including molecular biological manipulation and FIR.

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THE SURGEON XXX (2016) 1–7

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Appendix 10: Work submitted for publication “End-To-Side Versus Side-To-Side Anastomosis In Upper Limb Arteriovenous Fistula For Dialysis Access: A Systematic Review And A Meta-Analysis”:

Abstract:

Introduction:

An arteriovenous fistula (AVF) is the best modality for haemodialysis (HD) access. The end-to-side (ETS) technique has been suggested in the literature to produce superior results to the side-to-side approach; however, in the absence of a systematic review, this practice remains debatable.

Objectives:

To systematically assess the difference between both procedures in terms of access maturation, patency and postoperative complications.

Methods:

Online search for randomised controlled trials (RCTs) and observational studies that compared the end-to-side versus the side-to-side anastomosis techniques in creating an upper limb AVF.

Results:

Seven studies were included with 463 patients in the ETS group and 523 in the STS group. The difference between the two techniques was not significant in relation to patency rates at 3, 6, 12 and 24 months (P values: 0.28, 0.82, 0.54, and 0.21, respectively). There were fewer cases of postoperative haematoma in the ETS group, however the difference was not significant (P = 0.09). Arterial steal syndrome was found to be significantly associated with the STS configuration in pooled analysis (Pooled risk ratio = 0.11 [0.01, 0.88], 95% CI, P = 0.04).

Conclusion:

No evidence exists to suggest superior patency rates in AVFs created in an ETS configuration. Arterial steal syndrome was significantly associated with the STS technique in the studies that reported the incidence of this complication.

Appendix 11: Work submitted for publication “Arterio-Venous Fistula (AVF) in dialysis patients: Understanding the Pathophysiology behind arteriovenous fistulae non-maturation”:

Arterio-Venous Fistula (AVF) in dialysis
patients: Understanding the Pathophysiology
behind arteriovenous fistulae non-maturation

Abstract:

A well-functioning arteriovenous fistula (AVF) has been shown to be the best modality for vascular access in patients with end-stage renal disease (ESRD) going for haemodialysis (HD). A mature AVF has lower incidence of thrombosis and stenosis compared to the other two modalities; arteriovenous grafts (AVGs) and central venous catheters (CVCs). That translates into prolonged patency rates and lower risk for infection. However, it has been reported that around 20% - 50% of fistulae fail to mature into a useable access for haemodialysis. Mmaturation remains a measure concern with fistulae with as many as one third of first time created fistulae expected to fail. Intimal hyperplasia induced by altered biomechanical forces plays an integral role in stenosis within an AVF. Precoperative venous mapping and early salvage procedures can result in increased prevalence of mature fistulae, as well as surgical expertise. The aim of this review is to give an analysis of the factors implicated in the process of AVF maturation.

Appendix 12: Publication arising from data collected during the research period “*The Role of Shear Stress in Arteriovenous Fistula Maturation and Failure: A Systematic Review*”:



RESEARCH ARTICLE

The Role of Shear Stress in Arteriovenous Fistula Maturation and Failure: A Systematic Review

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Abstract

Introduction

Non-maturation and post-maturation venous stenosis are the primary causes of failure within arteriovenous fistulae (AVFs). Although the exact mechanisms triggering failure remain unclear, abnormal hemodynamic profiles are thought to mediate vascular remodeling and can adversely impact on fistula patency.

Aim

The review aims to clarify the role of shear stress on outward remodeling during maturation and evaluate the evidence supporting theories related to the localisation and development of intimal hyperplasia within AVFs.

Methods

A systematic review of studies comparing remodeling data with hemodynamic data obtained from computational fluid dynamics of AVFs during and after maturation was conducted.

Results

Outward remodeling occurred to reduce or normalise the level of shear stress over time in fistulae with a large radius of curvature (curved) whereas shear stress was found to augment over time in fistulae with a small radius of curvature (straight) coinciding with minimal to no increases in lumen area. Although this review highlighted that there is a growing body of evidence suggesting low and oscillating shear stress may stimulate the initiation and development of intimal medial thickening within AVFs. Further lines of evidence are needed to support the disturbed flow theory and outward remodeling findings before surgical configurations and treatment strategies are optimised to conform to them. This review highlighted

Appendix 13: Publication arising from data collected during the research period “In vivo validation of the in silico predicted pressure drop across an arteriovenous fistula”:

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In Vivo Validation of the *In Silico* Predicted Pressure Drop Across an Arteriovenous Fistula

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Associate Editor Umberto Morbiducci oversaw the review of this article.

Abstract—The creation of an arteriovenous fistula offers a unique example of vascular remodelling and adaptation. Yet, the specific factors which elicit remodelling events which determine successful maturation or failure have not been unambiguously determined. Computational fluid dynamic (CFD) simulations are increasingly being employed to investigate the interaction between local hemodynamics and remodelling and can potentially be used to assist in clinical risk assessment of maturation or failure. However, these simulations are inextricably linked to their prescribed boundary conditions and are reliant on *in vivo* measurements of flow and pressure to ensure their validity. The study compares *in vivo* measurements of the pressure distribution across arteriovenous fistulae against a representative numerical model. The results of the study indicate relative agreement (error \approx 8–10%) between the *in vivo* and CFD prediction of the mean pressure drop across the AVFs. The large pressure drop across the AVFs coincided with a palpable thrill (perivascular vibration) *in vivo* and fluctuations were observed in the numerical pressure drop signal due to flow instabilities arising at the anastomosis. This study provides a benchmark of the pressure distribution within an AVF and validates that CFD solutions are capable of replicating the abnormal physiological flow conditions induced by fistula creation.

Keywords—Vascular access, CFD, Hemodynamics, Transitional flow, Hemodialysis fistula, Maturation

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INTRODUCTION

Hemodialysis is the treatment modality of choice for patients with end stage renal disease (ESRD). Adequate and efficient hemodialysis requires a reliable vascular access which is easily accessible and provides consistently high flow rates greater than 600 mL/min.^{8,12} An arteriovenous fistula (AVF) is the preferred access type due to its superior patency rates and fewer complications compared with arteriovenous grafts and catheters.² However, the patency of this access type is far from optimal with primary patency rates ranging from 44 to 60%.^{14,28} Fistula non-maturation and venous access stenosis are the primary contributors to these failure rates. An AVF is deemed mature if after 6 weeks it supports a flow of 600 mL/min, it is located 6 mm from the surface of the skin and has a diameter greater than 6 mm.²⁶ Inadequate dilation or outward remodelling is a leading cause of maturation failure and is a factor that is often overlooked. Venous stenosis is the other leading cause of failure; it is a form of inward remodelling which is characterised by abnormal intimal hyperplasia which reduces the lumen area as shown in Fig. 1.³⁰ The abnormal hemodynamics arising from fistula creation are believed to provide a stimulus for both facets of remodelling. Methodological constraints make it difficult to decouple aspects of the hemodynamic difficult within the *in vivo* setting as the anastomosis of an AVF is known to exhibit unstable transitional to turbulent behaviour. Therefore, numerical and experimental models are often utilised and favoured to study the interaction between hemodynamic profiles and remodelling.^{8,18,22,27} Numerical studies such as

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