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Predicting Functional Outcomes in Aid of Decision-making in Major Lower Limb Amputation

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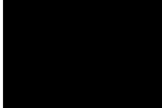
A thesis submitted for the degree of Doctor of Philosophy (PhD)
2022

Declaration

I, Arsalan Wafi, confirm that the work presented in this thesis is my own. Where appropriate, collaborators have been acknowledged. Some chapters are slightly modified versions of the work presented on podiums or submitted for peer-review publication.

Signature: 

Date: 01/02/2022

Abstract

Aim:

The purpose of this thesis was to understand and predict functional outcome after major lower limb amputation in vascular surgery, and to incorporate these findings into validated risk prediction tools to aid pre-operative decision making.

Methods:

The thesis utilised qualitative and quantitative methodologies and comprised six experimental chapters including systematic reviews, cross-sectional studies, and cohort studies. In addition, two supplementary experiments were included, each further exploring a novel finding from the core experiments. Construction of four databases enabled the exploration of health-related concerns of patients and the prediction of peri-operative, rehabilitation and palliative outcomes in patients with an unsalvageable limb.

Results:

Current lower limb interventions do not address the concerns of patients. A systematic review found that only 1/38 studies, assessing outcomes of multidisciplinary care, reported on a functional outcome. In contrast, psychosocial exploration of 76 patients showed that functional outcome before and after limb loss was their chief concern.

In a study of 262 amputees, a significant proportion of amputees (17.1%) did not progress to a stage of recovery that enabled rehabilitation post-amputation. Functional outcome remained unacceptably poor after specialist rehabilitation. In a regional study of 807 rehabilitees, only half of patients achieved independent prosthetic mobility. Active cancer was consistently a poor prognostic factor for functional outcome.

Palliation for the unsalvageable limb remains poorly understood and implemented. A study on 66 cases revealed that survival varies significantly with the aetiology of the unsalvageable limb, and that currently, we fail to meet expectations of dying patients.

Risk prediction models for functional outcomes were internally validated and incorporated in a web-based application for ease of clinical utility.

Conclusion:

In conclusion, findings showed that it is possible to predict functional outcome reliably, thus addressing the chief concern of patients facing limb loss, and to use such prediction tools to aid pre-operative decision making.

Acknowledgements

I am forever grateful to my supervisors for their support through an extraordinary time of our lives. COVID-19, with all its variants, threw many spanners in the works during my research years, but their wisdom and guidance got me through.

I owe all my successes to Professor Peter Holt, my primary supervisor. Nothing would have been possible without his guidance.

I am honoured to have had Professor Ian Loftus as a supervisor. A true pioneer and an inspiration.

I thank Mr Paul Moxey for supporting me not only in the academic and clinical settings, but also in life. His level of empathy and genuine desire to help his colleagues through personal hardships is rare.

This work would not have been possible without the collaboration of certain experts at St George's University Hospital Trust. I was fortunate enough to work and learn from many inspiring academics, clinicians, and other health-professionals. To name a few, they include Catherine Bewsey (a clinical psychologist in our diabetic foot multidisciplinary team), Ronnie Saha (the clinical lead for our diabetic foot multidisciplinary team) and Catherine MacGowan (the clinical lead for palliative care services).

Lastly, I owe a huge thank you to Vijay Kolli, the clinical lead for rehabilitation services at the Douglas Bader Unit at Roehampton. His collaboration and permission to access arguably some of the best quality clinical data on rehabilitation outcomes, anywhere in the country, allowed for the novel research on functional outcomes that made this PhD possible.

I dedicate this thesis to my brother, Masoud, who passed away at a young age.

You are always in our hearts.

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List of Abbreviations

AAA	Abdominal Aortic Aneurysm
ABI/ABPI	Ankle Brachial Index/Ankle Brachial Pressure Index
ACA/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-Converting Enzyme
ACM	All-Cause Mortality
AKA	Above-Knee Amputation
AKI	Acute Kidney Injury
ALI	Acute Limb Ischaemia
AMED	Allied And Complementary Medicine Database
AUD$	Australian Dollars
BKA	Below-Knee Amputation
BLART	Blatchford Allman Russel Tool
BMI	Body Mass Index
Ca	Cancer
CEA	Carotid Endarterectomy
CFS	Rockwood Clinical Frailty Score
CI	Confidence Interval
CINALH	Cumulative Index of Nursing And Allied Health Literature
CLI	Critical Limb Ischaemia
CLTI	Chronic Limb-Threatening Ischaemia
CRP	C-Reactive Protein
DF	Diabetic Foot
DFD	Diabetic Foot Disease
DFS	Diabetic Foot Sepsis
DM	Diabetes Mellitus
DOAC	Direct Oral Anticoagulant
eGFR	Estimated Glomerular Filtration Rate
EMBASE	Excerpta Medica Database
EWA	Early Walking Aid
F	Female
FI	Frailty Index
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HbA1C	Glycated Haemoglobin
ICD	International Classification of Disease Coding
IMDD	Index Of Multiple Deprivation Decile
IQR	Interquartile Range
IRAS	Integrated Research Application System
JBI	Joanna Briggs Institute

LV	Left Ventricular
M	Male
MACE	Major Adverse Cardiac Events
MALE	Major Adverse Limb Event
MDT	Multidisciplinary Team
MEDLINE	Medical Literature Analysis and Retrieval System Online
MLA	Major Lower Limb Amputation
MS PSS	Multidimensional Scale of Perceived Social Support Scale
N	Number
NCEPOD	National Confidential Enquiry into Patient Outcomes And Death
NICE	National Institute for Health And Care Excellence
NOAC	Novel Anticoagulant
ONS	Office Of National Statistics
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PAID	Problem Areas in Diabetes Scale
PAQ	Physical Activity Questionnaire
PASE	Physical Activity for The Elderly
PRISMA	Preferred Reporting Items for Systematic Reviews And Meta-Analyses And Meta-Analysis
PsycINFO	Psychological Abstracts Database
QIF	Quality Improvement Framework
QoL	Quality Of Life
ROC	Receiver Operator Curve
SD	Standard Deviation
SDCQ	San Diego Claudication Questionnaire
SEIPS	Systems Engineering Initiative for Patient Safety
SF-36	Short Form Survey 36
SIGAM	Specialist Interest Group in Amputation Medicine
TKA	Through-Knee Amputation
TSI	Townsend's Social Isolation
TUG	Timed-Up-And-Go
UCLA LS	University Of California Los Angeles Loneliness Scale
UK	United Kingdom
US	United States
VIF	Variance Inflation Factor
VSGBI	Vascular Society of Great Britain And Ireland
VTE	Venous Thromboembolism
WCC	White Cell Count
5FU	Fluorouracil

Chapter 1: Introduction

1.1 Outcomes Research in Vascular Surgery

Outcomes research, a branch of public health research, is applied to clinical and epidemiological studies that aim to optimise the end results of healthcare to benefit the patient and society (1). Research may be specific to certain treatments or be broad, such as in the provision of resources and services. Both forms may help to guide specific policies adopted by regulatory bodies. Patients also have a significant stake in outcomes research as decision-makers for their own healthcare, and as members of the public who must ultimately fund medical services.

Outcomes research in vascular surgery has allowed the clinician to reliably scrutinise the indications, costs, clinical and patient-centred endpoints for interventions, and the "real world" outcomes that can be expected. Decision analysis, and the use of administrative databases has identified important determinants of outcomes of procedures such abdominal aortic aneurysm (AAA) repair, carotid endarterectomy (CEA), and lower limb arterial revascularisation. One important example has been volume-outcome relationships. Used as surrogate markers of service quality, both hospital and surgeon volume has been shown to impact morbidity and mortality after vascular surgery, thus driving the centralisation of vascular services throughout the United Kingdom (UK) (2).

The area of vascular surgery currently missing a similar depth of focus, has been amputation outcomes research. Due to factors such as high mortality, loss of follow-up, and a deficiency of industry-led interest, there is a relative paucity in research aimed at improving outcomes of amputation surgery, in particular patient-centred outcomes such as physical function following surgery.

This thesis employs outcomes research, specifically the prediction of functional outcome, to aid clinicians and patients in their decision-making for amputation surgery when faced with an unsalvageable limb. For the purposes of this thesis, the term "unsalvageable limb" will exclusively refer to the lower limb, as such a presentation in the upper limb is rare and therefore not a focus of this body of work.

1.2 The Natural History of Limb Loss

To appreciate the relevance of functional outcome after limb loss, a prior understanding of the natural history of the unsalvageable limb is warranted. Patients with unsalvageable limbs due to vascular disease experience several distinct stages in their disease process, as illustrated in **Figure 1**. This section of the introduction will describe these stages in more detail:

1. Initial presentation with a threatened limb,
2. Attempts made to salvage the limb through revascularisation surgery,
3. Failure of limb salvage leading to an unsalvageable limb,
4. Undergoing a major amputation,
5. Or palliation if this option is deemed more suitable than amputation surgery,
6. Rehabilitation for the amputee,
7. Mobilisation with or without a prosthesis,
8. Early death, relative to the life expectancy of the general population.

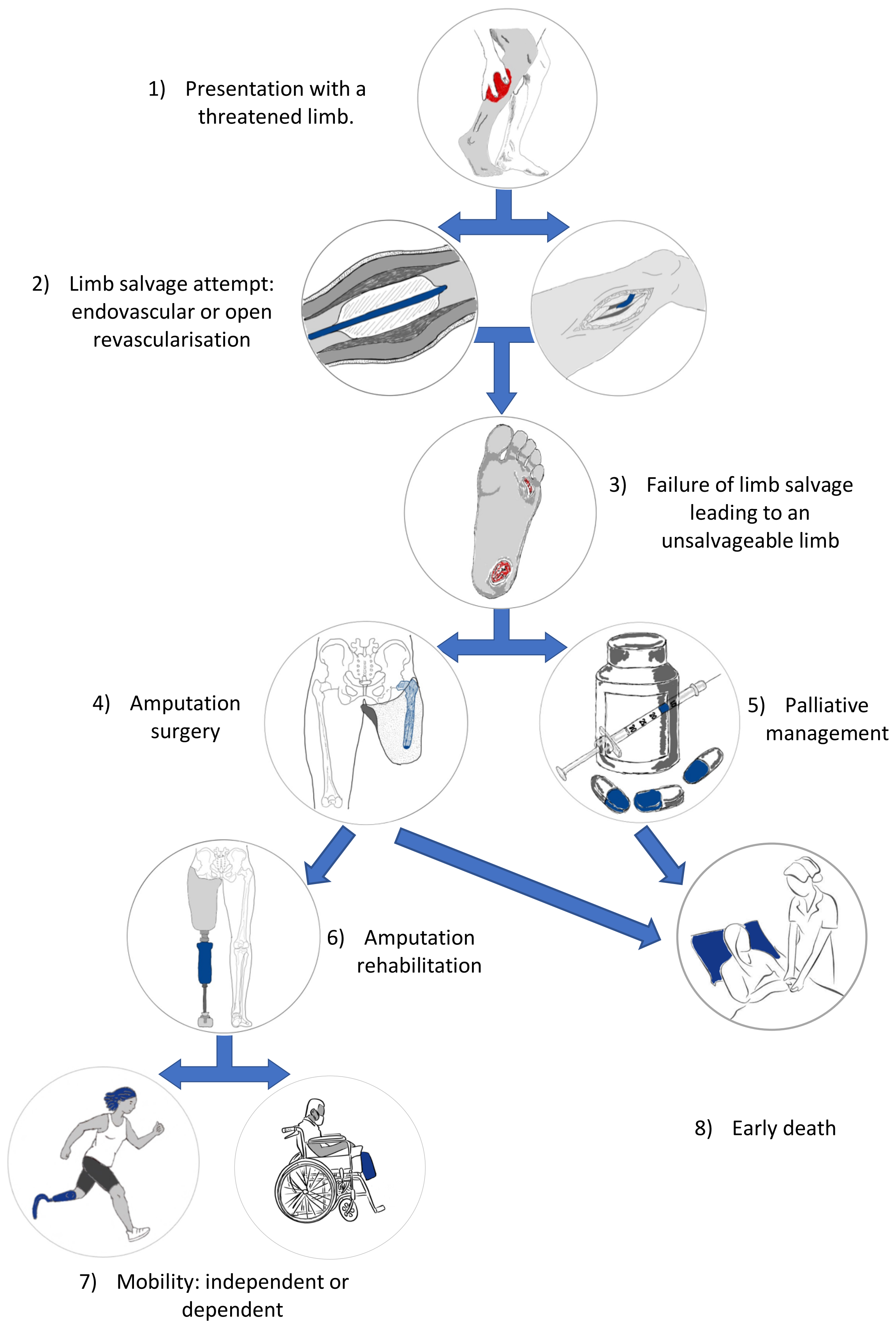

Figure 1: The natural history of limb loss in vascular surgery.

1.2.1 Presentation with a Threatened Limb

Broadly, a threatened limb refers to a limb at risk of amputation unless attempts at limb salvage prove successful. The aetiology of the threatened limb is ischaemia, often complicated by infection, and is driven either by acute or chronic pathological processes.

Acute pathologies cause sudden malperfusion by compromising an otherwise adequate arterial perfusion to the limb. The most common pathology presenting this way is a thrombo-embolus with less common causes being thrombosis of native arteries or reconstructions (stents or bypass grafts), aneurysmal disease, arterial dissection, and trauma. The reported incidence of acute limb ischaemia (ALI) is 1–1.5 individuals per 10,000 individuals per year (3,4). According to a recent report, the UK incidence rates were 46% for embolism, 24% for thrombosis due to an occlusive atherosclerotic lesion, 20% for complex factors, and 10% for stent or graft-related thrombosis (3).

Chronic pathologies represent a gradual deterioration in the arterial sufficiency of the limb. This occurs in the macrovasculature secondary to atherosclerosis and is termed peripheral arterial disease (PAD). It may also occur predominantly at the microvascular level, driven by metabolic processes which in most cases is diabetes mellitus (DM) leading to diabetic foot disease (DFD). A systematic review and meta-analysis found that that global diabetic foot ulcer prevalence is 6.3%, higher in male (4.5%) than in female patients (3.5%), and higher in type 2 diabetic patients (6.4%) than in type 1 diabetics (5.5%) (5).

The clinical picture among many patients is a mixture of both macro-and microvascular disease due to co-existence of atherosclerotic and metabolic disease processes. Ischaemia typically presents with limb pain on exercise, and progressively worsens to a state of intractable pain at rest associated with coldness. Depending on the severity of ischaemia, tissue loss may occur in the form of ulceration (loss of skin epidermis) or gangrene (loss of all layers of tissue including bone).

ALI is considered when symptom duration is less than two weeks. A symptom duration of greater than two weeks is considered to represent chronic limb ischaemia (6). Historically, the

term critical limb ischaemia (CLI) was used to described severe PAD requiring urgent intervention. CLI implies threshold values of impaired perfusion rather than a continuum. Over recent years, the term chronic limb threatening ischaemia (CLTI) has replaced CLI. This preferred term is a clinical syndrome defined by the presence of PAD in combination with rest pain, gangrene, or a lower limb ulceration of over 2 weeks duration (7). The multisystemic and severe nature of threatened limb requires a multidisciplinary approach to optimise chances of limb salvage.

1.2.2 Multidisciplinary Management of the Threatened Limb

As multisystemic problems, PAD and DFD affect the health of patients in numerous ways. They are frequently associated with medical and surgical complications, poor physical and cognitive function, and psychosocial problems.

Approximately one fifth of DFD patients may experience an unplanned 30-day readmission to hospital, with 59% of these comprising of medical complications (mainly cardiovascular, pulmonary, and renal) and 41% being due to wound problems (8). There has also been a strong association between the threatened limb and psychosocial problems, namely depression and anxiety. In a systematic review of 248 studies and 83,020,812 diabetic participants, 28% suffered from depressive disorders of different severity levels.

These poor clinical and patient-centred outcomes contribute towards a poor quality of life (QoL) and short life expectancy. Delivery of optimal holistic care for patients with threatened limbs and amputations, therefore requires an in-depth understanding of patient and treatment-related variables that determine outcomes, and should be simultaneously undertaken by multiple disciplines.

For amputations, the VSGBI (Vascular Society of Great Britain and Ireland) stipulates that accredited vascular centres must implement clear amputation pathways and that care must be overseen by designated multidisciplinary teams (MDT) (9). An MDT is defined as the

cooperation between different specialised professionals involved in the care of the patient with the overarching goal of improving treatment efficiency and patient care (10).

Depending on the stage of disease at presentation, patients will be offered medical, surgical, and other specialist input aimed either at maximising the likelihood of limb salvage or improving general health if MLA is inevitable. Figure 2 lists the different members of the MDT who provide specialist input.

Figure 2: Members of the MDT for lower limb vascular patients.

1.2.3 Attempt at Limb Salvage

Urgent limb salvage comes in the form of timely medical and surgical revascularisation (re-instatement of an adequate arterial circulation to limit the burden of ischaemia, infection, and tissue loss. Immediate medical interventions commonly include systemic anticoagulation for most cases and catheter-directed thrombolysis for select cases of acute thrombosis with a permitting anatomy, a low of risk of embolisation and an absence of absolute contraindications.

Surgical interventions may be performed via endovascular or open approaches. Endovascular interventions commonly consist of angioplasty and stenting of arterial stenoses or occlusions. The National Vascular Registry for the UK (NVR) publication in 2021 reported 6,390 endovascular procedures (4,221 elective and 2,169 non-elective) performed in 2020. Overall activity was lower than levels observed in 2019, with the reduction being concentrated in the elective pathway (6,188 elective procedures and 2,548 non-elective). Among these patients, there were 3,798 patients with CLTI admitted non-electively. Overall, 52% had their revascularisation within five days, as per best practice guidelines (11).

Open procedures aim to remove stenoses or occlusions through embolectomy, thrombectomy and endarterectomy, or to bypass the diseased area of artery with either autologous (commonly, harvested veins) or prosthetic grafts. NVR 2021 reported 5,071 (2,542 elective and 2,429 non-elective) bypass procedures performed in 2020. There were 6,300 procedures submitted in 2019, which consisted of a similar number of non-elective procedures (2,438) but a higher level of elective activity (3,862 procedures). Among these patients, 77% were admitted with CLTI. During 2019-2020, 47% of patients with CLTI who were admitted non-electively had their bypass within five days (11).

However, with non-reconstructable disease or extensive tissue death, the limb will eventually reach a stage of non-viability. This state of non-viability of the leg is termed the "unsalvageable limb". The unsalvageable limb is functionless, painful and poses a risk to life through spreading infection and metabolic derangement. Definitive management for the

unsalvageable limb is therefore time critical. Decisions regarding amputation versus palliation must be made without unnecessary delay.

Despite attempts and technological advances, limb salvage rates remain poor with pooled figures of up to a quarter of patients experiencing limb loss at one year after revascularisation surgery, as shown in a meta-analysis of 44 studies on 8602 patients (12).

1.2.4 Amputation Surgery for the Unsalvageable Limb

If managed with amputation surgery, then the unsalvageable limb will undergo a major lower limb amputation (MLA). The goal of MLA surgery is to provide the patient with a pain-free residual limb with maximal prosthetic potential.

In the UK, the incidence of MLA is estimated to be between 5 and 25 per 100 000 population (13). It is unclear whether the incidences have changed over the past decade due to conflicting epidemiological findings from various databases (14,15). Other reasons offering explanations for the conflicting findings include heterogeneity in study populations, definitions of MLA and methodology of follow-up.

In this thesis, an MLA has been defined as an amputation of the leg above the level of the ankle, and any performed below this level has been defined as a minor amputation (**Figure 3**). The three most common levels to perform an MLA are below-knee (BKA), through-knee (TKA) and above-knee (AKA), also known as transtibial, transgenicular and transfemoral amputations respectively. In extreme cases, more proximal amputations may be required such as hip disarticulation (also known as hindquarter) but due to their relative rarity, they will not be the focus of this body of work.

NVR 2021 data reported 3,169 MLAs performed in 2020. The majority of patients who had an MLA were admitted non-electively (80% non-elective vs 20% elective). The overall median time from vascular assessment to MLA was 8 days [interquartile range (IQR) 3-25 days]. The time differed for patients who had amputations as elective procedures [median=26 days; IQR:

8-73] compared with patients who had the procedure following a non-elective admission (median=8 days; IQR: 3 to 18). Among patients admitted non-electively, there were nine NHS Trusts where a quarter of patients had a wait longer than 30 days (11).

In 2020, there were 1,571 above knee and 1,598 below knee amputations, giving an overall AKA:BKA ratio of 0.98. Half of the NHS Trusts had a ratio of less than one, but 12 organisations had a ratio above 1.5 (11). The number of MLAs performed in 2020 were not significantly lower than 2019. TKAs, in contrast, constitute a very small proportion of the total number of MLA's performed, and are therefore not the focus of existing outcomes studies in large amputation series.

An MLA is considered major arterial surgery due to the operative trauma and the cardiovascular strain inflicted on a predominantly comorbid patient phenotype. Therefore, such high-risk surgery must be performed in the presence of senior surgeons and vascular anaesthetic and critical care support. Despite this pre-requisite, morbidity and mortality remain high.

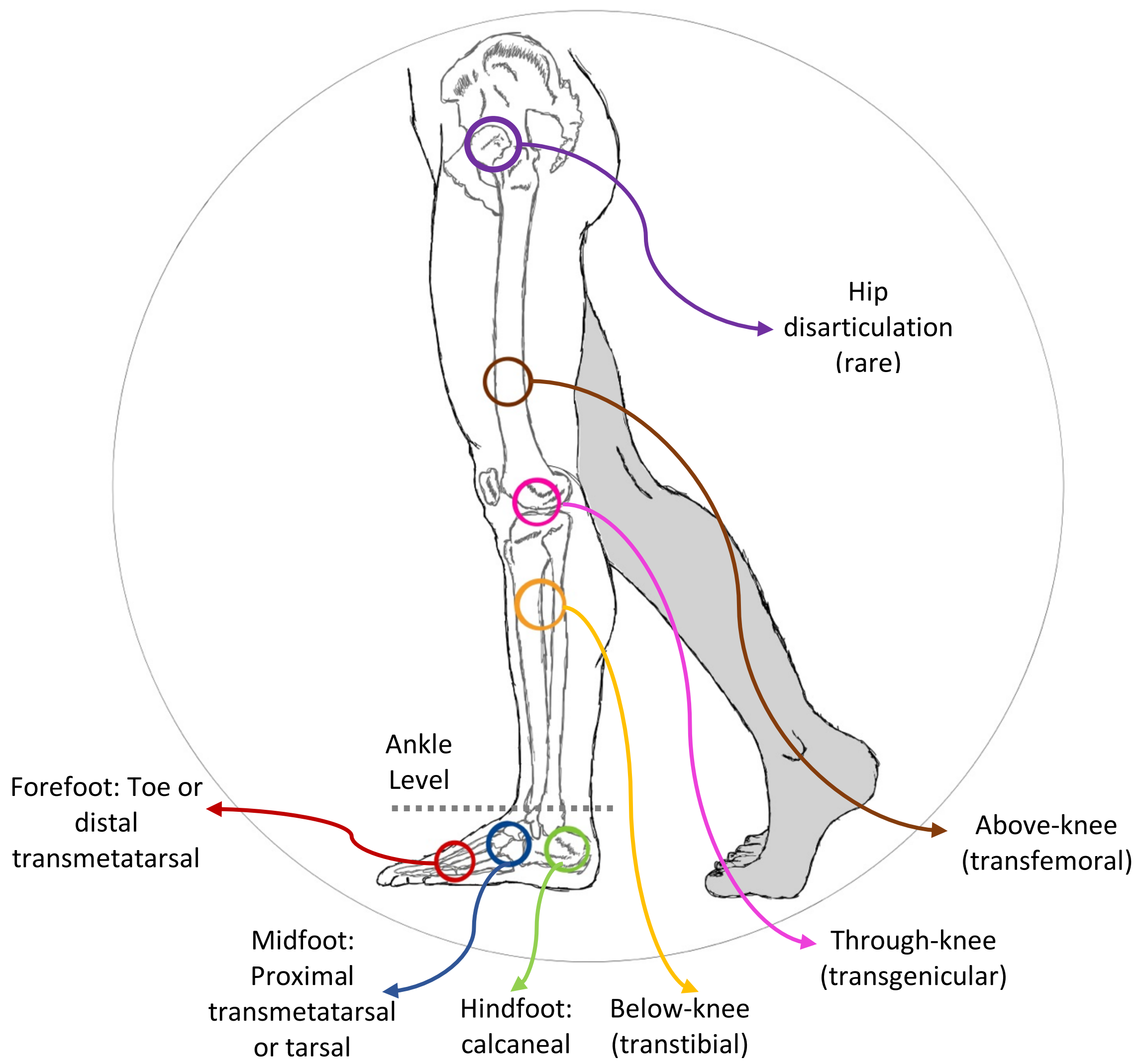

Figure 3: Levels of the leg at which minor and major amputations are performed.

1.2.5 Mortality in Major Amputation

The perioperative mortality rate after MLA in the UK was estimated to be 17% in 2010 (16). This is an unacceptably high mortality rate in modern medical practice.

In response to this, the VSGBI endorsed and adopted the Amputation Quality Improvement Framework (QIF) aimed at addressing poor outcomes of MLA (17). A further report by the National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) in 2014 supported the recommendations made by the VSGBI Amputation QIF by reporting a persistently high 30-day postoperative mortality of 12.4% (18).

More recent data from the NVR shows some improvement. The overall rate of 30-day in-patient death for major lower limb amputations in 2020 was 7.0%, which was higher than in 2019 (6.4%). As expected, it was higher for AKA (9.3%) than BKA (4.8%) due to worse disease and comorbidity burden. All NHS Trusts had an adjusted 30-day mortality rate that fell within the expected range of the overall 30-day in hospital mortality rate (6.1% for 3 years from 2018 to 2020) (11).

It is unclear what fraction of these mortalities are due to the common attributes of older age, multisystemic comorbities, end-stage disease processes and general frailty among vascular patients. Such factors are difficult to optimise or reverse in the typical acute setting of MLA surgery. However, a question of whether such high mortality rates are also a result of the failure of primary and secondary care strategies (including community-based care), must be raised (19).

Long term mortality rates are consequently very high. In a systematic review of sixty-one studies representing 36,037 MLA cases, the pooled mortality rates were 33.7%, 51.5%, 53%, 64.4%, and 80% at 1-, 2-, 3-, 5- and 10-year follow-up, respectively (20).

An alternative to such high-risk surgery is therefore the non-surgical management of symptoms, and due to the fatal nature of the unsalvageable limb, this takes the form of palliative care.

1.2.6 Palliation for the Unsalvageable Limb

With such high mortality rates, the NCEPOD has highlighted the need to make thoughtful decisions against MLA for some patients. Appropriate patient selection for major vascular surgery is crucial, and for some patients the unsalvageable limb may be one part of the process of dying.

All surgeons recognise that the following are important factors in advocating palliation for the unsalvageable limb:

- the patient being too frail to withstand surgery,
- the likelihood of having a poor quality of life,
- the likelihood of inevitable and imminent death,
- the patient's choice to opt for palliation over MLA.

Recognising the patient who will inevitably die is an important skill and depends on clinical experience. The clinical decision to withhold treatment is relatively straightforward when faced with imminent death or a competent patient's refusal of surgery after careful consultation.

Decisions may be more complicated for patients for whom the balance of medical and humanitarian considerations sway against intervention, but for whom amputation might save life, albeit of poor quality. For such patients, there must be clarity and sensitivity in the approach to clinical discussions on what is likely to happen if either surgery or palliation is chosen.

Understanding the outcomes of palliation for the unsalvageable limb is therefore important in equipping both patients and clinicians during the decision-making process. Despite this clear necessity, there is almost a complete absence of research on this topic in literature.

1.2.7 Rehabilitation after Major Amputation

For those who do undergo MLA, the process of rehabilitation becomes the post-operative priority. In the UK, patients with MLA are typically referred for a rehabilitation MDT assessment within 6 weeks of surgery. The British Society of Rehabilitation Medicine Amputee Guidelines (2018) state that it is best practice that all patients are assessed, even those who may not walk with a prosthesis (21). The rehabilitation MDT work together during the assessment to decide rehabilitation plans such as early walking aid (EWA) use, transfer practice (with or without prosthesis use), progression to walking training, or no intervention with further community input. Key members of the rehabilitation MDT performing the assessment are included in **Table 1**.

The optimal outcome from rehabilitation of the MLA patient is independent prosthetic mobility. The prescription of a prosthetic limb requires consideration of the most appropriate componentry to maximise safety, stability, protection of skin integrity, ease of donning and doffing and overall functional outcome.

Rehabilitation MDT	Key Roles
Rehabilitation consultant	• Optimise general health, the cardiovascular and respiratory reserve • Advise on treatment for nerve and nociceptive pain • Provide a general overview of care
Physiotherapist	• Assess muscle strength and joint restrictions • Provide the physical therapy to improve functionality
Occupational therapist	• Assess current functional level and needs • Enable independence in self-care, productivity, leisure, and mobility (both wheelchair and prosthetic use)
Prosthetist	• Assess previous activity, hobbies, and physical fitness • Determine the logistics of prosthetic type and utility

Table 1: Key roles of the members of the rehabilitation MDT.

1.2.8 Functional Outcome after Major Amputation

Although limb loss is widely considered to be the end result of the threatened limb, life does go on for MLA patients. With over 3000-5000 MLAs performed in the UK per year over the past decade, medical and social care of amputees represents a significant burden on society. There has been a significant shift in the metrics used to evaluate outcomes in MLA research. Amputation research is transitioning from a sole focus on mortality and morbidity to examining patient-centred outcomes. This is becoming increasingly topical in an ageing global population and increasing prevalence of diabetes. It is envisaged that issues such as social care will be at the heart of future healthcare policies.

A questionnaire-based study on patients facing MLA highlighted that immobility and loss of independence were their prominent concerns, even over the risk of death, and these were the strongest determinants of overall quality of life postoperatively (22,23). Understanding the basic question of which patient is likely to rehabilitate well, that is achieving independent prosthetic mobility, is therefore a crucial factor during decision-making. Naturally, there is avoidance of more proximal amputations among patients and clinicians. However, choosing the optimum amputation level remains challenging. Risks of surgical and medical complications, mortality, and loss of independent mobility must be considered.

The level of amputation is a strong determinant of overall functional outcome. Prosthetic mobility energy expenditure for AKA patients is almost twice that for BKA patients, leading to a significantly poorer prosthetic use among AKA patients (24). However, other important factors for functional outcome exist, and understanding these may improve pre-operative decision-making and consenting processes.

Uncertainty in predicting functional outcome has led to variability in practices and outcomes. In the United States, the BKA:AKA ratio in the Veterans Health Administration was reported to be 1:1.6 during 1994-2001 and 1:1.5 during 2002-2003, whereas in a comparable time period (1996) in a Medicare population, it was 1:0.81 (25). In the UK, the BKA:AKA ratios were 1:0.73 and 1:1.2 in different health districts between 2003 and 2008 (26). These data confirm the complexity and variability in amputation level selection as well as the need for patient-

specific prediction tools to better inform stakeholders during shared decision-making. Unfortunately, tools predicting such outcomes are uncommon, not externally validated and are seldom used in day-to-day clinical practice.

1.3 Importance of Predicting Functional Outcome after Amputation

Functional status bears implications for all stakeholders following amputation surgery: patients, caregivers, clinicians, health systems and policy makers.

1.3.1 The Patient

Reduced mobility has been shown to impact clinical and other patient-centred outcomes. Immobility is an independent predictor of peri-operative complications (27–29) and is detrimental for overall health status and long-term survival (30,31). There is also the psychosocial burden that is associated with reduced mobility. Amputees experience significant levels of social isolation, lethargy, and sleep and emotional disturbance (32).

The prevalence of social isolation in the United Kingdom ranges between 10-43% in community-dwelling older adults and is increasing (33), putting significant pressures on social care. Mobility, not amputation status, has been shown to be the most important predictor of quality of life (32,34).

Economic implications of poor functional outcome on individuals and households must also be recognised. Expenditures may relate to general household items as well as to disability-specific items including assistive devices, personal assistance and home adaptation (35). Costs will likely be influenced by the individual experience of the amputee: their physical impairment, resources and interactions with their environment (36).

1.3.2 The Caregiver

Informal caregivers experience a significant burden due to the emotional and physical strain of providing care to amputees. With a lack of support, caregivers compromise their own physical health (37,38) and quality of life (39,40) . An association exists between the duration of care and patients' functionality and the burden felt by caregivers (41). Caregivers may feel social and emotional isolation, often abandoning pleasure-generating activities (42).

1.3.3 The Clinician

Meeting patient expectations is crucial in the context of life changing surgery such as an amputation. Expectations of returning to normality appear to be a major part of the coping strategy following the physical and psychological trauma of limb loss. While a positive patient attitude is encouraged, it is the clinician's responsibility to address unrealistic expectations by providing an accurate picture of a "new norm" for the patient, where both physical and psychosocial hurdles for the patient are discussed.

Early involvement of the rehabilitation specialist is paramount in achieving this. A multidisciplinary approach with involvement of rehabilitation specialists as well as pre-operative assessment of functional potential has been widely recommended by relevant health bodies (9,17,43). Despite such clear guidance, there is a paucity of data on the impact of multidisciplinary intervention on functional outcomes in lower limb vascular surgery.

1.3.4 The Healthcare system

For healthcare systems, functional outcome data can serve to improve cost-effectiveness, quality assurance, public health promotion and policy making. In the United States of America (USA), the health care system is shifting toward a pay-for-performance system, aiming to reduce health care costs and promote equality (44). An important objective here is the evaluation of health and functional status as a key measure for reimbursement.

Typically, the cost of a major amputation depends upon several factors: the initial hospitalisation and all rehospitalisations for acute care related to the amputation, the inpatient rehabilitation, the outpatient clinical, physiotherapy and occupational therapy visits and the purchasing and maintenance of prosthetic devices. Understanding functional outcomes can therefore be used to predict and compare cost-effectiveness of interventions. Payers could use functional status information to adjust payment levels and capitation rates (45).

1.3.5 The Health Policy Maker

Functional status information could help public health practitioners monitor and evaluate the general health of the entire population, with the aims of increasing quality and years of healthy life and eliminating population health disparities. Potential policy applications of functional status information include helping decision-makers set research aims, prioritise local and national public health initiatives, and develop programs for priority populations.

1.4 Predictors of Functional Outcome after MLA: a Literature Review

There are conflicting findings in studies identifying pre-operative predictors of functional outcome in amputation surgery. Likely explanations are variations among study populations, interventions, and definitions of a good functional outcome.

1.4.1 Surgical Factors

Better walking ability and a reduction on wheelchair dependence has been demonstrated after distal and unilateral MLAs compared with more proximal or bilateral (46). Stump length may also be a predictor of functional outcome, while fixed contractures of lower limb joints limit walking potential (47,48). A trend towards better walking ability and prosthetic use has been reported in those with better quality stumps (49), fewer wound problems and less stump pain (50).

1.4.2 Demographics

Older age at time of amputation has been shown to have an adverse effect on walking potential in most studies. Although this association may be confounded by co-morbidity, analyses have demonstrated that age has a more significant impact on walking ability than co-morbidity (47,51–53). Gender-related disparities in outcome after vascular surgery is topical in literature. In AAA and lower limb revascularisation surgery therapy, women have demonstrated longer hospitalisation and higher rates of complication and mortality (54,55). There is however debate on the impact of gender on functional outcome after limb loss. Although many studies found no such association (47,56,57), there have been some reporting superior walking ability in men (58,59).

Possible gender differences may be due to a higher age and comorbidity of women at time of presentation. Biological (genetic, hormonal and anatomical) and psychosocial differences in gender may also play their part (60).

1.4.3 Comorbidities

Aetiology of amputation and walking potential are strongly related. PAD and diabetic amputees achieve poorer functional outcomes than those due to trauma or other non-vascular causes (34–38). However, age difference is likely a major confounder, with the latter groups being considerably younger.

The evidence on an association between comorbidity and walking ability is conflicting with some supporting this finding (61–63), while others indicate no significant relationship (47,48). There is potential for referral bias associated with co-morbidity. Evidence suggests that amputees with prior stroke are less likely to be referred for prosthetic rehabilitation (64). Increased severity of comorbidities may also prevent access to rehabilitation, further increasing the bias in methodology.

Despite interest in body mass index (BMI), studies have not shown BMI to be an independent predictor of functional outcome when adjusted for other co-morbidities, age and sex (53,65). Similarly, no significant association has been demonstrated between smoking and walking ability after amputation (53,58,59). Age, again, may be the confounder as smoking is more common among younger patient groups.

1.4.4 Frailty

There is little doubt that pre-operative frailty is likely to be an important determinant of post-operative function as the latter represents a continuum of the same process.

Frailty is a multidimensional variable and its association with outcomes after surgery may be challenging to analyse. Many frailty scoring tools exist, each carrying a different emphasis on how frailty is assessed. For example, some tools rely on the patient's strength, mobility and level of functional independence such as the Rockwood Clinical Frailty Score (CFS) (66). Other scoring tools rely on the presence of pre-operative comorbidities such as the modified Frailty Index 11 (mFI-11) and modified Frailty Index 5 (mFI-5) (67).

Frailty has been shown to be a strong predictor of readmission rates following MLA. In one study of 379 MLA patients, 30-day readmission rates increased significantly with an increasing mFI-11 score: rates were 8.6%, 13.5%, 16.3%, 19.7%, 31.4%, and 37.0% for mFI-11 scores of 0, 1, 2, 3, 4, and ≥5, respectively (68). Another study on 211 MLA cases showed that one-year mortality rates were 38.4%, 38.6%, 52.6% in the low, moderate and high mFI-11 categories, respectively (69).

1.4.5 Functional status

The impact of physical ability, cognition, and dependency for self-care on outcomes have been examined. Naturally, pre-amputation walking status is predictive of post-operative walking ability (52,58,61). In one study, individuals who were able to walk at least 100 metres after rehabilitation had significantly higher pre-rehabilitation maximal oxygen consumption (%VO2max – higher values indicate better exercise tolerance) (70). It also highlighted the ability to stand on one leg as indicative of better walking potential after an MLA (70,71).

Cognitive function is a significant predictor of walking ability following rehabilitation (72,73). Dependency for selfcare prior to amputation is an independent negative predictor of walking ability for up to 18 years after surgery (46). One study found a positive impact of employment at the time of prosthetic provision on functional outcome at one year, after adjustment for age (50). A problem, however, with functional status is that it is a spectrum and inferences on its association with outcomes depends heavily on the modality used to measure it.

1.4.6 Psychosocial Factors

A better understanding of the impact of psychosocial factors is necessary in MLA surgery. In one study, amputees were classified as good or poor rehabilitation candidates based on psychological testing using a variety of cognitive and personality tests. A greater proportion of those considered good candidates maintained their pre-amputation walking status (46).

Depression has also been reported to impede walking ability after amputation (71) but not all studies support this association (73,74).

Greater level of perceived social support was predictive of superior mobility scores in one study (75) but others using more robust walking ability measures failed to replicate this association (71,76). A statistically significant association has been reported between patient “motivation” and the ability to learn to walk with a prosthesis (77). However, the method of grading participants’ motivation was subjective, and heavily based on a retrospective review of the multidisciplinary discussion and physiotherapy records.

1.5 Assessing Functional Outcome

Currently, we lack the use of a validated measurement of functional outcome post-MLA surgery. Urgent collaboration and consensus within the vascular community is necessary to develop a standardised assessment of functional outcome. This has the potential of being a primary endpoint, enabling research models incorporating rehabilitation, fundamentally shifting the focus of research to patient-centred issues.

A dynamic assessment tool encompassing the following components is required:

1. the bodily functions and structure,
2. the activities (related to tasks and actions by an individual),
3. social participation (involvement in a life situation).

To facilitate this, functional status information should be included in patient records and be reported at appropriate intervals in standardised data sets. There are several barriers to the quality of functional outcome record keeping. Privacy and ethical issues surrounding the collection and reporting of functional status information also require consideration. Resources and time must be allocated towards the training of healthcare professionals in assessing functional outcomes and administrative staff in coding functional status information. Decision-making will depend on the reliability and validity of data recorded, necessitating the auditing of data quality.

1.6 Functional Outcome for Decision-making

Shared decision-making is recognised as the ethical and moral standard in medical decision-making. It is essential for respecting the patient's autonomy, especially when patients and clinicians are facing complex decisions. Typically, the urgent nature of MLA surgery restricts the quality of shared decision-making.

Time constraints may impede the adequate communication between the patient, their relatives, and the clinical team. The values and perceptions of individuals, and their attitudes towards risks, may be different from those of their health professional. A paternalistic attitude towards amputation surgery risks leaving patients unsupported and ill-equipped to make decisions regarding such life changing surgery.

As a general outline, improving shared decision-making in MLA surgery requires considerations for three domains:

1. the patients' concerns, expectations, and health-related behaviours towards MLA,
2. the predicted clinical outcomes,
3. the predicted patient-centred outcomes, most importantly, functional outcome.

Decision aids may be used for complex decisions that need more detailed information and careful consideration. They are defined as tools designed to help people participate in decision-making about health care options (78). Although such tools can support better decisions, their use depends on the attitudes and skills of health professionals. These aids should not advise patients to choose one option over another, or replace the consultation between the patient and their health professional. Instead, they are intended to supplement or support the interaction.

Decision aids that provide the patient with individualised prediction of functional outcomes are viewed as potentially beneficial in the setting of MLA surgery but are not utilised in common practice.

1.7 Aims and Objectives

The overarching aim of this thesis is to understand and predict functional outcome after MLA surgery in vascular patients and incorporate this information into a decision aid that has the potential for integration into day-to-day clinical practice.

As functional outcome is a broad topic, this thesis will limit the definition of a good functional outcome post-MLA to:

"Functional survival after surgery and achievement of independent mobility with a prosthesis after rehabilitation."

Functional survival will be defined as:

"The survival of surgery with a satisfactory level of functional potential permitting successful progression to starting rehabilitation."

Independent mobility will be defined as:

"The ability to walk with a prosthesis both indoor and outdoor without assistance from others."

The aims of this thesis are to test the following three null hypotheses:

1. There is no inconsistency between clinicians and patients in the prioritisation of functional outcome for their decision-making when facing MLA;

2. It is not possible to predict functional outcome after MLA;

3. It is not possible to construct a valid decision aid based on the prediction of functional outcome after MLA.

To test these null hypotheses, several analytical methods will be used to produce a systematic comparative analysis using the following approach:

1. Assess the current level of evidence pertaining to the importance of functional outcome research in the MDT care of the threatened and unsalvageable limb through a systematic review of published literature and meta-analysis;

2. Develop methods to ascertain the concerns of patients before and after MLA;

3. Develop methods to identify predictors of functional survival after MLA;

4. Develop methods to identify predictors of functional outcome after rehabilitation;

5. Understand the fate of patients undergoing palliation for their unsalvageable limb to provide patients with the likely outcomes if palliation is chosen over MLA;

6. Construct validated risk prediction models for the prediction of functional outcome after MLA, and their incorporation into a decision aid.

Chapter 2: Methods

2.1 A Summary of the Methodology of the Thesis

The experimental chapters adopted in this thesis include systematic reviews, cross-sectional and cohort studies. There are six core experimental chapters used to address the aims and objectives of this thesis. In addition, there are two supplementary experimental chapters that were performed to further explore findings from two of the core experimental chapters, thus evaluating the strength of inferences drawn from those core chapters. **Figures 4 to 6** below summarise the structure of thesis.

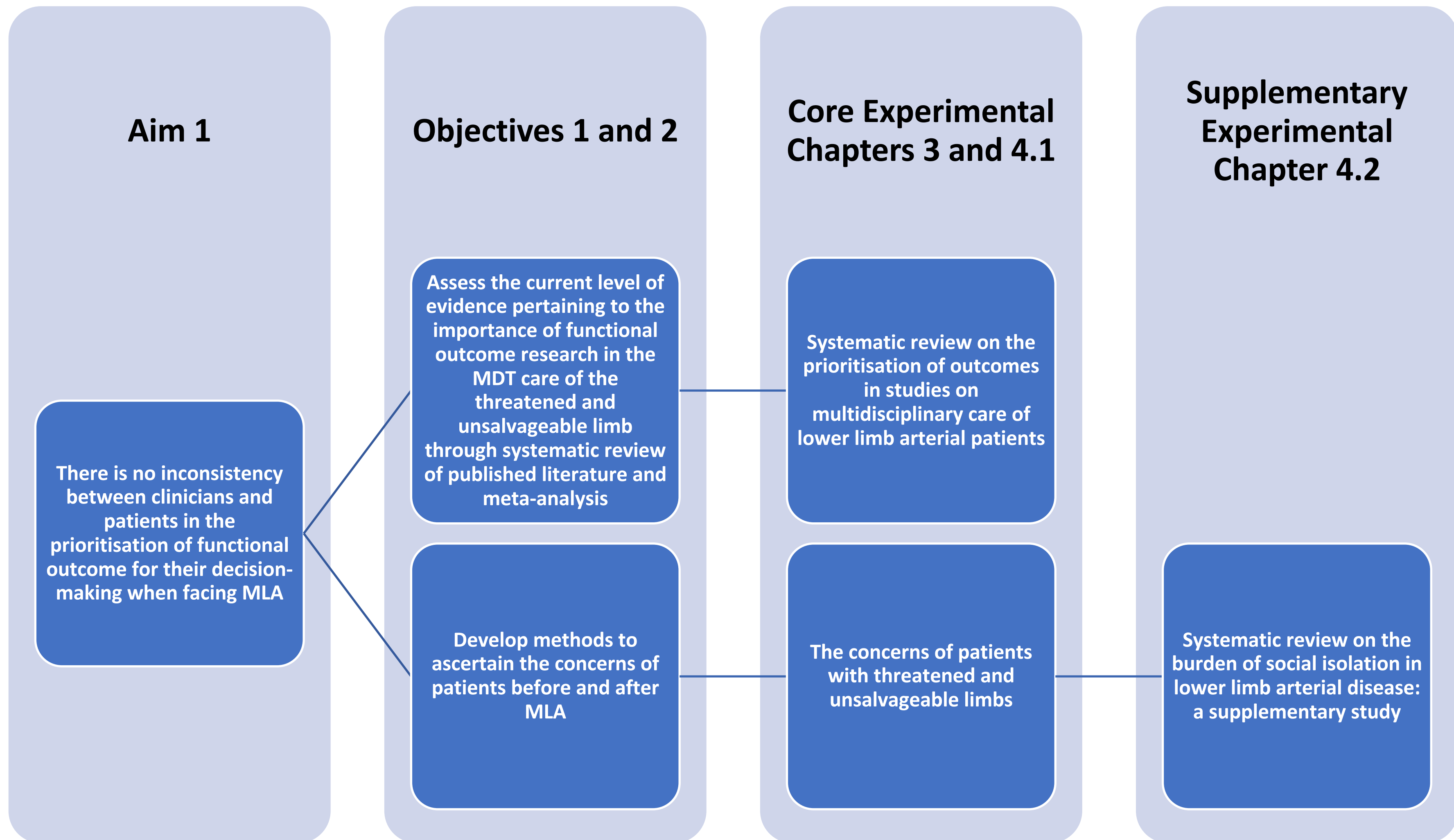

Figure 4: Structure of Thesis for Aim 1 involves Objectives 1 and 2, Chapters 3 and 4.1 and Supplementary Chapter 4.2.

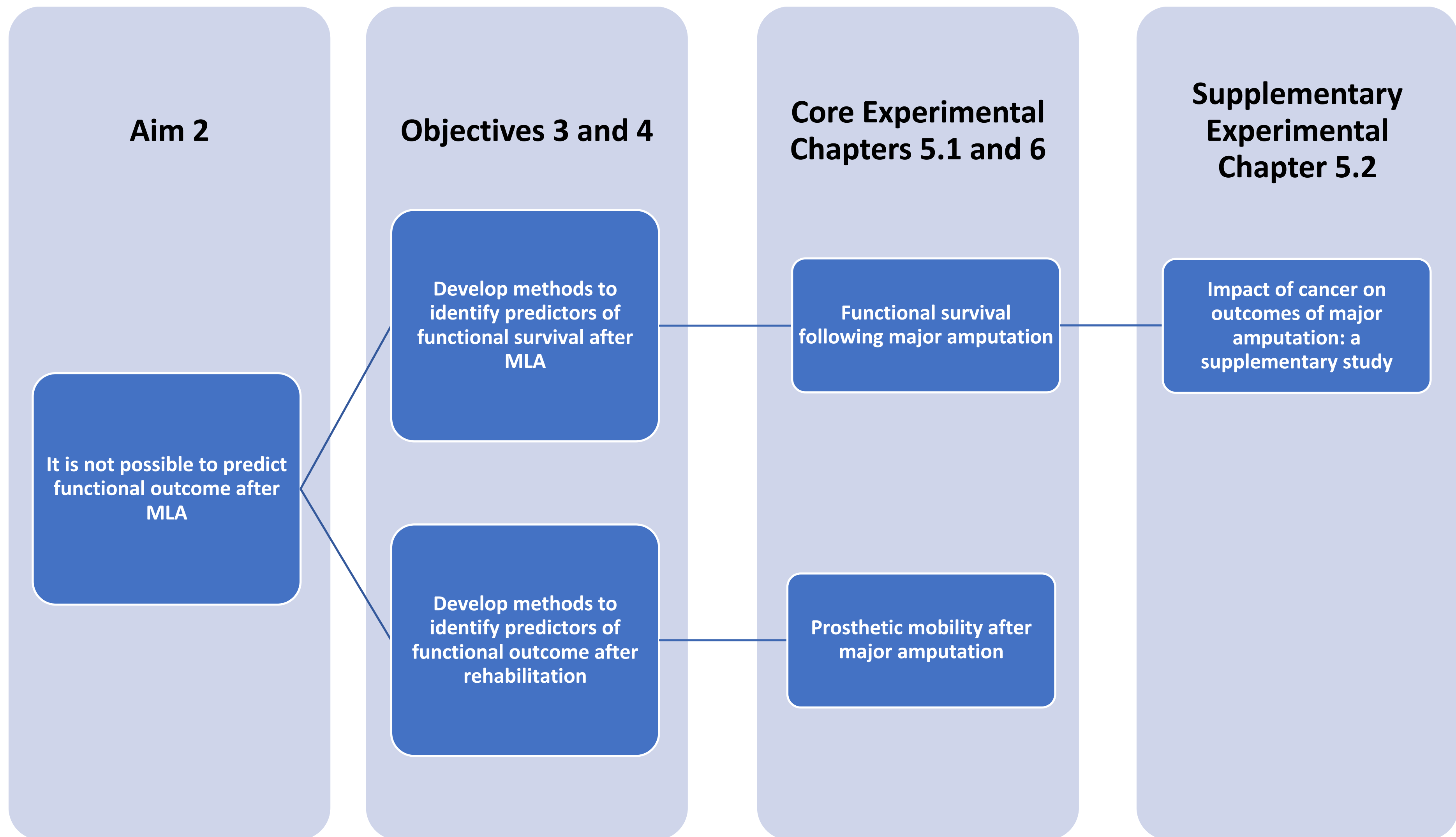

Figure 5: Structure of Thesis for Aim 2 involves Objectives 3 and 4, Chapters 5.1 and 6, and Supplementary Chapter 5.2.

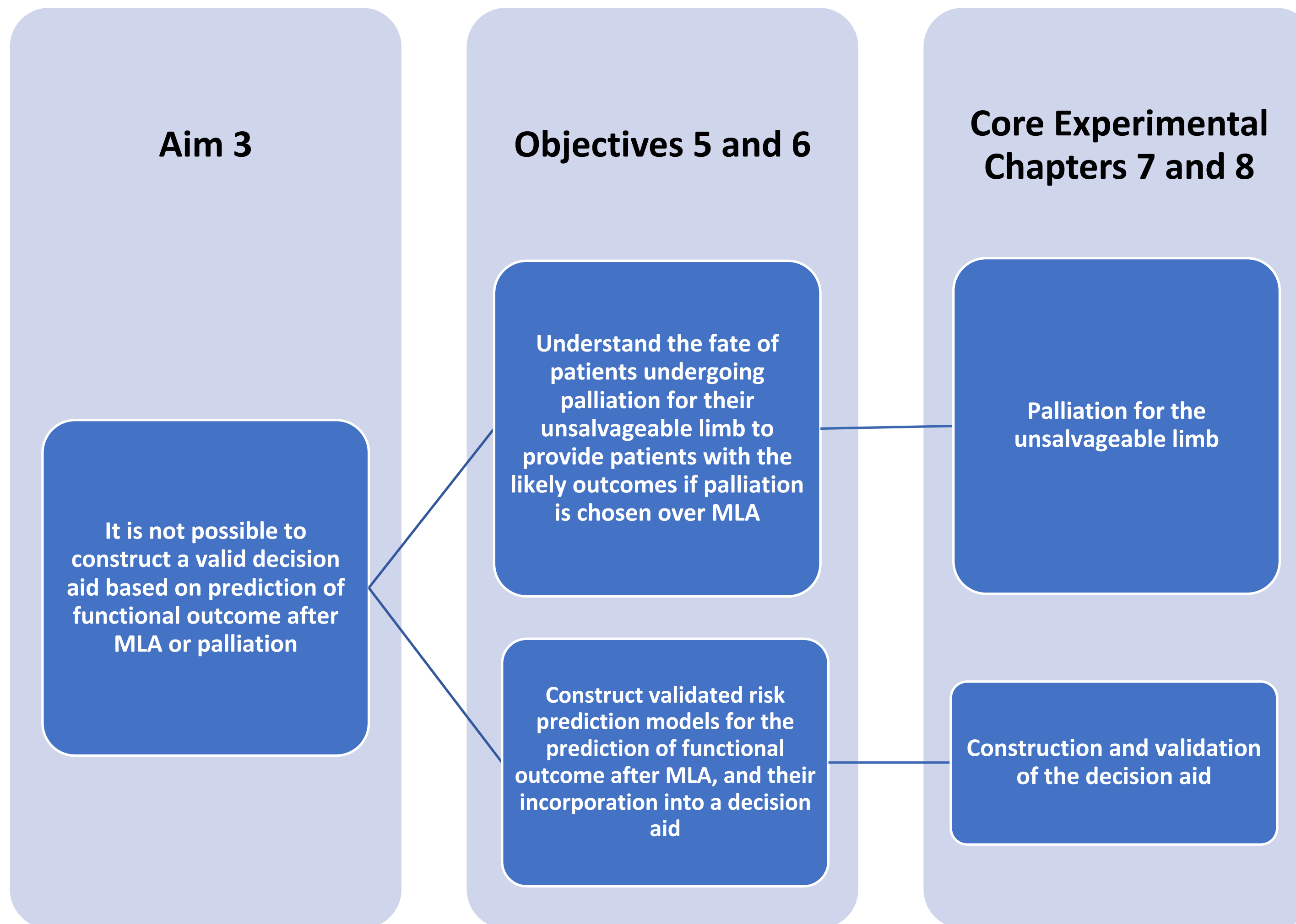

Figure 6: Structure of Thesis for Aim 3 involves Objectives 5 and 6, Chapters 7 and 8.

2.2 Systematic review on the prioritisation of outcomes in studies on multidisciplinary care of lower limb arterial patients (Chapter 3)

2.2.1 Chapter Overview

- This chapter addresses Objective 1 of this thesis: to assess the current level of evidence pertaining to the importance of functional outcome research in the MDT care of the threatened and unsalvageable limb.
- Study design: a systematic review and meta-analysis.
- The study conformed with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis Of Observational Studies in Epidemiology (PRISMA) guidelines (79).

2.2.2 Literature Search

A comprehensive search strategy was developed using controlled vocabulary and keywords. These included free-text and MeSH terms (rehabilitation, mobility, prosthetic, function, functional, peripheral arterial disease, ischaemia, acute, chronic, CLI, CLTI, ALI, diabetic foot, ulcer, amputation, multidisciplinary, interdisciplinary, multispecialty, patient care team). The following databases were searched from their inceptions through to Feb 24, 2020: PubMed, Scopus, Medline, Cumulative Index to Nursing and Allied Health, Cochrane Central Register of Controlled Trials and PROSPERO.

2.2.3 Study Selection

Inclusion criteria were kept broad to preserve the generalisability of findings. All original studies that met the following criteria were included:

- The study reported outcomes of MDT-led care for patients with DFD, PAD, or amputations resulting from these pathologies.
- Care was considered as MDT-led if two or more specialties were involved in care algorithms or if a group of different specialists described themselves as a team.

- The study compared MDT interventions with standard care (care provided without the involvement of a designated MDT).

Where reported, the basis for confirming PAD ranged from ankle-brachial index (ABI) ≤0.90, post-exercise fall in ABI, ultrasonography, angiography, computed tomography, or magnetic resonance imaging scans. For confirmation of DFD: random glucose, fasted glucose, and glycated haemoglobin (HbA1c) levels in combination with tissue loss (ulcer, gangrene, or minor amputation) were a requirement.

Studies were excluded if they were not written in English, were published as abstracts only, or were unpublished. All titles and abstracts of the studies identified were screened by two independent reviewers. Discrepancies were resolved by a third independent reviewer. The process was repeated using full-text articles during the second phase of screening.

2.2.4 Quality Assessment

Two independent reviewers assessed the methodologic quality and risk of bias for each included study using a modified Downs and Black checklist for randomised and nonrandomised studies of health care interventions (80). Higher scores indicated higher quality studies, with a maximum score of 25. Scores within 3 points of each other were averaged. Otherwise, reviewers discussed discrepancies and agreed on a final score. Studies were also assigned descriptors of study quality (excellent, good, fair, or poor) based on the final score.

2.2.5 Data Extraction and Analysis

Two reviewers independently abstracted all data using standardised, Microsoft Excel-based forms. The following study attributes were abstracted: publication year, design, location, sample size and length of enrolment. The following patient attributes were abstracted: age, sex, aetiology, and foot presentation. A meta-analysis was performed if patient, intervention, and outcome data among studies were of satisfactory homogeneity.

2.3 The concerns of patients with threatened and unsalvageable limbs (Chapter 4.1)

2.3.1 Chapter Overview

- This experimental chapter addressed Objective 2 of this thesis: to develop methods to ascertain the concerns of patients before and after MLA.
- The study design: a mixed-methods cross-sectional study, involving both quantitative and qualitative analyses.

This retrospective study was carried out from June 2019 to January 2020 on all in-patient DFD patients reviewed by a dedicated psychologist, as part of the MDT in a tertiary centre for vascular surgery.

The broader MDT was comprised of an endocrinologist, vascular and orthopaedic surgeons, microbiologist, musculoskeletal and interventional radiologists, rehabilitation consultant, podiatrists, and clinical pharmacologist, in addition to the psychologist.

2.3.2 Inclusion Criteria

All patients being managed by the MDT were given the option of speaking to the psychologist, and those who agreed went on to receive semi-structured therapy sessions aimed at exploring their health-related concerns and psychosocial problems and delivering patient-specific psychotherapy. Patients were identified from the MDT lists, with those under the age of 18 and adults lacking capacity to consent being excluded from the study.

2.3.3 Data Collection

Data were collected on demographics, comorbidities, psychiatric history, use of psychiatric medications (antidepressant, anxiolytic, or antipsychotic medication), and social situation of the patient (place of residence, next-of-kin availability, etc). Health-related concerns and psychosocial problems were collated from all patient-psychologist encounters documented in the clinical notes.

For comparisons, patients were grouped according to gender and amputation status:

1. No amputation: patients with ulcers or dry gangrene with no current history of an amputation.
2. Minor amputation: patients with a history of only forefoot or midfoot amputation within the last year.
3. Pre-major leg amputation (pre-MLA): patients with an unsalvageable limb offered an MLA.
4. Post-major leg amputation (post-MLA): patients with limb loss having after-care or being treated for the disease of the contralateral foot.

2.3.4 Data Analysis

Quantitative analysis was performed using R version 3.6.0 (81), in R Studio version 1.3.1056 (R Studio PBC. Boston, MA. 2020) (82). Categorical variables were presented as count and percentage per cohort with the use of Fisher's test for comparative analyses. Continuous variables were presented as median [IQR] and were compared using the Mann-Whitney U test and one-way ANOVA tests. All p-values were two-tailed and considered statistically significant when $p \leq 0.05$ and 95% confidence interval (CI).

For the qualitative component of this study, content and thematic analysis of psychology documentation were performed, with the aim of identifying principal concerns expressed by patients. These concerns were grouped into themes and presented in a socioecological framework model to explain patient-environment interactions. This model of research in sociology and public health, emphasises the hypothesis that patients' health-related behaviours both shape and are shaped by their environment, and that there are multiple levels of influence (such as personal, interpersonal, organisational, and community) (83,84).

2.3.5 Ethical Approval

This retrospective study was performed under the purview of a service evaluation using routine clinical data available and therefore no ethical approval was required.

2.4 Systematic review on the burden of social isolation in lower limb arterial disease: a supplementary study (Supplementary Chapter 4.2)

2.4.1 Chapter Overview

- Findings made, of social isolation in lower limb vascular patients, in the preceding chapter warranted an in-depth focus.
- This study was included as a supplementary chapter to complement findings from Chapter 4.1.
- The aim of this chapter was to report on prevalence of social isolation in lower limb arterial patients and its impact on clinical and other patient-centred outcomes.
- Study design: a mixed-methods systematic review of quantitative and qualitative studies was performed, with narrative syntheses.
- The study conformed with PRISMA guidelines (79).

A contingent segregated approach was utilised in which syntheses of quantitative and qualitative data were performed sequentially to address two questions (85–88). The quantitative component of the review addressed the first question: what is the prevalence, severity, and impact of social isolation on clinical outcomes? The qualitative component addressed the second question: what is the impact of social isolation on patient-centred outcomes?

2.4.2 Literature Search

A literature search was performed on CINALH, PsycINFO, MEDLINE, AMED, EMBASE, Web of Science, directory of Open Access repository websites and PROSPERO, for studies between 1974 and December 2019. Combinations of free-text and MeSH search terms included (social* OR isolation OR loneliness OR alone OR social support) AND (peripheral arterial disease OR vascular OR dysvascular OR diabetic foot OR ulcer OR gangrene OR amputation).

2.4.3 Study Selection

Titles and abstracts were screened by two independent reviewers for assessment against the inclusion criteria.

Peer-reviewed studies containing quantitative or qualitative findings on social isolation in PAD and DFD were included. Where reported, the basis for confirming PAD ranged from ankle-brachial index (ABI)≤0.90, post-exercise fall in ABI, ultrasonography, angiography, computed tomography, or magnetic resonance imaging scans. For confirmation of DFD: random glucose, fasted glucose and HbA1c levels in combination with tissue loss (ulcer, gangrene, or minor amputation) were a requirement.

Quantitative studies were included if validated tools screening for, and assessing severity of, social isolation were used. Qualitative studies were included if they reported on social isolation using open discussion, focus groups and semi-structured interviews.

Articles were excluded if the participant cohorts were under the age if 18 years, could not consent or were palliated. Studies were also excluded if they were not of a minimum level of quality based on their quality assessment.

2.4.4 Quality Assessment

Studies were independently assessed by two reviewers for methodological quality using the Joanna Briggs Institute (JBI) Critical Appraisal Tool. This tool marks studies according to ten criteria of potential bias and has been used for quality assessment in similar mixed-method systematic reviews (88).

The decision to include a study was made based on meeting a pre-determined proportion of criteria for quality (minimum of six out of ten criteria), and any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer.

2.4.5 Data extraction and synthesis

Data was extracted from studies using the JBI data extraction tools designed for use in mixed-methods reviews (86,89). Initial extraction of data relating to demographics and study design was consistent across qualitative and quantitative papers. Data on prevalence/severity of social isolation and associations with clinical outcomes were extracted from quantitative studies. Due to the heterogeneity of study designs, quantitative analysis was reported as a narrative synthesis. Qualitative data underwent thematic analysis to categorise the impact of social isolation on patient-centred outcomes as per the socio-ecological framework model.

2.5 Functional survival following major amputation (Chapter 5.1)

2.5.1 Chapter Overview

- This chapter addresses Objective 3 of this thesis: to develop methods to identify predictors functional survival after MLA.
- The study design: a retrospective cohort study.

2.5.2 Inclusion Criteria

All consecutive MLAs performed in a tertiary regional service for vascular surgery between 2013 and 2018 were compiled into a database. MLAs performed secondary to trauma were excluded. Follow-up for the study ended in April 2021.

2.5.3 Patient Variables

Data were collected on demographics, aetiology, frailty scores, comorbidities, psychosocial problems, level of MLA, and blood results. Aetiologies were grouped into the following: ALI, acute-on-chronic CLTI, CLTI and diabetic foot sepsis (DFS). Frailty scores were calculated using the mFI-5 score (90,91). MLA levels were categorised into AKA, TKA and BKA levels. Blood results included were the most recent laboratory-based results in the 24 hours prior to amputation.

Psychosocial variables included pre-existing psychiatric diagnoses, social problems and area-deprivation scores based on residential postal code. Psychiatric diagnoses included mood, anxiety and psychotic disorders, and cognitive impairment (chronic confusional states). Acute confusional states (delirium) were not classified as a psychological problem due to their temporary course.

Social problems included history of drug misuse, being a vulnerable adult and pre-amputation functional dependency. Drug misuse was defined as a history of psychoactive drug, alcohol or tobacco dependence documented in notes or as international classification of disease coding (ICD code Z86.4) (92,93). A vulnerable adult was defined by evidence pertaining to a

deficiency of social support, self-neglect, being a victim of abuse or housing problems such as residence of no fixed abode.

Pre-amputation functional dependence was defined as dependency on support for activities of self-care, daily living, mobility (being a falls risk, wheelchair use or bedbound status), and visual or hearing problems. Postcode deprivation scores were obtained using the 2016 publication of the national index of multiple deprivation deciles (IMDD), where higher deciles correspond to lower deprivation (94,95).

2.5.4 Post-operative Outcomes

The primary outcome was functional survival (post-operative survival and successful progression to rehabilitation after surgery). Secondary outcomes were post-operative complications, length of stay, place of discharge and long-term survival.

Progression to rehabilitation was based on patients' prosthetic rehabilitation potential at time of discharge, which was determined by independent physiotherapy assessment on the ward, during acute recovery phase following MLA. Assessments were based on post-operative clinical and functional status and categorised into three types:

1. Suitable for rehabilitation and commenced specialist amputee rehabilitation at time of discharge from MLA.
2. Suitable for rehabilitation but experienced delays to their rehabilitation due to medical or surgical complications.
3. Unsuitable for rehabilitation and therefore did not undergo prosthetic rehabilitation.

Length of stay (LOS) was categorised into three time points:

- pre-amputation LOS (from admission to amputation)
- post-amputation LOS (from amputation to discharge)
- total LOS (from admission to discharge)

2.5.5 Statistical Analysis

Univariate analyses (Chi square test for categorical and ANOVA test for continuous variables) were used to identify associations between pre-MLA variables and outcomes. Multivariate analysis, for the identification of independent predictors, was performed during the construction and validation of the risk-prediction models and reported in Chapter 8. Continuous variables were expressed by median and IQR in the case of non-normal distribution. Categorical variables were stated as absolute frequencies and percentages. Survival was analysed by the Kaplan-Meier method. A p value <0.05 at 95% CI was considered significant. Statistical analyses were performed with R version 3.6.0 (82).

2.6 Impact of cancer on outcomes of major amputation: a supplementary study (Supplementary Chapter 5.2)

2.6.1 Chapter Overview

- The database from the preceding study (Chapter 5.1) was further analysed to study the impact of cancer on outcomes after amputation based on cancer-related findings.
- Study design: a retrospective cohort study.
- The same list of outcomes was analysed in this supplementary study as in the preceding study.

2.6.2 Patient Variables

Patients were divided into four groups according to their cancer status. Those with an active cancer diagnosed in the six-month period preceding-, or in the same admission as their MLA, were considered new cancers. Active cancers diagnosed prior to six months before their MLA were considered as established cancers. Historic cancers were defined as those treated successfully and discharged from cancer follow-up at least a year before their MLA. Patients with no history of cancer were considered as the non-cancer group. This cohort acted as a control group to provide context over the study period.

In-depth characterisation of the new and established cancer groups was performed by collecting data on primary lesion of cancer, chronicity (timing of cancer diagnosis in relation to amputation), metastatic status, chemo/adjuvant therapy at time of amputation, and type and timing of ipsilateral revascularisation attempts.

2.6.3 Comparisons made with Outcomes of Palliation for the Unsalvageable Limb

As a further analysis, survival data on outcomes of cancer patients undergoing MLA were compared to those of palliated patients with an unsalvageable limb. This step was performed after the completion of the experimental chapter on palliation for the unsalvageable limb and reported in Chapter 7. The aim of this comparison was to confirm if survival was comparable between the two groups.

2.7 Prosthetic mobility after major amputation (Chapter 6)

2.7.1 Chapter Overview

- This experimental chapter addresses Objective 4 of this thesis: to develop methods to identify predictors of functional outcome after rehabilitation.
- The study design: a retrospective cohort study of prospectively collected data.

The Douglas Bader Amputation Rehabilitation Centre in Queen Mary's Hospital, Roehampton, was established during World War One, and is a national centre for amputation rehabilitation. All referrals are reviewed by their MDT consisting of rehabilitation clinicians, physiotherapists, occupational therapists, orthotists, prosthetists, dieticians, and psychologists. Patients receive rehabilitation therapy either as outpatients or inpatients, based upon clinical and social needs. All patients receive daily physiotherapy during their rehabilitation period. An established in-house prosthetics department manufactures and services the prosthetics. Patients typically receive six weeks of intensive active rehabilitation therapy. Upon discharge, they receive a six-week and six-month follow-up review.

The study data were compiled from a detailed prospectively maintained database of functional outcomes for all MLA patients within the rehabilitation programme since the inception of the database in 2007 to 2020. Follow-up for the study ended in April 2021.

2.7.2 Inclusion Criteria

Rehabilitation outcomes for patients receiving therapy between December 2007 and January 2020 were retrospectively analysed. Inclusion criteria was primary referrals (new amputees receiving their first rehabilitation episode) for MLA secondary to DFD or PAD. Established referrals (established amputees receiving further rehabilitation for their ipsilateral amputation) and all other aetiologies (cancer, trauma, complex regional pain syndrome, non-diabetic osteomyelitis, and other infections) were excluded.

2.7.3 Patient Variables

The following patient variables were included: demographics, residential area deprivation ranks, comorbidities, post-amputation weights, medication (pre-amputation). Frailty was calculated as per the mFI-5, a validated scoring system, based on functional activity pre-surgery and four comorbidities: diabetes, hypertension, respiratory disease and heart failure (96).

Therapy related factors included time between amputation and first therapy (wait for therapy), engagement with an early-walking aid (EWA) prior to therapy, prothesis use (and type of prosthesis) during therapy, therapy duration and number of physiotherapy sessions.

2.7.4 Outcomes

The primary outcome was functional outcome following rehabilitation, in particular independent prosthetic mobility. The secondary outcome was survival. Independent prosthetic mobility was assessed using the Specialist Interest Group in Amputation Medicine (SIGAM) scores. Additional measures of prosthetic function were timed-up-and-go (TUG) times and 2-minute distances. SIGAM is a single-item scale comprising six clinical grades (A-F) of amputee mobility. Grades A to C were classified as dependent prosthetic mobilisers. Grades D-F were classified as independent prosthetic mobilisers (97). SIGAM grades are described in **Table 2**.

Grade	Disability	Definition
A	Non-limb user	No use or only aesthetic use of the prosthetic limb
B	Therapeutic	Use of prosthetic limb only for transfer
C	Limited/Restricted	Use of prosthetic limb indoors or up to 50m outdoors on even ground with or without walking aids
D	Impaired	Use of prosthetic limb indoors and more than 50m outdoors on level ground with walking aids in good weather
E	Independent	Use of prosthetic limb more than 50m without walking aids in adverse terrain or weather
F	Normal	Normal or near normal walking with prosthetic limb

Table 2: Definitions of SIGAM grades.

TUG time is utilised in physiotherapy to assess dynamic stability (and risk of falls) and is defined as the time taken for a patient to get up from a chair, walk three metres, turn around, walk back to chair and sit (98). A TUG time of over seven seconds is indicative of increased risk of falls. To assess exercise capacity, all patients were asked to walk for two minutes on a flat surface (2-minute distance) (99).

2.7.5 Limiting Bias

Clinician bias was reduced by ensuring that all functional outcomes were measured independently and in real time by the physiotherapy team. Moreover, the therapy team were not given access to the full data on patient characteristics, thus further reducing bias.

2.7.6 Ethical Approval and Study Registration

The study was registered with IRAS (263542). As this was a retrospective study of a prospectively maintained clinical database, formal ethical approval was deemed inessential after discussion with the university research and ethics committee.

2.7.7 Statistical Methodology

All statistical analyses were performed in the R statistical programming environment, version 4.1.0. Missing data underwent sensitivity analysis and deemed to be missing at random. Univariate analysis was performed using univariable logistic and linear regression for categorical (SIGAM) and continuous (TUG time and 2-minute distance) outcomes, respectively.

Multivariate analysis, for the identification of independent predictors, was performed during the construction and validation of the risk-prediction models and reported in Chapter 8. Survival was analysed by the Kaplan-Meier method. A p value <0.05 at 95% CI was considered significant. Statistical analyses were performed with R version 3.6.0 (82).

2.8 Palliation for the unsalvageable limb (Chapter 7)

2.8.1 Chapter Overview

- The purpose of this experimental chapter was to address Objective 5 of this thesis: to understand the fate of patients undergoing palliation for their unsalvageable limb.
- The study design: a retrospective cohort study.

Patients who received palliation under the palliative care team during a four-year period between March 2016 and April 2020 were identified from a prospectively maintained electronic database in a tertiary centre for vascular surgery. Follow-up period ended in April 2021.

Patients were referred to the palliative care team once the decision to no longer undertake active surgical management had been made. The decision to refer to palliation was made by an MDT, encompassing the input of vascular surgeons, interventional radiologists, physicians, nursing staff, physiotherapists and occupational therapists and anaesthetists together with the wishes of the patient.

The specialist palliative care team provided a face-to-face clinical review within 24 hours of the referral. If deemed appropriate for discussion with patients, their preferred place of palliative care and place of death were explored. When suitable, patients were discharged to their usual place of residence, a nursing home, or a hospice. All patients who died in hospital were put on individualised end-of-life care plans.

2.8.2 Inclusion Criteria

Patients included in this study were those with an unsalvageable limb secondary to either PAD or DFD. Patients were excluded if an MLA was performed prior to commencement of palliation. For consistency of comparisons, aetiologies were grouped into ALI, acute-on-chronic limb acute-on-chronic CLTI, and CLTI, as in previous experimental chapters.

2.8.3 Patient Variables

Data were collected on demographics, comorbidities, deprivation ranks, laboratory tests at time of decision to palliate, and ipsilateral vascular surgery in the same admission prior to palliation (minor amputation or revascularisation). A frailty score (mFI-5) was calculated for each patient (96).

2.8.4 Outcomes

Outcomes measured were time to palliation, length of stay, place of death and survival from time of palliation commencement.

2.8.5 Statistical Analysis

Data were compared between ALI, acute-on-chronic CLTI and CLTI cohorts. The Kruskal-Wallis test was used for non-normally distributed continuous variables, and the Fisher's exact test for categorical variables. Survival comparisons were performed with Kaplan-Meier analysis and log rank tests. All statistical tests were two-sided, with a statistical significance defined as $p<0.05$ at 95% CI. Analyses were performed using the computer software Jamovi (version 1.6.15.0) [The Jamovi project (2021)] (100).

2.9 Construction and validation of the decision aid (Chapter 8)

2.9.1 Chapter Overview

- This experimental chapter addresses Objective 6 of this thesis: to incorporate findings of the previous objectives into risk prediction tools for the prediction of good functional outcome after MLA.
- The chapter reports on the construction and validation of the risk prediction models generated from experimental Chapters 5.1 and 6.
- Model 1 (generated from Chapter 5.1) was for the prediction of functional survival following MLA.
- Model 2 (generated from Chapter 6) was for the prediction of independent prosthetic mobility (using dichotomised SIGAM scoring) after rehabilitation.
- Internal validation was performed using bootstrapping for both models.
- Criterion Validation for the Model 2 was performed using prediction of TUG time and 2-minute distance.
- This study reported the construction and validation of risk prediction models in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (101).
- Outcome data for patients receiving primary palliation for unsalvageable limb disease were included as narratives within the decision aid.
- Risk calculators were built using variable coefficients from the logistic regression equations generated by each model and incorporated into a web-based application.

2.9.2 Variable Selection for Models

Important considerations for variable selection were set. Variables were selected if they would be known at the time the prediction were to be made, and if they were readily obtainable (e.g., cost, invasiveness and how ubiquitously it is encountered in routine practice). Ultimately, the balance of prior knowledge about which factors were likely to be predictive and the need for data-driven discovery of novel predictors guided this study's approach to variable selection. Therefore, variable selection utilised both pre-specification

and stepwise regression. The benefits of this hybrid approach were that all predictors grounded in plausibility ("strong priors") were considered, the vulnerability to overfitting and data idiosyncrasies were accounted for, and the method remained computationally simple and reproducible for future external validation. Penalisation methods such as LASSO or Ridge regularisation were avoided as these statistical techniques for variable selection may exclude features that are moderately predictive, discarding valuable information. They may also include implausible features and omit predictive features. It is also known that these techniques perform poorly when predictors are highly correlated (102).

As functional survival and independent prosthetic mobility were binary outcomes, continuous predictor variables were dichotomised prior to logistic regression for the aid of interpretation. Cut-off values for dichotomisation were based on median values for the entire study population. Strength of associations in the logistic regression models were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

For prediction of continuous outcomes, (TUG time and 2-minute distance), which served as the criterion validation of SIGAM prediction, the categorical predictor variables in the linear regression analyses were assigned effect sizes (ES) with 95% CI to represent the mean difference in the continuous outcome variable between the reference and comparison groups. Multicollinearity within both models was addressed by exclusion of variables with variance inflation factor (VIF) above 1.1 and/or tolerance level below 0.9.

2.9.3 Risk model performance

The accuracy of the logistic regression models was assessed by their discrimination and calibration. Discrimination measures how well a model can distinguish between cases (outcome) vs non cases (no outcome). Discrimination was assessed by the C-statistic, also known as the area under the curve (AUC) in the model's receiver operating characteristic (ROC) curve. The C-statistic ranges from 0.50 (no better than flipping a coin) to 1.00 (model is 100% correct).

Calibration measures a model's ability to generate predictions that are close to the observed outcomes in the data. The most widely used method for doing this for binary outcome models is the Hosmer-Lemeshow test, which examines how well the percentage of observed outcome matches the percentage of predicted outcome over deciles of predicted risk.

2.9.4 Weighting of Predictor Variables within the Risk Calculators

Once Models 1 and 2 were constructed, they were used to develop risk calculators, which took the form of an interactive spreadsheet that accepts patient variable information and returned the estimated probability percentage of each binary outcome of interest. Weight of each predictor variables within the models was based on their estimated coefficients from their regression models. These coefficients were used to estimate the logit ($\hat{L}$) for a patient using the standard binary logistic regression equation. The estimated probability percentage of the binary outcomes were then computed using **Equation 1**.

$$estimated\ probability = 100\% * \frac{e^{\hat{L}}}{1 + e^{\hat{L}}}$$

Equation 1: Estimation of the probability of a binary outcome.

The interactive spreadsheet was then implemented into a web-based application using the programming language R using the "shinyR" library (103).

2.9.5 Internal Validation of Models 1 and 2

The performance of the models was validated via bootstrapping. Bootstrap samples were drawn with replacement and with the same size as the original sample. Model selection was carried out for each bootstrap sample and model performance assessment compared with that on the original sample. This was repeated 2000 times to obtain stable estimates of the average optimism of the AUC (C-statistic) for each logistic regression model.

There are advantages of bootstrap validation over other methods of internal validation. The optimism-corrected performance estimate is stable because samples of size *N* are used to develop the model as well as to test the model. This benefit is not offered by other methods such as split-sample and cross-validation methods. Compared with apparent validation, some uncertainty is added by having to estimate the optimism but if sufficient bootstraps are taken, this uncertainty becomes negligible. Simulations have shown that bootstrap validation can appropriately reflect all sources of model uncertainty, especially variable selection (104).

2.9.6 Criterion Validation for Model 2

The presence of alternative and validated measurements of prosthetic function (TUG and 2-minute tests) for each patient permitted criterion validation (concurrent-subtype of this validation technique) for Model 2. Criterion validity is defined as an estimate of the extent to which a measure agrees with a gold standard i.e., an external criterion of the phenomenon being measured (105,106).

This was achieved by evaluation of a correlation between the results of this (SIGAM) logistic regression analysis and those of TUG time and 2-minute distance linear regression analyses. The rationale was that if there was a high correlation between the list of variables that were predictive of SIGAM, TUG and 2-minute scores, then it would be justified to assume confidence that Model 2 was a valid tool for the prediction of independent prosthetic mobility.

Although a consensus is required on what the "gold standard' for measurement of independent prosthetic mobility should be, this study utilised TUG time and 2-minute distance as reliable modes of functional assessment as they are measured using standard and calibrated techniques and therefore deemed suitable to compare with assessment and prediction of dichotomised SIGAM scores.

Chapter 3: Systematic review on the prioritisation of outcomes in the multidisciplinary care of the lower limb arterial patients

3.1 Introduction

Recognition of the complexity of disease processes and patient groups has led to the rise of the MDT model of care in the contemporary management of the vascular patient. This is regarded as the gold standard in clinical care. What interventions MDTs choose to prioritise and how they evaluate their success, strongly reflect what the clinicians view as essential in their decision-making on managing threatened and unsalvageable limbs.

There is a heavy focus on surgical outcomes with very little reported on more holistic measures. Arguably, medical and patient-centred outcomes including functional outcome, psychosocial problems, and quality of life weigh an equal importance for patients.

Existing systematic reviews have prioritised the reporting of limb salvage rates as the measure of success for MDT-led care (107,108). Although a clear benefit of adopting an MDT model has been demonstrated in reducing amputation rates in these reviews, a question remains on how MDTs in these studies managed the patient holistically. Moreover, variability in MDT composition, disparities in provision of care, and heterogeneity of outcome measures, paint a confusing picture of what the gold standard in MDT-led care should be.

Evaluation of MDT interventions for threatened and unsalvageable limbs must involve a global assessment of outcomes. The aim of this systematic review was to report the outcome measures chosen by studies focussing on the impact of MDT interventions for the management of lower limb arterial patients. In the interests of this thesis, the rationale for doing this was to determine if MDTs in contemporary practice assign significance to improving functional outcomes. A secondary aim was to perform a narrative synthesis of all reported outcomes, and where possible to perform a meta-analysis.

3.2 Methods

The methodology of this experimental chapter is described in full in Chapter 2. In brief, a systematic review with narrative synthesis, and where possible, a meta-analysis was performed in accordance with PRISMA guidelines.

3.3 Results

3.3.1 Literature Search

A PRISMA flow chart for this review is shown in **Figure 7**. The literature search identified 1284 distinct articles, of which 756 were excluded during title screening and a further 481 were excluded after abstract screening. After full text screening, a further nine studies were excluded because these studies reported outcomes of MDT care without having a comparative standard care group (**Supplementary Table 1**). This left 38 studies that met the inclusion criteria.

3.3.2 Study Characteristics

Most (36/38, 94.7%) studies were observational, with global centre representation (**Table 3**). Only two randomised trials met the inclusion criteria and this distinct lack of randomisation and blinding among most studies commonly detracted from study quality. Thirty-seven studies (97.4%) included at least 50 patients treated by their respective MDT. Fourteen (36.8%) studies reported length of enrolment which varied greatly, in terms of calendar time or time to clinical endpoints.

Follow-up was unclear in studies using a historically controlled (pre-post design), which involved comparison of outcomes between two different time periods: the periods prior to- and during an MDT-led service, respectively. The mean bias score was 15.9 [Standard Deviation (SD) 2.36], and most studies (73.0%) ranked fair.

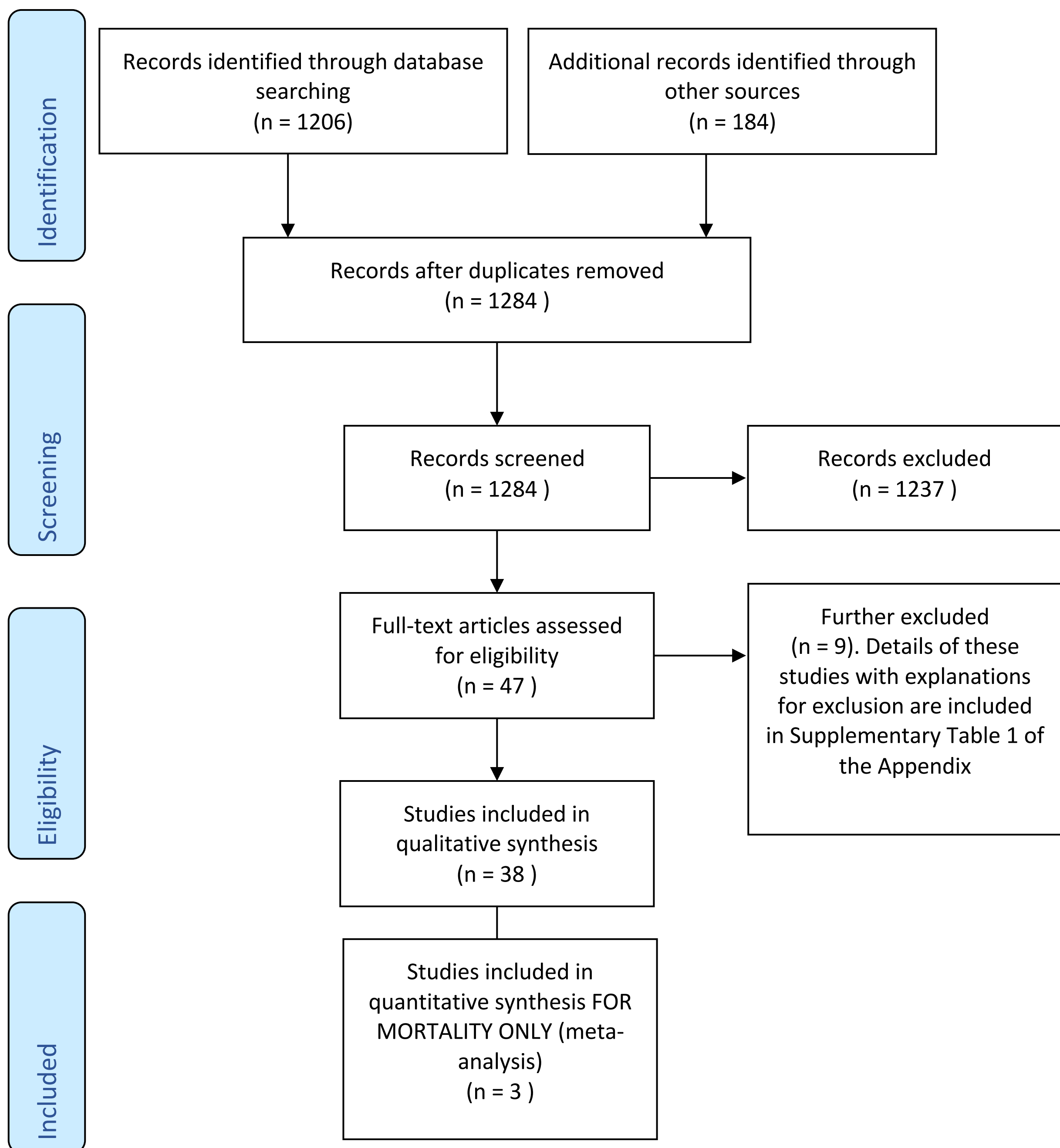

Figure 7: PRISMA flow chart for the systematic review in Chapter 3.

Paper	Study Design	Participants	Outcome of Interest	Setting, Geographical & Cultural	Bias
Armstrong 2014 (109)	Retrospective, single-centre, 2006 to 2013 Follow-up= 3 years	All PAD/CLTI patients, n=739 DM= 38%	3- year adverse cardiac events, MLA, Revascularisation, Mortality	Inpatient, Tertiary centre, USA	16.5
Lovell 2011 (110)	Prospective, single-centre, 2005-2008 Follow-up=528 days	ALL CLTI patients with suboptimal CVS protection, n=103	Blood pressure, Serum cholesterol and HbA1C control	Outpatient clinic, Tertiary centre, Canada	17
Chung 2015 (111)	Retrospective, single-centre, 2010 to 2012, Median follow-up = 539 days	All CLTI patients, n=146	MLA, Mortality, Ulcer healing, Mobility	Inpatient, Tertiary centre, USA	20
Weck 2013 (112)	Prospective, multi-centre, 2000-2007, Follow-up=2 years	All DFD patients, n=1092	Ulcer healing, MLA, In-patient Mortality	Clinic, Ward and Rehabilitation, Germany	18.5
Riaz 2019 (113)	Retrospective, single-centre, 1997-2016, Follow-up= unclear	All DFD patients, n=7994	Ulcer healing, MLA	Tertiary centre, Pakistan	16.5
Rerkasem 2009 (114)	Retrospective, 2003-2005, single centre, Follow-up= unclear	All DFD, n=73	Quality of Life, Cost effectiveness	Tertiary centre, Thailand	16
Simson 2008 (115)	Randomised control trial, 2004-2005, Follow-up= duration of inpatient stay	All DFD inpatients, n=30	Hospital anxiety and depression score (HADS) and Problems Areas in Diabetes	Clinic, Germany	20.5
Lincoln 2008 (116)	Randomised control trial, single centre, Follow-up=12 months	All DFD patients, n=172	Ulcer incidence, Mood problems, Quality of life, Protective behaviours	Tertiary centre, UK	20.5
Cahn 2014 (117)	Retrospective, single-centre, 2010 to 2011, Follow-up 10 months	All DFD patients, n=194	MLA, In-patient Mortality	Tertiary centre, Israel	16.5
Martinez-Gomez 2014 (118)	Retrospective, single-centre, 1998-2012, Follow-up=730 days	All DFD patients, n=1460	Amputation, Length of admission, In-patient mortality	Tertiary centre, Spain	16
Laakso 2016 (119)	Historically controlled (pre-post), 2006-2007 and 2013-2014, Follow-up=unclear	All DFD patients with active infection, n=272	MLA, Time to surgery, Length of Hospitalisation	Tertiary centre, Finland	17.5
Chiu 2011 (120)	Case-control, single centre, 2006-2009, Follow-up=until wound healing	All DFD patients, n=736	MLA and Re-amputation	Tertiary centre, Taiwan	17
Kim 2018 (121)	Historically controlled (pre-post), 2002-2015, Follow-up=unclear	All DFD patients, n=338	Glycaemic control, Minor amputation, MLA, Length of Hospitalisation	Tertiary centre, Korea	16.5

Crihana 2014 (122)	Historically controlled (pre-post), Follow-up=duration of admission	All DFD patients, n=230	MLA, Length of Hospitalisation, Post-operative Complications	Tertiary centre, Romania	16.5
Setacci 2013 (123)	Historically controlled (pre-post), Follow-up=182 days	All DFD+CLTI patients, n=375	Ulcer healing, MLA, Mortality	Tertiary centre, Italy	16.5
Alexandrescu 2009 (124)	Historically controlled (pre-post), Follow-up= Mean: 700 days (range 30 – 2040 days)	All DFD+CLTI patients, n=163	MLA	Two tertiary centres, Belgium	16.5
Yesil 2009 (125)	Historically controlled (pre-post), Follow-up= 300 days after discharge	All DFD patients, n=437	MLA	Tertiary centre, Turkey	16
Hedetoft 2009 (126)	Case-control, Follow-up=Unclear	All DFD patients, n=88	Minor amputation and MLA	Tertiary centre, Denmark	16
Dargis 1999 (127)	Prospective cohort, Follow-up=730 days	All DFD (excluding ischaemia patients), n=145	Ulcer Incidence and MLA	Tertiary centre, Lithuania	16
Jiménez 2017 (128)	Historically controlled (pre-post), Follow-up= until ulcer healing	All non-traumatic MLA patient, n=664 and 486 (73%) were DFD patients	MLA	Tertiary centre, Spain	15.5
Wang 2016 (129)	Historically controlled (pre-post), 2004-2013, Follow-up= duration of admission	All DFD patients, n=648	MLA	Tertiary centre, China	15.5
Williams 2018 (130)	Historically controlled (pre-post), 2004-2012, Follow-up=Unclear	All PAD/DFD patients, n=1000	MLA	Primary centre, UK	16.5
Plusch 2015 (131)	Retrospective cohort, Follow-up=duration of admission	All DFD patients with infection, n=156	MLA	Tertiary centre, Australia	15.5
Denjalic 2014 (132)	Historically controlled (pre-post), 1999-2006, Follow-up= until ulcer healing	All DFD patients, n=120	MLA	Tertiary centre, Bosnia and Herzegovina	15
Nather 2010 (133)	Historically controlled (pre-post), 2002-2007, Follow-up= duration of admission	All DFD patients, n=939	Length of Hospitalisation, Readmission, Cost-effectiveness, MLA, Post-operative Complications	Tertiary centre, Singapore	15
Crane 1999 (134)	Historically controlled (pre-post), 1995-1996, Follow-up= duration of admission	All DFD patients, n=103	Length of Hospitalisation, MLA	Tertiary centre, USA	15

Study	Design	Population	Outcomes	Setting	Score
Hsu 2015 (135)	Historically controlled (pre-post), 2004-2013, Follow-up= until ulcer healing	All DFD patients who had undergone an MLA, n=240	Hospitalisation, MLA	Tertiary centre, Taiwan	14.5
Armstrong 2012 (136)	Historically controlled (pre-post), Follow-up= until ulcer healing	All DFD patients undergoing surgery, n=374	Revascularisation, MLA	Tertiary centre, USA	14.5
Witsø 2010 (137)	Historically controlled (pre-post), 1994-2007, Follow-up= unclear	All MLAs in DFD patients, n=254	MLA	Tertiary centre, Norway	14.5
Aydin 2010 (138)	Historically controlled (pre-post), 2002-2007, Follow-up= duration of admission	All DFD patients, n=74	MLA	Tertiary centre, Turkey	14.5
Meltzer 2002 (139)	Historically controlled (pre-post), Follow-up= 1-1095 days	All DFD patients, n=234	MLA	Tertiary centre, USA	14.5
Anichini 2007 (140)	Historically controlled (pre-post),1999-2003, Follow-up= unclear	All DFD patients, n=205	Hospitalisation, MLA	District general hospital, Italy	14
Nason 2013 (141)	Historically controlled (pre-post), 2006-2010, Follow-up= unclear	All DFD patients, n=221	MLA, Cost-effectiveness	Tertiary centre, Ireland	13.5
Holstein 2000 (142)	Historically controlled (pre-post), 1981-1995, Follow-up= unclear	All DFD patients, n=463	Revascularisation, MLA	Tertiary centre, Denmark	13.5
Gibbons 1993 (143)	Historically controlled (pre-post), 1984-1990, Follow-up= 365 days	All DFD patients, n=79	Length of Hospitalisation, Cost-effectiveness	Tertiary centre, USA	15
Troisi 2016 (144)	Historically controlled (pre-post), Follow-up= unclear	All DFD patients, n=103	MLA	Tertiary centre, Italy	14
McGill 2003 (145)	Retrospective cohort, Follow-up=unclear	All DFD patients, n=90	Hospitalisation, Length of Hospitalisation, Cost-effectiveness	Tertiary centre, Australia	12.5
Somayaji et al 2017 (146)	Retrospective cohort, reginal centre for wound care, 2013-2014 Follow-up=6 months	DFD patients (over 6 weeks ulcer duration), n=308, M=67.3%, F=32.7%	Wound care, QoL	Regional community care centre, Canada	16

Table 3: Study characteristics of the studies reporting outcomes for MDT-led care of lower limb arterial patients.

3.3.3 Patient Characteristics

Patient characteristics are reported in **Table 3**. The mean patient age ranged from 56 to 76 years. Between 34% and 100% of the patient groups with the studies were male. Five studies reported patient race; four included predominantly (>80%) Caucasian patients, and one included 100% Asian patients. When reported, patient characteristics were generally well balanced between those who received MDT-led care and those who did not (control group).

Thirty-two studies exclusively treated those with DFD. The proportion of patients with PAD ranged from 42–100% in the other five studies. Three studies were entirely comprised of patients with PAD. The proportion of patients with peripheral neuropathy ranged from 64–100%. In the eleven studies reporting mean haemoglobin A1C values, two were less than 8%. Most studies (29/3, or 76.3%) limited their recruitment to patients with ulcers severe enough to warrant hospitalisation. A further six studies were restricted to patients requiring either revascularisation, major or minor amputation, or plastic surgery reconstruction. Only one study focused on MDT-led optimisation of MLA patients.

3.3.4 Outcomes Reported

Outcomes reported were surgical (major amputation, re-amputation, revascularisation, ulcer incidence and ulcer healing rates), medical (diabetes control, cardiovascular health status, post-operative complication, and mortality rates), organisational (hospitalisation, length of hospitalisation, time to surgery, readmission, and cost-effectiveness) and patient-centred (quality of life, psychiatric health, and mobility) (**Table 4**). The outcome most reported was MLA (in thirty-two studies) and the reporting of other surgical outcomes, in contrast, were significantly less common. The next most reported outcome was length of hospitalisation (in nine studies). Mortality was the most common medical outcome to be reported (in six studies). Cost-effectiveness was another organisational outcome to be reported relatively frequently (in five studies).

Patient-centred outcomes were among the least reported in studies; three studies reported quality of life, two reported psychiatric health and only one study reported mobility.

Outcome Reported	Number of Studies	% of Studies	Studies
Surgical Outcomes			
MLA	32	84.2	Chung 2015 (111), Weck 2013 (112), Laakso 2017 (119), Chiu 2011 (120), Alexandrescu 2009 (124), Crihana 2014 (122), Setacci 2013 (123), Kim 2018 (121), Riaz 2019 (113), Dargis 1999 (127), Hedetoft 2009 (126), Martinez-Gómez 2014 (118), Rerkasem 2008 (114), Williams 2018 (130), Yesil 2009 (125), Cahn 2014 (117), Wang 2016 (129), Jiménez 2017 (128), Crane 1999 (134), Denjalic 2014 (132), Nather 2010 (133), Armstrong 2012 (136), Aydin 2010 (138), Hsu 2015 (135), Meltzer 2002 (139), Witsø 2010 (137), Anichini 2007 (140), Gibbons 1993 (143), Holstein 2000 (142), Nason 2013 (141), Troisi 2016 (144), McGill 2003 (145)
Re-amputation	1	2.63	Chiu 2011 (120)
Revascularisation	3	7.89	Holstein 2000 (142), Armstrong 2012 (136), Armstrong 2014 (109)
Ulcer Recurrence	1	2.63	Dargis 1999 (127)
Ulcer Healing rate	4	10.5	Chung 2015 (111), Weck 2013 (112), Riaz 2019 (113), Setacci 2013 (123)
Medical Outcomes			
Diabetes Control	2	5.26	Lovell 2011 (110), Kim 2018 (121)
Cardiovascular Health Status	2	5.26	Armstrong 2014 (109), Lovell 2011 (110)
Post-operative Complication	1	2.63	Crihana 2014 (122)
Mortality	6	15.9	Armstrong 2014 (109), Weck 2013 (112), Cahn 2014 (117), Matinez-Gomez 2014 (118), Setacci 2013 (123), Chung 2015 (111)
Organisational Outcomes			
Hospitalisation	3	7.89	Hsu 2015 (135), Anichini 2007 (140), McGill 2003 (145)
Length of Hospitalisation	9	2.37	Martinez-Gomez 2014 (118), Laakso 2016 (119), Kim 2018 (121), Crihana 2014 (122), Nather 2010 (133), Crane 1999, Gibbons 1993 (143), McGill 2003 (145), Anichini 2007 (140)
Time to Surgery	1	2.63	Laakso 2016 (119)
Readmission	1	2.63	Nather 2010 (133)
Cost-effectiveness	5	13.2	Rerkasem 2009 (114), Nather 2010 (133), Nason 2013 (141), Gibbon 1993 (143), McGill 2003 (145)
Patient-centred Outcomes			
Quality of Life	3	7.89	Rerkasem 2009 (114), Lincoln 2008 (116), Somayaji 2017 (146)
Psychiatric Health	2	5.26	Simson 2008 (115), Lincoln 2008 (116)
Mobility	1	2.63	Chung 2015 (111)

Table 4: Outcomes reported in studies on MDT-led care of lower limb arterial patients.

3.3.5 Surgical Outcomes

Major Amputation Rates

Thirty-two (84.2%) studies reported MLA rates. Thirty studies (78.9%) reported a decrease in MLA rates with MDT-led care. Narrative synthesis of these studies has previously been reported by two systematic reviews which highlighted the significant impact of MDT-led care on reducing MLA rates (108,147). One of these reviews (108), on twenty-five studies (111–114,117,119–125,127,129,131–135,138,139,141,143,145,148), showed that absolute percentage change in MLA rates secondary to MDT-led care ranged from a 2% increase [OR 1.14; 95% CI 0.59-2.20] to a 51% absolute or 89% relative reduction [OR 0.11; 95% CI 0.05-0.25]. However, due to heterogeneity of data, the authors did not perform a meta-analysis.

Revascularisation Rates

Three (7.89%) studies, one retrospective and two historically controlled, reported the impact of MDT-led care on revascularisation rates. In the retrospective study of 739 PAD and CLTI patients (of whom 38% were diabetic), MDT-led care was associated with a reduction in the need for leg bypass surgery over a three-year follow-up [Hazard ratio (HR) 0.55; 95% CI 0.32 to 0.95] (109).

The other two studies reported an increase in rates of revascularisation (rather than reporting the need for revascularisation) once MDT-led care was introduced. A historically-controlled study of 374 DFD patients reported that rates of vascular reconstructions increased by 44.1% (136). A Danish study on 463 DFD patients reported that the total number of revascularisation procedures increased from 2.6 to 19.2 per 100,000 population after the introduction of MDT-led DFD service (142).

Ulcer Recurrence

One (2.63%) prospective cohort study on 145 DFD patients, reported the association between MDT-led care and rates of ulcer recurrence. Significantly fewer recurrent ulcers were seen in

MDT-led intervention group than in the standard treatment group during the two-year period (30.4% vs. 58.4%, respectively) (127).

Wound Healing

Four (10.5%) studies reported on the impact of MDT-led care on wound healing for a total of 9271 patients.

In one retrospective study of 146 CLTI patients, wound healing time favoured patients being treated by an MDT vs the no-MDT model of care, although findings were not statistically significant (444.5 ± 33.2 days vs 625.2 ± 126.5 days, respectively) (111). A prospective multi-centre study on 1092 DFD patients, however, did highlight a significantly lower level of ulcer severity and higher healing rates at discharge in the MDT group vs the standard care group (28.3% vs 23%, respectively) (112).

These results were similar to those of another retrospective study on 7994 patients, where wound healing rates at discharge were reported to be significantly higher in the MDT group vs the no-MDT group (89% vs 79%, respectively) (113). A historically controlled study on 375 DFD patients also reported that wound healing was achieved in 17.8% in standard care group versus 20.8% in MDT-led care group (123). Due to an uncertainty about timing of discharge and follow-up in these studies, a meta-analysis was not performed.

3.3.6 Medical Outcomes

Cardiovascular Health

Three (7.89%) studies reported cardiovascular health outcomes after MDT-led secondary prevention. One study prospectively analysed the combined impact of secondary prevention (cardiovascular assessment, medical optimisation, smoking cessation, and dietary assessment) delivered by an MDT. Over a median follow-up of 528 days, secondary prevention was significantly associated with lower resting blood pressures and serum cholesterol compared to patients not receiving MDT-led secondary prevention (110) . The second study retrospectively analysed the impact of adherence to MDT-led secondary

prevention on major adverse cardiac events (MACE) and mortality. Findings showed a significant association between adherence and lower MACE [HR 0.64; 95% CI 0.45 to 0.89], and mortality rates [HR 0.56; 95% CI 0.38 to 0.82] (109). The third historically controlled study on 338 DFD patients reported that glycaemic control had improved after the introduction of an MDT-led service (mean glycosylated haemoglobin of 9.48% vs. 8.50%, respectively) (121).

Post-operative Complications

Two (5.56%) historically controlled studies on DFD patients reported the association between MDT-led care and rate of post-revascularisation complications. The first, on 939 patients, reported a significant reduction in overall complication rate from 19.67 to 7.34% after the introduction of an MDT service (133). The second study showed a similar trend (122).

30-day Mortality

Three (7.89%) studies (112,117,148) reported 30-day mortality rates. All three studies evaluated the impact of MDT-led care on DFD patients. Patient characteristics and nature of interventions were similar between the groups, permitting meta-analysis of the data. The pooled 30-day mortality rate in 1223 patients in the MDT-led care group was significantly lower compared to that in 918 patients in the standard care group [OR 0.38; 95% CI 0.24; 0.59] (**Figure 8**).

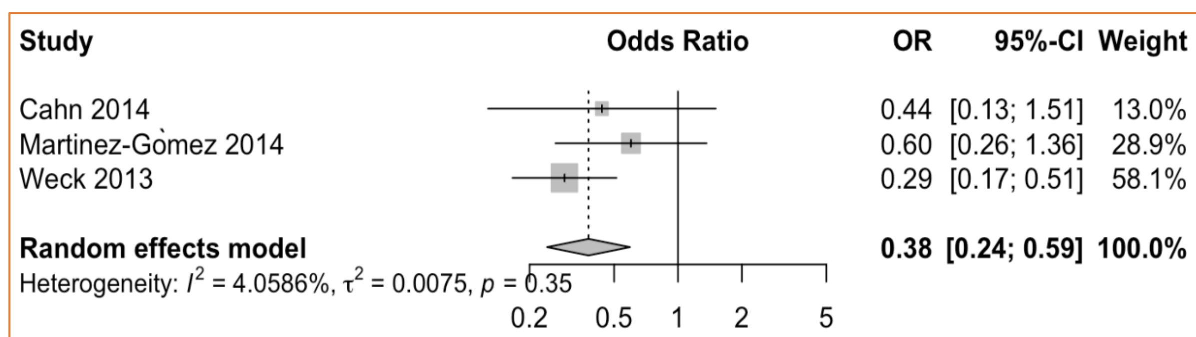

Figure 8: Random effects forest plot for 30-day mortality in DFD patients managed with MDT-led care vs standard care.

3.3.7 Organisational Outcomes

Cost-effectiveness

Five (13.2%) studies reported the cost-effectiveness associated with the introduction of an MDT-led service. Four (114,133,143,145) reported reductions in the hospitalisation cost per patient and readmission rate after the formation of an MDT but findings were not statistically significant. An Australian study (145) showed that preventing 168 DFD-related admissions with an MDT-led programme (with an average stay of 18 days at $450 per day), a cost saving of approximately AUD$1.3 million was achieved. In an Irish study on cost-effectiveness of outpatient clinic care on 221 DFD patients, there was an overall saving of €114,063 per year associated with the introduction of the MDT-led service (141).

Time to surgery

One (2.63%) historically controlled study (119) on 272 DFD patients with an active infection reported the impact of MDT-led care on time-to-surgery. The median time from admission to surgical intervention decreased, with statistical significance, from five days to two days after the initiation of an MDT-led service.

Length of Hospitalisation

Seven (18.4%) studies reported on the impact of MDT-led care on length of hospitalisation. Studies varied in design and follow-up and a meta-analysis was not performed. However, all reported a statically significant reduction in length of hospitalisation ranging from two to twenty days of reduction (119,122,133,134,140,143,145).

Incidence of Hospitalisation

Three (7.89%) studies reported that MDT-led care was associated with reduced incidence of hospitalisation. A historically controlled study on 240 DFD patients who had undergone an MLA showed that the incidence of hospitalisation fell from 2.83% in 2004 to 1.51% in 2013 (135). A similar finding was seen in a historically controlled study of 205 DFD patients

following the implementation of an MDT-led service (140). In another retrospective study of 90 DFD patients, outpatient visits to different specialists fell after the introduction of an MDT-led service. The fall was from a median of three visits [IQR 1–8 visits] in the first six months of the programme to one visit [IQR 1–3 visits] in the subsequent period (145).

3.3.8 Patient-centred Outcomes

Quality of Life

Three (3.89%) studies reported QoL outcomes. The first retrospectively analysed the impact of MDT-led care on the quality of life for 73 DFD patients. QoL was measured using the 36-item Short Form Survey (SF-36). Over a two-year follow-up period, patients who received MDT-led care had significantly better SF-36 physical, mental and total scores than those who received standard care (114).

The second study focussed on patient education with a view to analyse the impact of education protocols on self-foot-care behaviour and wound healing. This was a randomised control study of 172 subjects, and it showed that patients who received MDT-led targeted education adhered to significantly better self-care behaviour at one year follow-up compared to those who received standard care. Patient education, however, was not significantly associated with a lower ulcer incidence or improvement in mood and QoL (116).

The third study analysed the impact of MDT-led care on precision of diagnostics as well as on QoL in 306 DFD patients with wounds of more than six weeks duration. Although 36.7% reported an improvement in their QoL, no standardised comparisons were performed between the MDT-led care and standard care groups (146).

Anxiety and Depression

One (2.63%) study, a randomised-control trial, analysed the impact of supportive psychotherapy as part of the MDT-led care of 30 diabetic foot patients (115). The therapy was

run by an interdepartmental psychosomatic liaison service for the duration of inpatient admission (consisting of an average of five 30-minute sessions and no use of antidepressants).

Outcomes such as anxiety and depression were assessed using scoring systems at the start and end of therapy; Hospital Anxiety and Depression Scale (HADS) and Problem Areas in Diabetes Scale (PAID). In the MDT-led care group, depression, anxiety and diabetes-related problems scores decreased. In contrast, in the standard care group, depression did not improve, and anxiety symptoms increased during in-patient treatment.

Functional Outcome

One (2.63%) study, focussed on the impact of MDT-led care on independent ambulation, as a secondary outcome (111).

In this study, 85 patients requiring wound care were followed up for a median of 539 days, and of these, 82% were diabetic. No definition of independent ambulation was provided by the authors. Findings revealed that significantly more patients ambulated independently in the MDT-led care group vs the standard care group (73% vs 47%, respectively). However, the MDT-led care group also had a significantly higher median ABPI compared with the standard care group (0.65 vs 0.41, respectively; $p=0.03$). These findings suggest that selection bias likely factored in the superior results with MDT-led care, i.e., patients with higher likelihood of ambulation and less severe peripheral arterial disease may have been selected in MDT-led rehabilitation care. There were no studies focusing on mobility after MLA.

3.4 Discussion

This review was performed to confirm if functional outcome is a primary consideration for clinicians in current practice during decision-making for the management of threatened and unsalvageable limbs. The review illustrates that a disproportionately small number of studies focussed on improving medical and patient-centred outcomes, and only one study out of the thirty-eight reported a parameter of functional outcome ("ambulation"). Moreover, this study failed to provide a definition for this parameter. It is therefore evident that functional outcome is not a priority for the clinician within MDT-led care.

A disconnect between the disciplines of surgery and rehabilitation exists, as studies that do report functional outcomes of amputees are reported by the latter discipline. The focus of current literature is heavily biased towards improving limb salvage rates, and although this is a crucial outcome measure, an opportunity to simultaneously address other domains of patient health are being overlooked. The paucity and heterogeneity of instruments used to measure functional outcomes make it difficult to compare this in revascularisation- or MLA-based studies. Through highlighting studies that have addressed some patient-centred outcomes, this systematic review provides an insight into the future potential of MDT-led care.

Findings from this review also support the inferences of a previous systematic review: there remains a disparity in how gold-standard care is delivered by MDTs (108). In complex interventions such as MDT-led care, a lack of consistency in the way care is provided to patients leads to avoidable discrepancies in outcomes and introduces uncertainty of their overall success. Reproducibility of results may be further hampered by the lack of structured and standardised protocols for multidisciplinary care, as encountered in many of the studies included this chapter.

A possible approach to the enhancement of current frameworks of care would be to use the Systems Engineering Initiative for Patient Safety (SEIPS) model. SEIPS provides a framework for understanding the structures, processes and outcomes in health care and their relationships (149). Based on the SEIPS model, to achieve better holistic care, MDT

frameworks would benefit from homogeneity of team structures, well-defined roles (especially nursing and allied health professionals), timely and coordinated task performance, and well-defined treatment algorithms.

Based on the findings of this systematic review, recommendations can be made on improving current MDT practices for the provision of a more holistic framework of care (Figure 9). MDTs should develop holistic interventions targeting all outcomes and provide more clarity in future research about frameworks of care. In addition to improving surgical outcomes such as wound healing, limb salvage and survival (a), this study recommends that an equal weight of focus should be provided for medical and patient-centred outcomes, including medical optimisation (b), mobility and frailty (c), psychosocial health (d) and quality of life (e). Future researchers should seek to use high-quality assessment, risk-stratification, and decision-making instruments to achieve the end goals.

Figure 9: A schematic of the holistic model of MDT care in lower limb arterial disease.

Chapter 4.1: The concerns of patients with threatened and unsalvageable limbs

4.1.1 Introduction

Uncertainty in predicting outcomes and the inability to address patients' concerns complicate the clinical decision-making in the management of limb-threatening diabetic foot disease. This problem is particularly relevant for amputation surgery, and the incidence of major amputation can be as high as 600 per 10^5 patients a year with diabetes (150). The ability to walk successfully with a prosthesis has been shown to have the most substantial positive impact on the quality of life after limb loss in peripheral arterial disease (34). However, DFD patient cohorts are heterogenous in demographics, comorbidities and in the severity of foot disease (151,152). Such factors contribute towards the high prevalence of psychosocial problems in DFD that need to be better addressed in amputation surgery (153).

Emerging evidence highlights the detrimental impact of DFD on the psychological and social wellbeing of patients. Over a third of these patients suffer from depression, and the dominant source of emotional distress appears to be the fear of limb loss rather than death itself (154,155). Conversely, depression is associated with an increased risk of deteriorating foot problems through non-compliance and non-attendance, limb loss and mortality, suggesting that such a feedback cycle contributes towards the overall deterioration of health (154–156). Caregivers and family members also experience a negative impact on their quality of life, highlighting the heavy burden of DFD on social networks (157,158).

These findings necessitate a focus on understanding the impact of psychosocial problems on health-related behaviours of patients and how their concerns affect their decisions about their health.

A clear deficiency in addressing functional outcomes exists among clinical interventions, as summarised in the previous experimental chapter. To establish if this was consistent with the patients' viewpoint, this chapter aimed to characterise the psychosocial problems and concerns of patients facing interventions for their threatened or unsalvageable limb in an MDT setting of care.

4.1.2 Methods

The methods of this experimental chapter are described in full in Chapter 2. In brief, a retrospective cross-sectional study with a mixed-methods approach, involving both quantitative and qualitative analysis, was performed. The study was carried out from June 2019 to January 2020 on all in-patient DFD patients reviewed by a dedicated psychologist, as part of the MDT in a tertiary centre for vascular surgery.

4.1.3 Results

4.1.3.1 Patient Characteristics

Patient characteristics are described in **Table 5**. There were 76 consecutive patients with severe diabetic foot disease being considered for, or having just undergone, MLA who underwent psychologist evaluation. The median age was 65.7 [55.7, 72.6] years, and 21 (27.6%) were female. Much of the cohort (56, 73.7%) were of White-British ethnicity, with other ethnic groups comprised of Asian-British, Black-British, Eastern European, Asian, and African backgrounds. Seven patients (9.21%) required a formal translator service. The usual place of residence was either a house (56, 73.7%), or flat (17, 22.4%), and a small number (2, 2.63%) were from a nursing home. A large proportion (29, 38.2%) of patients lived alone, and ten (13.2%) had no documented next-of-kin.

Amputation status varied; 29 (38.2%) had no history of amputation, 25 (32.9%) had a minor amputation, 13 (17.1%) were in the pre-MLA and nine (11.8%) were in the post-MLA stage. Cardiovascular comorbidities were prevalent such as hypertension (40, 52.6%), hypercholesterolaemia (21, 27.6%), renal failure (30, 39.5%), ischaemic heart disease (17, 22.4%), congestive cardiac failure (11, 14.5%) and atrial fibrillation (8, 10.5%). A history of prior revascularisation was also common (34, 44.7%).

Comparison by gender showed no significant differences in demographics and living conditions. However, a greater number (7/21, 33.3%) of female patients were in the pre-MLA stage compared to males (6/55, 10.9%), p=0.020.

Compared to female, male patients had higher rates of cardiovascular problems such as hyperlipidaemia [2/21 (9.52%) vs 19/55 (34.5%), p=0.046], ischaemic heart disease [1/21 (4.76%) vs 16/55 (29.1%), p=0.03], congestive cardiac failure [0/21 (0%) vs 11/55 (22.0%), p=0.029] and previous revascularisation [6/21 (28.6%) vs 28/55 (50.9%), p=0.121] and lower rates of chronic pain [4/21 (19.0%) vs 5/55 (9.1%), p=0.251). There were no significant differences in comorbidities when compared by amputation status (**Supplementary Table 2**).

		Total (76)	%	Female (21)	%	Male (55)	%	p-value
Age		65.7 [55.7-72.6]		62.5 [52.3, 82.4]		65.8 [56.6, 71.8]		0.744
Race	White-British	56	73.7	14	66.7	42	76.4	0.398
	Asian-British	4	5.26	1	4.76	3	5.45	1.000
	Black-British	3	3.95	2	9.52	1	1.82	0.183
	Asian non-British	2	2.63	1	4.76	1	1.82	0.479
	Afro-Caribbean	6	7.89	2	14.3	3	5.45	0.338
	Eastern-European	5	6.58	0	0	5	9.09	0.314
Need for Translator		7	9.21	2	9.52	5	9.09	1.000
Residence Type	House	56	73.7	15	71.4	41	74.5	0.778
	Flat	17	22.4	6	28.6	11	20.0	0.353
	Nursing Home	2	2.63	0	0	2	3.64	1.000
	Visiting from Abroad	1	1.32	0	0	1	1.82	1.000
Lives Alone		29	38.2	8	38.1	21	38.2	1.000
No Next of Kin		10	13.2	2	9.52	8	14.5	0.518
Amputation Status	None	29	38.2	8	38.1	21	38.2	0.994
	Minor	25	32.9	4	19.0	21	38.2	0.112
	Pre-MLA	13	17.1	7	33.3	6	10.9	**0.020**
	Post-MLA	9	11.8	2	9.52	7	12.7	0.699
				Comorbidities				
Hypertension		40	52.6	9	42.9	31	56.4	0.316
Hyperlipidaemia		21	27.6	2	9.52	19	34.5	**0.046**
Smoker		7	9.21	1	4.76	6	10.9	0.666
Previous Revascularisation		34	44.7	6	28.6	28	50.9	0.121
Ischaemic Heart Disease		17	22.4	1	4.76	16	29.1	**0.030**
Congestive Cardiac Failure		11	14.5	0	0	11	22.0	**0.029**
Atrial Fibrillation		8	10.5	1	4.76	7	12.7	0.432
Chronic Obstructive Pulmonary Disease		8	10.5	6	10.9	2	3.64	1.000
Renal Failure		30	39.5	6	28.6	24	43.6	0.230
Cerebrovascular Disease		4	5.26	1	4.76	3	5.45	1.000
Chronic Pain		9	11.8	4	19.0	5	9.09	0.251

Table 5: Patient characteristics by gender among the DFD patients receiving MDT-led psychology input.

4.1.3.2 Psychiatric History

Overall, 25 (32.9%) had a pre-existing psychiatric diagnosis (**Table 6**). Of these, sixteen (21.1%) were depression disorders, four (5.26%) were anxiety disorders, one (1.32%) was psychosis, one (1.32%) was dementia and five (6.58%) were substance abuse. Patients with a positive history of depression, psychiatric medication use, or anxiety were significantly younger compared to those without these pre-existing diagnoses. The mean difference in age was 12.6 years for depression (p=0.001), 8.15 years for psychiatric medication use (p=0.022) and 21.7 years for anxiety (p=0.006).

Psychiatric History	Yes (25)	No (51)	Mean Difference (years)	p-value
Any	56.1 [49.4, 66.6]	70.0 [59.2, 75.2]	9.65	**0.004**
Depression	53.9 [49.1, 64.5]	67.6 [58.6, 74.4]	12.6	**0.001**
Psychiatric Medication	57.4 [50.5, 64.5]	67.6 [57.1, 73.8]	8.15	**0.022**
Anxiety	45.5 [37.1, 51.2]	66.1 [56.6, 73.0]	21.7	**0.006**
Psychosis	53.7 [53.7, 53.7]	65.8 [55.9, 72.7]	12.0	0.338
Substance Abuse	66.2 [49.6, 72.8]	65.7 [55.9, 72.4]	3.51	0.753
Dementia	75.5 [76.5. 76.5]	65.7 [55.6, 72.4]	10.7	0.254

Table 6: Median [IQR] age and mean difference by presence of psychiatric diagnosis of DFD patients receiving MDT-led psychology input.

Female patients had a higher overall rate of depression [8/21 (38.1%) vs 8/55 (14.5%), p=0.024], anxiety [4/21 (19.0%) vs 0/55 (0%), p<0.001] and psychiatric medication use [9/21 (42.9%) vs 9/55 (16.4%), p=0.033) (**Table 7**).

Psychiatric History	Female (21)	%	Male (55)	%	Odds ratio [95% CI]	p-value
Any	11	52.4	14	25.5	3.22 [1.13, 9.20]	**0.025**
Depression	8	38.1	8	14.5	3.62 [1.14, 11.5]	**0.024**
Anxiety disorder	4	19.0	0	0	28.5 [1.46, 557]	**<0.001**
Psychosis	1	4.76	0	0	8.12 [0.318, 207]	0.103
Substance Abuse	1	4.76	4	7.27	0.64 [0.067, 6.06]	0.693
Dementia	1	4.76	0	0	8.12 [0.318, 207]	0.103
Psychiatric Medication	9	42.9	9	16.4	3.73 [1.19, 11.6]	**0.033**

Table 7: Prevalence of psychiatric problems by gender of DFD patients receiving MDT-led psychology input.

Overall rates of psychiatric diagnoses were similar between the no amputation (10/29, 34.5%), minor amputation (9/25, 36.0%), pre-MLA (3/13, 21.4%) and post-MLA groups (3/9. 33.3%), p=0.823 (**Table 8**). Although not statistically significant, a history of depression was most common in the minor amputation group, whereas anxiety and substance abuse were most common in the post-MLA group.

Psychiatric History	None (29)	%	Minor (25)	%	Pre-MLA (13)	%	Post-MLA (9)	%	p-value
Any	10	34.5	9	36.0	3	21.4	3	33.3	0.823
Depression	4	13.8	9	36.0	2	14.3	1	11.1	0.211
Anxiety	2	6.90	0	0	1	7.69	1	11.1	0.304
Psychosis	1	3.45	0	0	0	0	0	0	1.000
Substance Abuse	2	6.90	0	0	1	7.79	2	2.22	0.080
Dementia	1	3.45	0	0	0	0	0	0	1.000
Psychiatric Medication	7	24.1	9	36.0	2	15.4	2	2.22	0.538

Table 8: Prevalence of psychiatric history by amputation status of DFD patients receiving MDT-led psychology input.

4.1.3.3 Patient Concerns

Patient concerns expressed in psychology sessions are illustrated in **Figure 10**, a graphical representation of key terms in which the font size correlates with their frequency of presentation. Terms with the largest fonts i.e., expressed most by patients, included "mood", "isolation", "work", "family", "anxiety", "cognition", "bereavement", "mobility", and "support".

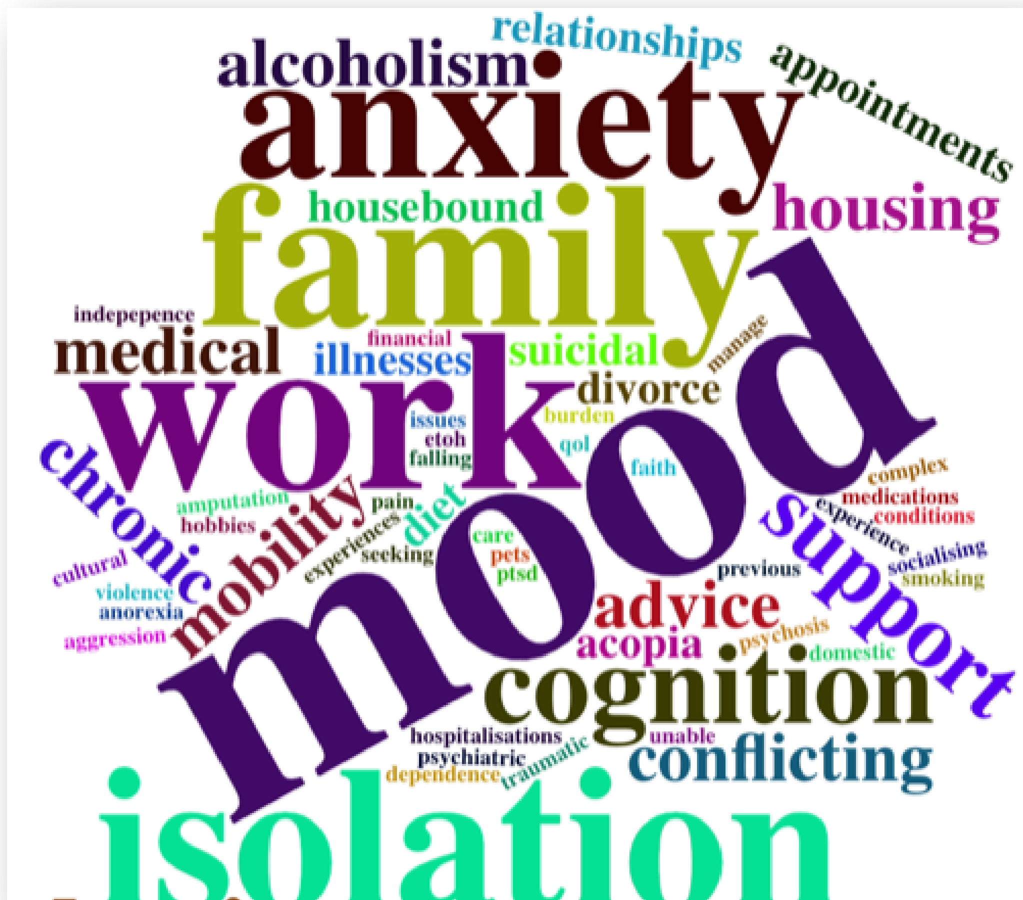

Figure 10: Graphical representation of the concerns of DFD patients receiving MDT-led psychology input.

Through thematic analysis, these concerns were categorised into four levels of influence within a socio-ecological framework: personal, interpersonal, economic, and healthcare problems (Figure 11).

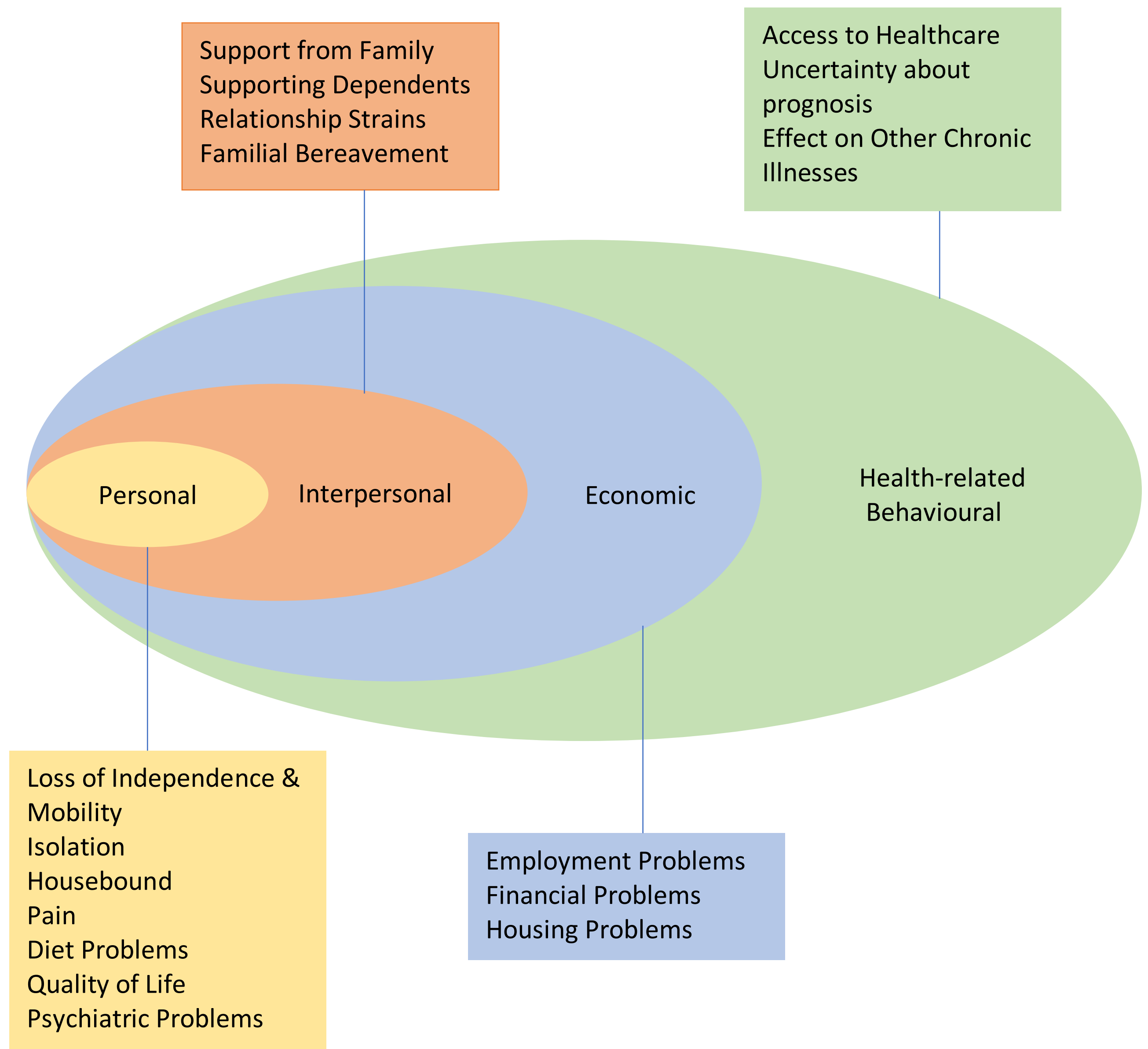

Figure 11: Socio-ecological framework for concerns and health-related behaviours of DFD patients receiving MDT-led psychology input.

A total of 167 concerns were identified, of which 91 were associated with personal, 40 with interpersonal, 25 with economic and 12 with healthcare level problems (broken down according to amputation status in **Table 9**. As described below, it was evident that chief concerns at all levels of influence were related to poor functional outcomes.

At the personal level, concerns centred heavily around the loss of mobility, independence, and becoming housebound, and isolation (39/71, 54.9%). These were particularly common in the pre-MLA group (14/23, 60.1%). Another common concern was the impact DFD was having on their psychological state, with 25/91 (27.5%) of problems centred around the detrimental effect on mood and anxiety, and 15/91 (16.5%) around increased aggression, suicidal thoughts, impaired cognition, associations with traumatic experiences, and drug or alcohol abuse.

At the interpersonal level, commonly expressed concerns were becoming dependent on family members or carers (17/40, 42.5%), inability to support dependents (11/40, 27.5%), and strains in household and social relationships (7/40, 17.5%). Anxiety about feelings of loneliness was present in both those living with family members and those living alone. Some patients, with young children, were concerned about the level of support they were providing for their families. Other patients attributed their spousal problems directly to their DFD, with one patient fearing marital breakdown following amputation. Three patients indicated that they were against a major amputation, citing religious and cultural perceptions of amputations.

Inability to work (11/25, 44.0%), financial strains (11/25, 44.0%), and housing problems (3/25, 12%) were prevalent concerns at the economic level. Patients experienced difficulties at the workplace, such as an inability to perform specific tasks, long periods of sick leave and job loss, which they attributed to their foot problems. Inability to access healthcare (7/12, 58.3%), and the negative impact of persistent foot problems on the management of other chronic illnesses (2/12, 16.7%), were common concerns at the healthcare level.

Theme and Category of concerns		None (91)	Minor (40)	Pre-MLA (25)	Post-MLA (12)	Total (167)
Personal Level		**17**	**31**	**23**	**20**	**91**
Loss of Independent Mobility		3	6	8	3	20
Isolation		4	2	3	5	14
Housebound		0	1	3	1	5
Pain		0	1	1	1	3
Diet Problems		0	1	0	0	1
Quality of Life		0	1	0	3	4
Psychiatric Problems	Low mood and Anxiety	8	10	3	4	25
	Suicidal thoughts	0	1	1	2	4
	Increased aggression	0	1	0	0	1
	Traumatic experiences	1	1	0	0	2
	Impaired cognition	1	3	0	0	4
	Drug and alcohol abuse	0	2	2	0	4
Cultural and Faith Problems		0	1	2	1	4
Interpersonal Level		**17**	**7**	**7**	**9**	**40**
Support from Family		5	3	3	6	17
Supporting Dependents		7	2	0	2	11
Relationship Strains		3	1	2	1	7
Familial Bereavement		2	1	2	0	5
Economic Level		**13**	**6**	**4**	**2**	**25**
Employment Problems		5	2	3	1	11
Financial		7	3	0	1	11
Housing Problems		1	1	1	0	3
Healthcare Level		**4**	**4**	**2**	**2**	**12**
Access to Healthcare		3	1	2	1	7
Uncertainty about prognosis		1	1	0	1	3
Effect on Other Chronic Illnesses		0	2	0	0	2

Table 9: Breakdown of concerns by amputation status in DFD patients receiving MDT-led psychology input.

4.1.4 Discussion

This study employed a mixed methods approach to understand more about the psychosocial problems and concerns of patients with threatened or unsalvageable limbs. Its findings confirmed that, for patients, functional outcome is a primary consideration in their decision-making on the management of their limb.

Poor function affected the lives of patients at all levels of influence as demonstrated by the socio-ecological model. Together with the findings of Chapter 3, this study disproves the first null hypothesis of this thesis: that there is no inconsistency between clinicians and patients in the prioritisation of functional outcome for their decision-making when facing MLA.

The results demonstrated considerably higher levels of depression among DFD patients (21.1%) when compared to its global prevalence (5.5%) (159). Sociodemographic variables were also identified that may have significant consequences on QoL, health-related behaviours and consequently, overall health status.

In this cohort, there was a high prevalence of psychiatric problems among female (52.4%) compared to male patients (25.5%), a finding supported in prior literature (160). Higher proportion of female patients were in the pre-MLA stage compared to males, but the prevalence of psychiatric problems and concerns were similar by amputation status. This signifies there is likely to be gender-related differences. Roumia et al. 2017 showed that the female sex was independently associated with lower physical functioning, social problems, and quality of life scores in lower limb arterial patients. In their study, women were more often living alone, suffered from clinical depression and avoided seeking care due to cost compared to men (161). Additionally, physical function, general health, and walking impairment has been shown to be poorer for female patients when compared to male patients with PAD (162).

Other demographic differences may also contribute to the burden of psychosocial problems. In a systematic review, on the global prevalence of depression in diabetic patients, rates were lower in Europe (24%) and Africa (27%), but higher in Australia (29%) and Asia (32%).

Depression was more common in subjects younger than 65 compared with over-65s (31% vs. 21%) (163), as seen in this experimental chapter.

A large proportion (38.2%) of patients lived alone, and social isolation was a common concern. Although our study was not designed to quantify any negative impact of social isolation on dysvascular patients, previous studies have shown that amputees who were more socially isolated had inferior clinical rehabilitation outcomes (164) and higher mortality rates (165). Diabetic patients may be at a particularly higher risk of the negative outcomes arising from social isolation with poorer functionality and general health compared with patients without diabetes (166).

Predictably, our study showed that concerns about independent mobility were more common in those who had experienced a minor amputation or were facing a major amputation. Pell et al. 1993 showed that amputees experience significantly more problems with mobility, social isolation, lethargy, pain, sleep, and emotional disturbance than non-amputees. However, their study also showed that mobility, and not amputation status, was the most important predictor of quality of life (32).

These findings support an inference from this chapter; clinicians should perform an early assessment of mobility and rehabilitation potential irrespective of the patients' amputation status. However, due to the urgent nature of DFD, timely assessment of rehabilitation potential is not always undertaken ahead of amputation despite their advocation in national guidelines (17).

This study was pragmatic in design and attempted to capture a broad spectrum of patients and their concerns. However, the small comparative groups in this study limit the strength of the associations identified. Moreover, patients who opted out of meeting the social psychologist were not included and, therefore, remain an unstudied subgroup containing potentially important information, introducing selection bias.

Nonetheless, a more detailed understanding of the factors identified by this study, particularly gender, age, ethnicity, cultural beliefs, psychology, and amputation status may

improve outcomes in the holistic management of DFD and PAD. Standardised delivery of social and psychological therapy may have a positive impact on health-related behaviours of all patients, irrespective of previous psychological history. Finally, validated tools for predicting independent mobility, coupled with a better understanding of psychosocial and demographic differences, will aid clinical decision-making, and help address principal patient concerns.

Chapter 4.2: Systematic review on the burden of social isolation in lower limb arterial disease: a supplementary study

4.2.1 Introduction

The challenge of improving outcomes in MLA is confounded by the influence of demographic, socioeconomic, and psychological factors, as illustrated in Chapter 4.1. There is emerging evidence identifying these factors as significant predictors of clinical and patient-centred outcomes. For example, being female is associated with higher levels of depression, poorer mobility and quality of life in PAD (167). Living in deprived areas is associated with a higher prevalence of PAD (168–170). A qualitative systematic review on patient experience in PAD highlighted social isolation as an additional determinant of patient-centred outcomes (171).

A key concern of patients is the risk of social isolation that limb loss and poor mobility may bring, as identified in Chapter 4.1.

Social isolation (“loneliness” or “social dysfunction”) is defined as the absence of social interactions, contacts, and fulfilling relationships with family and friends on an individual level, and with "society at large" on a broader level (172). Its prevalence ranges between 10-43% in community-dwelling older adults and is increasing (33). The Office of National Statistics (ONS) predicts that by the year 2041, 26% of the total population will be aged 65 or over, with the fastest growth in the over-85 group (173). Evidence supports the correlation between social isolation and poor outcomes such as all-cause mortality, dementia, hospital readmission, and risk of falls (174–179).

Its impact in PAD and DFD, an increasingly frail and ageing patient group, requires a comprehensive evaluation.

This supplementary experimental chapter was performed to explore the notion that social isolation secondary to poor functional outcomes in lower limb arterial disease is a significant problem. A systematic review was performed to ascertain the prevalence and severity of social isolation in PAD and DF patients and to report its impact on clinical and other patient-centred outcomes.

4.2.2 Methods

The methodology of this experimental chapter is described in full in Chapter 2. In brief, a mixed methods systematic review of qualitative and quantitative studies was performed in accordance with PRISMA guidelines.

4.2.3 Results

The PRISMA flow for this review is shown in **Figure 12**. The initial search yielded eighty-six articles, of which twelve were duplicates, and fifty-three studies were excluded after screening article titles and abstracts. A further six papers were excluded following full-text and eligibility assessment. Fifteen studies were included in the final syntheses: eight quantitative and seven qualitative.

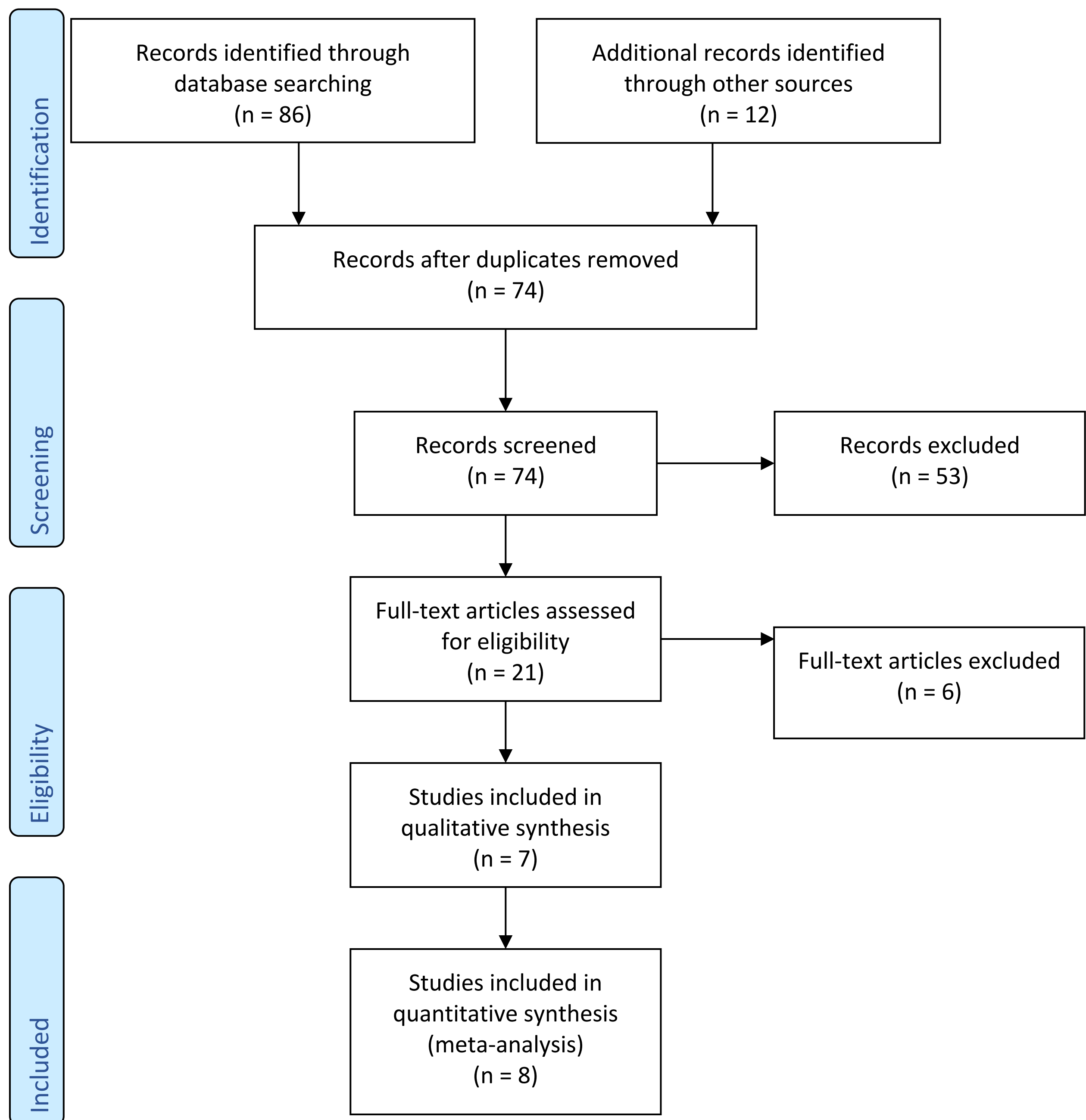

Figure 12: PRISMA flow-chart for the systematic review in Chapter 4.2.

4.2.3.1 Study Characteristics

The characteristics of the quantitative studies included in the review are shown in **Table 10**. Four of the eight studies were prospective and four cross-sectional in design. The number of patients varied from 92 to 12965. There were a mixture of PAD and DFD patients in most studies. Primary outcomes of interest varied with three studies reporting QoL, two reporting walking impairment, three reporting psychosocial problems (including social isolation) and one reporting mortality. Four studies were carried out in the USA, three in the UK and one in Turkey.

The characteristics of the qualitative studies included in the review are shown in **Table 11**. Study designs included qualitative descriptive, cross-sectional, grounded-theory, inductive, hermeneutic, and phenomenological. Method of sampling varied and included semi-purposive and purposive methods with some studies not reporting sampling methods at all. The number of patients varied from 8 to 80. Most studies had PAD patients with two reporting on DFD patients. Studies were based in developed countries: three in Sweden, two in UK, one in USA and one in Australia.

A total of 165 patients were included from the seven qualitative studies, with 98 male and 67 female patients and ages ranged between 44 and 92. Aetiology, disease severity and time point of treatments varied among studies; the majority were intermittent claudicants (78/165) and the rest were “critical limb ischaemia” (20/165), PAD with unspecified severity (38/165) or DFD patients (29/165). The number of pre-existing amputations in patients was not reported in all studies. In three studies, intervention type (medical vs surgical vs combination) was not reported (180–182). The phenomena of interest in these studies were mainly patients’ experiences of living with PAD or DFD, concerns about their illnesses, QoL and perceived levels of social support.

Study, date, country	Study design	Participants, age, gender	Outcome of interest	Main finding
Collins 2006, USA (162)	Cross-sectional study on walking impairment and QoL in PAD.	N=403 67 PAD patients 195 males, Age: 63-64	QoL and walking impairment	Scores for physical function, walking ability and general health were lower for women versus men with PAD.
Roumia 2017, USA-Dutch (161)	Longitudinal prospective study on gender differences in physical activity levels in claudicants.	N=1274 All PAD patients 793 males, Mean Age: 67	Quality of care and health status outcomes in patients with PAD	As compared with men, women were more often living alone, had depression, and avoided care due to cost.
Kusaslan 2018, Turkey (183)	Cross-sectional study on loneliness in diabetes patients.	N=325 All DM patients < 20 had foot disease 141 males, Age: 18-85	Loneliness	Levels of loneliness was greater in patients diagnosed with complications of diabetes including DFD.
Oka 2005, USA (184)	Prospective, descriptive study on walking distance and QoL in DM and PAD compared with PAD alone.	N=92 All PAD patients 52 males, Age: 65-83	Walking distance and QoL	Diabetic patients with PAD reported impaired role function, general health, and social function compared to PAD-only group.
Pell 1993, UK (32)	Cross-sectional study on QoL between amputees and controls.	N=245 130 Amputees 115 Controls 151 males, Median Age: 73	QoL	Amputees reported significantly more problems with mobility, social isolation, lethargy, pain, sleep, and emotional disturbance than controls.
Thompson 1983, UK (185)	Cross-sectional study on social and psychological problems in amputees.	N=134 134 New and established MLA patients 100 males, Age: >65	Social and psychological problems	Social isolation present in 47%-59% of new amputees and 12% to 73% of established amputees. Non-isolation was conducive to good rehabilitation outcomes.
Wattanakit 2005, USA (186)	Prospective cohort study on association of psychosocial variables with incidence of PAD.	N=12965 6512 males Age: 45–64	Incidence of PAD	Compared with the highest level of social support, individuals with low levels had increased risk of incident PAD.
Singh 2016, UK (165)	Prospective study on population or treatment features associated with mortality post amputation.	N=105, 70 males Age: 46-78	Mortality	Social isolation was more prevalent in patients who had died than who were alive at end of follow-up.

Table 10: Characteristics of quantitative papers on social isolation in PAD and DFD.

Study, date, country	Study design, sampling, data collection and analysis methods	Participants, age, gender	Phenomenon of interest	Setting	Geo-graphical cultural	Key outcomes, findings, authors conclusion
Galeet 2017, UK (187)	Qualitative descriptive; Semi-purposive sampling; Semi-structured face-to-face interview; Framework analysis	N=19, 13 males, Age: 44–79 Disease duration: ≥2y=53%; <2y=47%	Experiences of and beliefs about illness and walking with claudication	Patient home/ University facility	UK	Psychological impairment Physical limitations Employment
Hallin 2002, Sweden (188)	Mixed study (cross-sectional study); Sampling: Not clear; Semi-structured interview; Content analysis	N=80, 47 males, Age:56-88 20 Claudicants; 20 Critical Limb Ischaemia patients	Patients' concerns and subjective effect of PAD on QoL and life satisfaction	Clinic facility, Patient home	Swedish	Psychological impairment Burden to others Medical care Family
Egberg 2012, Sweden (180)	Qualitative descriptive design, Purposive sampling; One-on-One interview; Thematic analysis;	N=15 PAD patients 8 males Age: 64-81	Patients' experiences of living with PAD/IC	Patient home, hospital	Swedish	Housebound Psychological impairment
Treat-Jacobson 2002, USA (181)	Grounded theory, Purposive sampling; Open-ended interview; Thematic analysis	N=38 PAD patients 24 males Age: 44–83	Effect of PAD on health related QoL from the patients' perspective	Facility outside hospital	USA	Psychological Burden to others Employment limitations Parenting
Wann-Hassan 2005, Sweden (182)	Inductive qualitative design; Purposive sampling; One-on-One Semi-structured interview; Content analysis	N=24 Claudicants 12 males Age: 60-92	Patients' experiences of living with PAD, and the influence on activities of daily living	Patient home	Swedish	Psychological impairment Housebound
Palaya 2018, Australia (189)	Hermeneutic phenomenology design; Purposive sampling; Semi-structured interview; Hybrid thematic analysis	N=8 DF patients 4 males Age:48-74 Amputations: 4 minor, 1 major	Perception of social support in individuals living with a diabetic foot	Public podiatry service	Tasmania Australia	Psychological impairment Housebound Medical care Employment
Kinmond 2002, UK (190)	Phenomenological design; Sampling: Unclear Semi-structured conversational interviews; Interpretative phenomenological analysis	N=21 DF patients 15 males Mean Age: 58.4	QoL in patients living with diabetic foot ulceration	DFD clinic	UK	Psychological impairment Burden to others Role and employment limitations

Table 11: Characteristics of qualitative studies on social isolation in PAD and DFD.

4.2.3.2 Questionnaires Assessing Social Isolation

In total, eleven tools for assessing social isolation were found in studies, as described in **Table 12**.

Scoring tools that include assessment of social isolation	Definition
Physical Activity for the Elderly (PASE)	Assessment of duration, frequency, exertion level, and amount of physical activity undertaken over seven days by individuals 65 years and older (191).
San Diego Claudication Questionnaire (SDCQ)	Assessment of lower extremity ischemic pain on effort, an indicator of (atherosclerotic) PAD (192).
Walking Impairment Questionnaire	A subjective measure of patient-reported walking performance developed for PAD (193).
36 Item Short-Form Health Survey (SF-36)	A 36-item tool measuring eight scales: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health (194)
Physical Activity Questionnaire (PAQ)	Self-reported tool for measurement of physical activity (195).
University of California Los Angeles Loneliness Scale (UCLA LS)	A 20-item scale designed to measure one's subjective feelings of social isolation (196).
Nottingham Health Profile Questionnaire	A general patient-reported outcome measure which seeks to measure subjective health status (197).
Townsend's Social Isolation (TSI) Scale	Measures social isolation by measuring frequency, size, and closeness of contacts of the respondent's social network by assessing the perceived level of support they get from friends and families (198).
Spielberger Anger Score	A 20-item scale assessing anger expression (199).
Maastricht Questionnaire	A 21-item questionnaire assessing the degree of fatigue and depressive symptoms secondary to chronic illness (200).
Multidimensional Scale of Perceived Social Support Scale (MS PSS)	A 12-item questionnaire that measures the perceived adequacy of the available amount of social support (201).

Table 12: Assessment tools for social isolation reported in included studies.

4.2.3.3 Assessment of Quality

Of the eight quantitative studies, the majority fulfilled seven or eight of the ten criteria of the critical appraisal tool (**Supplementary Table 3**). A common source of bias was the lack of identification of subpopulations using objective criteria. One study met the minimum of six criteria, and its primary source of bias was the inadequate representation of the patient population. This study focussed on a specific subset of the amputee population, i.e., only those who received rehabilitation, omitting a large subset not receiving rehabilitation.

The seven qualitative studies met between five and nine criteria (**Supplementary Table 4**). The common sources of bias were the uncertainty about the influence of the researcher on the research process (in five studies), the cultural and theoretical beliefs of the researcher (in three studies), the adequate representation of participants (in three studies) and the status of ethical approval (in three studies).

4.2.3.4 Prevalence of Social Isolation

Two studies reported the prevalence of social isolation, both focussing on MLAs secondary to PAD or DM. The first study (32) compared rates of social isolation (using the Nottingham Health Profile Score) in 130 amputees with 115 controls matched for age and gender. Amputees reported significantly more problems with mobility, social isolation, lethargy, pain, sleep, and emotional disturbance than controls. However, mobility was the only significant factor after matched logistic regression analysis, signifying a strong correlation between poor mobility and social isolation.

The second study (185) reported social isolation rates (using the Townsend Social Isolation Scale) of up to 59% and 73% in new and established amputees (one to two years of prosthesis use) respectively. By comparing severity of PAD in the contralateral leg, it was shown that amputees without contralateral disease had lower rates of social isolation (12.5% vs 73%, significance of differences were not tested).

4.2.3.5 Gender and Social Isolation in PAD

In one study (162) analysing gender-differences in patients with PAD, impaired social functioning was more severe in women than men, although not statistically significant (SF-36 score of 64.0 SD 25.5 vs 72.4 SD 27.7, respectively). A more extensive prospective study (161) focussing on gender outcomes in 1274 PAD patients showed that compared to male, female patients had lower social functioning and QoL measures at baseline (PAQ social functioning adjusted mean difference of -6.8, $p<0.001$; QoL adjusted mean difference of -6.7, $p<0.001$). A correlation between social isolation and poorer physical functioning was also seen, the latter being worse in female patients.

4.2.3.6 Diabetes and Social Isolation in PAD

A prospective study comparing 56 non-diabetic PAD and 18 diabetic PAD patients showed that diabetics scored significantly worse on walking ability and social function measured using the SF-36 tool (40.0 SD 8.9 versus 34.1 SD 9.7) (184). A cross-sectional study of 325 diabetic patients demonstrated that prevalence of loneliness was significantly higher with DFD (UCLA Loneliness Score of 52.25 SD 16.04) compared to other complications such as retinopathy (35.96 SD 9.57), nephropathy (37.50 SD 14.79) and neuropathy (38.78 SD 12.11), $p=0.003$. Comparison groups were small, only 20/325 of patients had either diabetic foot, retinopathy or nephropathy (183).

4.2.3.7 Incidence of PAD in Social Isolation

One prospective cohort study (186) focussed on the incidence of PAD in patients with social isolation (measured with the Interpersonal Support Evaluation List). In 12,965 middle-aged adults with no prior history of PAD, 854 developed PAD over a mean follow-up time of 9.7 years, yielding an incidence rate of 6.8 per 1000 person-years. Compared with the highest level of perceived social support, individuals with the lowest level of support had a PAD relative risk of 1.18 (95% CI 1.01–1.37) when adjusted for age, gender, and race. Although this association was not statistically significant, their data did show significant correlations between depression, immobility, and PAD incidence.

4.2.3.8 Mortality in Social Isolation

In a prospective study of 105 MLA patients receiving rehabilitation, mortality at three years was 33.0%. Social isolation (measured at start of study) was more prevalent in those who had died (18/35, 51.4%) than those alive (29/70, 41.4%) at end of study period, but this did not reach statistical significance. The subject numbers were small and omitted the large subgroup of amputees who did not survive the perioperative period (165).

4.2.3.9 Patient-centred Outcomes

Through thematic analysis, findings from qualitative studies were grouped into seven categories; each representing patient-reported problems directly attributed to social isolation. These categories were subsequently grouped into four levels of influence consistent with a socio-ecological framework model: personal, interpersonal, economic, and healthcare levels (**Figure 13**). At the personal level, fourteen findings associated social isolation to being housebound and frequent negative emotions such as anger, anxiety, and depression. At the interpersonal level, there were fourteen findings of relationship problems (parenting, marriage, friends and at work) which patients attributed to their feelings of social isolation and a self-image of being a “burden”.

At the economic level, there were four findings of employment problems encountered by patients. Patients who were unable to work expressed strong statements of social isolation, and those who relied on family for financial support also expressed feelings of “inadequacy”, adding to their thoughts of loneliness. Some patients, who had to change jobs or job-roles, mentioned difficulty in working with colleagues leading to feelings of isolation in the workplace and poor performance. At the healthcare level, two findings demonstrated the difficulty that socially isolated patients experienced in receiving appropriate healthcare in the community and hospitals. Some patients mentioned that lack of compliance with walking exercises and adherence to hospital visits were due to lack of social support.

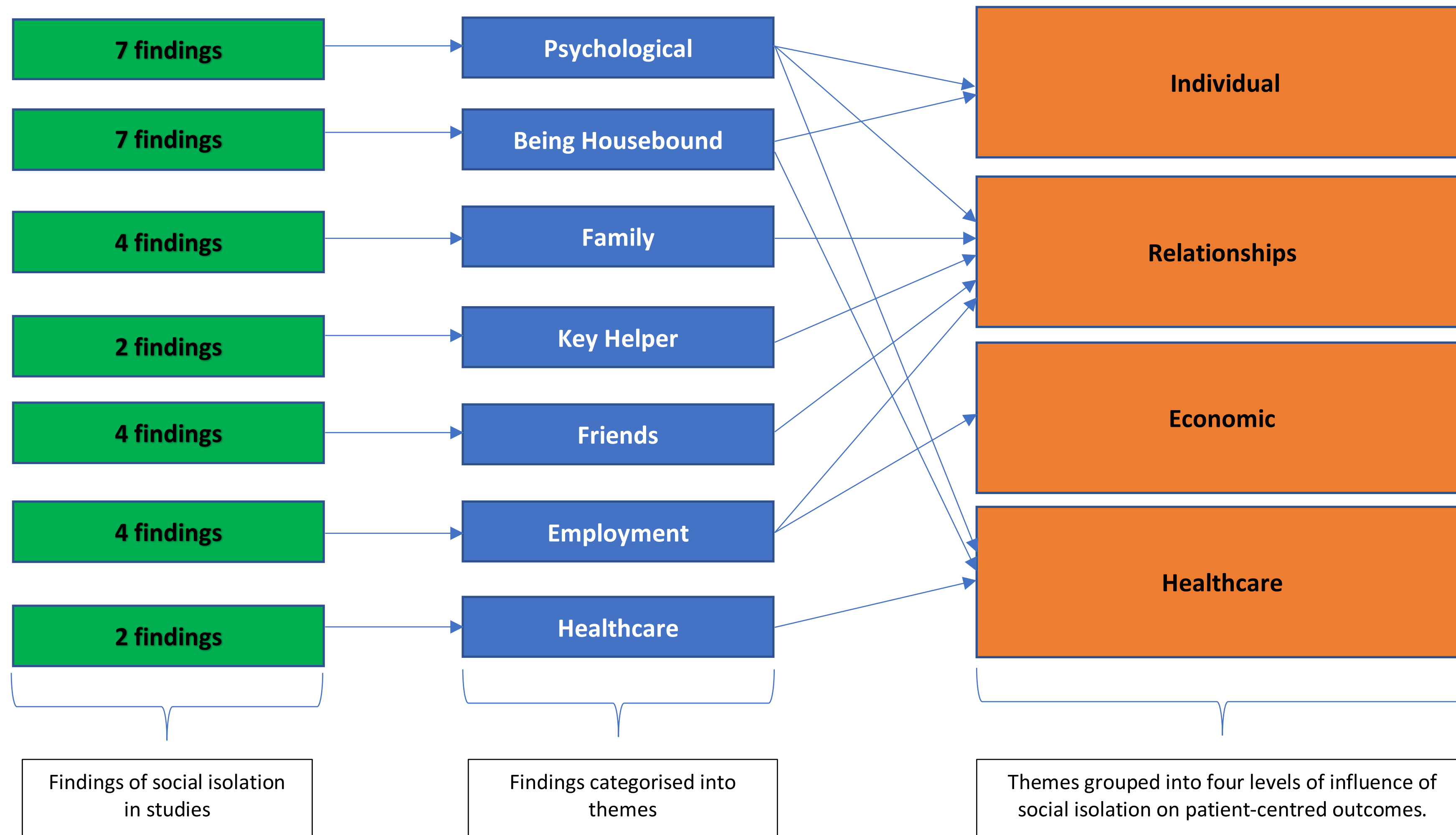

Figure 13: Socioecological framework model of social isolation in PAD and DFD.

4.2.4 Discussion

This supplementary systematic review comprehensively explores the burden of social isolation in PAD and DFD patients, encompassing both quantitative and qualitative studies. As shown in this review, evidence in literature signifies an association between social isolation and poor outcomes in lower limb arterial patients.

According to ONS, in 2016 to 2017, there were 5% of adults in England who reported feeling lonely “often” or “always” (202) but rates of up to 73% have been reported in certain PAD/DFD groups. A strong association between poor mobility and social isolation in lower limb arterial patients is suggested and if appropriately assessed could form a target for quality improvement. This has implications on clinical decision-making such as the optimisation of mobility versus limb salvage as the primary goal.

Social isolation in amputees worsens with the presence of contralateral limb disease, and with time after the amputation, suggesting a progressive process. Moreover, social isolation may predispose patients to higher incidence of PAD and mortality among amputees. This necessitates long-term follow-up of amputees by appropriate medical and social care specialists.

This review also demonstrated that certain factors such as diabetes and demographics may govern severity of loneliness. Female patients and diabetic patients with foot complications may be at greater risk for experiencing severe levels of social isolation, reduced perceptions of general health, and impaired functional capacity. Consistency with the literature, such as higher rates of depression and poorer rehabilitation among female patients (203) and diabetics (204), demands a better understanding of causality in these patient groups. The direction of such research may be guided by the qualitative findings in this chapter.

There are some limitations to this review. There was a paucity in the number of studies exploring issues relating to social isolation in lower limb arterial surgery. In many studies, quantitative data on social isolation was extracted from quality-of-life scoring tools which lose specificity in addressing social isolation. Only studies written in English were included, and

most were performed in Europe. This limits the generalisability of findings at the global level, especially in more socioeconomically deprived populations. In the qualitative synthesis, a weakness in studies was the bias introduced by patient sampling and data gathering methodologies, which requires consideration in future qualitative work.

Although this review was designed pragmatically to include a broad spectrum of PAD and DFD presentations, comparison groups in many studies were small, putting the significance of some identified associations into question. While comprehensive, it is acknowledged that this review does not address the issue of social isolation in lower limb arterial surgery in its entirety.

Holistic care in lower limb arterial surgery is strongly advocated in national guidelines. The National Institute for Health and Care Excellence (NICE), VSGBI and the American College of Cardiology/American Heart Association Task Force (ACA/AHA) recommend the utilisation of standardised multidisciplinary teams for provision of holistic care (17,43,205). However, certain areas of care, such as psychosocial care remain undervalued. Provision of psychological and emotional support to help patients adapt to their medical condition, access and adhere to medical treatment, and develop coping skills to incorporate their illness successfully into their lives, must be promoted (206).

This review suggests that provision of psychosocial care and optimisation of mobility, which appear inter-related, should be standardised in multidisciplinary teams. Future research into the development of tools predicting social isolation, particularly after MLA surgery, may support this argument.

Patients at risk of poor mobility and isolation may be referred to physiotherapy, psychosocial therapy, and community-based social support schemes. Further research into how this can address treatment compliance, readmission rates, protracted hospital-stay and health costs is also desirable. For the interests of this thesis, this chapter provides additional support for the need to develop more risk-prediction tools for functional outcomes.

Chapter 5.1: Functional survival following major amputation

5.1.1 Introduction

Surgical research on MLAs has predominantly focussed on predictors of mortality and complication rates, while rehabilitation research focuses on success of prosthetic mobility (20,207–210). There remain many unanswered questions on how MLA patients fare both short- and long-term.

One major issue is that the fraction of patients receiving prosthetic rehabilitation continues to be poorly reported in literature. Due to high peri-operative complication rates, there is a significant proportion of patients who die prior to commencement of rehabilitation. Moreover, frail amputees may be deemed unsuitable for rehabilitation on assessment in the post-operative period and not referred to specialist rehabilitation services.

Regression of the patients' health status due to death or unsuitability for rehabilitation after MLA surgery represent the least desirable outcomes of amputation surgery, and at-risk groups must therefore be identified. If patients have predictably poor functional outcomes from MLA, then this information can be used to improve the processes of consent and consideration of alternative treatment strategies to amputation. For this purpose, the concept of functional survival was introduced in this thesis. Functional survival describes the favourable outcome of surviving the peri-operative period of MLA surgery and preservation of a level of cognitive and physical function permitting progression to rehabilitation. Its prediction is therefore a vital component of any functional outcome risk prediction tool in MLA research.

The aim of this experimental chapter was to find pre-operative patient variables associated with functional survival following MLA. Findings from this study were used to produce a validated risk prediction model for this binary outcome as a constituent of the overall decision aid constructed in experimental Chapter 8. Secondary aims of this chapter were to explore other outcomes including all-cause mortality, complications, length of stay and place of discharge. Trends in survival by MLA level and rehabilitation status after MLA surgery were also analysed to determine if these parameters were surrogate predictors of long-term survival.

5.1.2 Methods

The methodology for this experimental chapter is described in full in Chapter 2. In brief, a retrospective cohort study of all MLAs performed in a single tertiary vascular centre over a five-year period.

5.1.3 Results

5.1.3.1 Patient Characteristics

Pre-operative patient characteristics are presented in **Table 13**. A total of 262 patients underwent an MLA, with BKA being performed in 113 (43.1%), TKA in 22 (8.4%) and AKA in 127 (48.5%) cases. BKA patients were significantly younger than TKA and AKA patients: median age of 63, 73 and 74 years respectively, p=0.029. Ratio of male to female was approximately 3:1. No differences were seen in gender distribution by amputation level.

BKA (81/113, 72.1%) and TKA (13/22, 61.9%) patients were significantly more likely to be diabetic compared to AKA (43/127, 34.7%), p<0.001. The rate of prior stroke diagnoses was lower in BKA (10/113, 8.85%) compared to TKA (5/22, 23.8%) and AKA (23/127, 18.5%) patients, p=0.055. Conversely, AKA patients had higher rates of active malignancy (16/127, 12.6%) compared to TKA (1/22, 4.54% and BKA (9/113, 7.96%), p=0.331. There were no significant differences in the pre-operative frailty scores by amputation level.

The rate of ALI, as the aetiology of amputation, was significantly higher in AKA patients (36/127, 28.3%) compared to TKA (3/22, 13.6%) and BKA (7/113, 6.19%) groups, p<0.001. A similar trend was seen for acute-on-chronic CLTI. In contrast, rates of CLTI were similar between BKA (41/113, 36.3%) and AKA (47/127, 37.0%) groups but significantly higher in the TKA group (14/22, 63.6%), p=0.046. Diabetic foot sepsis was predominantly seen in the BKA group (52/113, 46.0%) compared to TKA (3/22, 13.6%) and AKA (13/127, 10.2%), p<0.001.

Pre-existing psychiatric diagnoses were identified in 51/262 (19.5%) patients. Mood and anxiety disorders were present in 30/262 (11.5%) patients, while 4/262 patients (1.53%) had psychosis and 19/262 (7.25%) had cognitive dysfunction. A social problem was identified in 181/262 (69.1%) patients. This comprised of 36/262 (13.7%) patients being a vulnerable adult, 175/262 (66.7%) with history of substance misuse and 137/262 (52.3%) with pre-amputation functional dependence. There were no significant differences in rates of social problems by amputation level but deprivation scores (in deciles ranked one to ten, with one being most

deprived) was significantly worse in the TKA patients (4.5) compared to BKA (7) and AKA (6), p=0.004.

	Total (262)	%	AKA (127)	%	TKA (22)	%	BKA (113)	%	P value
Age	71 [62-78]		74 [63-80]		73 [64-78]		63 [59-75]		**0.029**
Male	192	73.3	89	70.1	18	81.8	85	75.2	0.427
Hypertension	192	74.7	88	71.0	15	71.4	89	79.5	0.304
Hypercholesterolaemia	53	20.6	24	19.4	4	19.0	25	22.3	0.839
Diabetes Mellitus	137	53.3	43	34.7	13	61.9	81	72.1	**<0.001**
Coronary Arterial Disease	118	45.9	60	48.4	12	57.1	46	41.1	0.298
Atrial Fibrillation	48	18.7	27	21.8	3	14.3	18	16.1	0.461
Congestive Cardiac Failure	24	9.16	9	7.09	5	23.8	10	8.85	**0.054**
Chronic Kidney Disease	81	31.5	32	25.8	8	38.1	41	36.6	0.162
ESRF	21	8.02	6	4.72	2	9.09	13	12.0	0.146
COPD	50	19.1	28	22.0	5	22.7	17	15.0	0.349
Cerebrovascular disease	38	14.8	23	18.5	5	23.8	10	8.85	**0.055**
Active Cancer	26	9.90	16	12.6	1	4.45	9	7.96	0.331
Clinical Diagnosis of Sepsis	60	24.1	26	21.7	3	14.3	31	28.7	0.253
Aetiology of MLA									
ALI	46	17.6	36	28.3	3	13.6	7	6.19	**<0.001**
Acute-on-chronic CLI	45	17.2	31	24.4	2	9.09	12	10.6	**0.011**
CLI	102	39.1	47	37.0	14	63.6	41	36.3	**0.046**
Diabetic Foot Sepsis	68	26.1	13	10.2	3	13.6	52	46.0	**<0.001**
Psychosocial History									
Any psychiatric diagnosis	51	19.5	27	21.3	2	9.09	22	19.5	0.412
Mood/Anxiety	30	11.5	15	11.8	2	9.09	13	11.5	0.934
Psychosis	4	1.53	0	0	0	0	4	3.54	0.069
Cognitive Dysfunction	19	7.25	12	9.45	0	0	7	6.19	0.244
Any social problem	181	69.1	93	73.2	16	72.7	72	63.7	0.262
Vulnerable adult	36	13.7	22	17.3	3	13.6	11	9.73	0.234
Drug Misuse	175	66.8	87	68.5	16	72.7	72	46.0	0.607
Pre-amputation Functional Dependency	137	52.3	73	57.5	12	54.5	52	46.0	0.202
Frailty Score (MFI-5)	2 [1-3]		2 [1-3]		2.5 [2-3]		2[2-3]		0.121
Deprivation (IMDD)	6 [4-8]		6 [4-8]		4.5 [2.8-7]		7 [5-9]		**0.004**

Table 13: MLA patient characteristics compared by amputation level.

5.1.3.2 Pre-MLA Same-admission Vascular Surgery

Same-admission ipsilateral vascular surgery was common with 94/262 (35.9%) of the patients having undergone a procedure prior to their MLA, as shown in **Table 14**. Endovascular revascularisation was performed in 45/262 (17.2%), while open revascularisation was performed in 20/262 (7.63%) of patients. Minor amputations were performed in 29/262 (11.1%) of cases. There were significant differences in the rate of surgery by MLA level and aetiology. Open revascularisation was more commonly performed in patients prior to their AKA (16/127, 12.6%) compared to TKA (0/22, 0%) and BKA (4/113, 3.54%), p=0.011. Conversely, minor amputations were more common prior to a BKA (24/113, 21.2%) compared to a TKA (0/22, 0%) or an AKA (5/127, 3.94%), p<0.001.

Same Admission Ipsilateral Surgery	Total (262)	%	AKA (127)	%	TKA (22)	%	BKA (113)	%	P value
Endovascular	45	17.2	20	15.7	2	9.09	23	20.4	0.406
Open	20	7.63	16	12.6	0	0	4	3.54	**0.011**
Minor Amputation	29	11.1	5	3.94	0	0	24	21.2	**<0.001**

Table 14: Same-admission ipsilateral vascular surgery in MLA patients by amputation level.

Repeating the same comparison by aetiology showed that open revascularisation was more commonly performed for ALI (12/46, 26.1%) compared to acute-on-chronic CLTI (6/45, 13.1%), CLTI (1/102, 0.980%) and DFS (1/68, 1.47%), p<0.001. Conversely, minor amputations were more commonly performed for DFS (21/68, 30.9%) compared to ALI (0/46, 0%), acute-on-chronic CLTI (0/45, 0%) and CLTI (8/102, 7.84%), p<0.001 (**Table 15**).

Same Admission Ipsilateral Surgery	ALI (46)	%	Acute-or chronic CLTI (45)	%	CLTI (102)	%	DFS (68)	%	P value
Endovascular	9	19.6	4	8.89	23	22.5	9	13.2	0.172
Open	12	26.1	6	13.3	1	0.980	1	1.47	**<0.001**
Minor Amputation	0	0	0	0	8	7.84	21	30.9	**<0.001**

Table 15: Same-admission ipsilateral vascular surgery in MLA patients by aetiology.

5.1.3.3 Haematological Markers

Pre-operative anaemia and hypalbuminaemia were common in all amputation groups (**Table 16**, with values expressed as median and IQR). White cell counts (10^9/L) were significantly elevated in AKA (13.1[10.5, 16.0]) and TKA (12.1[9.32, 14.4]) patients compared to BKA (10.7[7.96, 14.2]), p=0.001. Similarly, C-reactive Protein (mg/L) was significantly elevated in AKA (125[69.2, 201]) and TKA (115[30.8, 166]) patients compared to BKA (79.9 [40.9, 131]), p=0.002. No differences were seen by MLA level for serum urea, electrolytes or eGFR.

	Total	AKA	TKA	BKA	P value
Haemoglobin (g/L)	99 [89.0-109]	96.5 [87.0-109]	103 [92.0-110]	100 [89-109]	0.444
White Cell Count (10^9/L)	12.1 [9.30-15.2]	13.1 [10.5-16.0]	12.1 [9.32-14.4]	10.7 [7.96-14.2]	**0.001**
Urea (mmol/L)	5.6 [3.80-9.00]	5.5 [3.4-9.0]	5.4 [3.4-7.1]	5.75 [4.2-9.7]	0.284
Sodium (mEq/L)	137 [134-140]	137 [134-140]	136 [134-138]	137 [134-140]	0.734
Potassium (mEq/L)	4.6 [4.20-5.0]	4.5 [4.2-5.0]	4.5 [4.2-4.8]	4.7 [4.2-5.1]	0.208
Albumin (g/L)	21.0 [17.0-25.0]	21 [18.0-25.0]	20.5 [18.8-24.3]	21 [17.0-25.5]	0.987
eGFR (ml/min/1.73m^2)	60 [53.0-60]	60 [56.5-60]	60 [54.8-60]	60 [42.8-60]	0.186
C-reactive Protein (mg/L)	98.5 [52-173]	125 [69.2-201]	115 [30.8-166]	79.9 [40.9-131]	**0.002**

Table 16: Pre-operative haematological markers for MLA patients by amputation level.

5.1.3.4 All-cause Mortality

Cumulative all-cause mortality (ACM) was higher with proximal MLAs but not statistically significant up to year one (**Table 17**). Significant differences were seen after year one when ACM among more proximal level MLAs became significantly higher. At two years, ACM was significantly higher in AKA (46/127, 36.2%) and TKA (6/22, 27.3%) compared to BKA (24/113, 21.2%), p=0.034. Interestingly at three years, ACM was highest among the TKA group (12/22, 54.5%) compared to the AKA (60/127, 47.2%) and BKA (32/113, 28.3%) groups, p=0.004.

ACM	Total (262)	%	AKA (127)	%	TKA (22)	%	BKA (113)	%	P value
15-day	8	3.05	4	3.15	0	0	4	3.54	0.675
30-day	14	5.34	8	6.30	1	4.45	5	4.42	0.800
60-day	23	8.78	13	10.2	2	9.09	8	7.08	0.688
90-day	31	11.8	17	13.4	4	18.2	10	8.85	0.349
180-day	38	14.5	21	16.5	5	22.7	12	10.6	0.223
1-year	54	20.6	29	22.8	5	22.7	20	17.7	0.598
2-year	76	29.0	46	36.2	6	27.3	24	21.2	0.038
3-year	104	39.7	60	47.2	12	54.5	32	28.3	0.004

Table 17: Cumulative all-cause mortality in MLA patients by amputation level.

5.1.3.5 Post-operative Outcomes

In-patient post-operative complications, rehabilitation potential at discharge and length of stay are presented in **Table 18**.

Complications

A total of 87/262 (33.2%) patients experienced a medical or surgical complication or died in the same admission after their amputation. Fourteen patients (5.34%) died in the same admission. Medical complications comprised mainly of pulmonary (14/262, 5.34%), gastrointestinal (10/262, 3.82%), cardiac (9/262, 3.43%), and renal (9/262, 3.44%) adverse events. Surgical complications were predominantly amputation wound infections (27/272, 10.3%), stump revision surgery (24/262, 9.16%) and contralateral major limb amputation (22/262, 8.40%). There were no significant differences in complication rates by amputation level. Revision surgery was more common in TKA (3/22, 13.6%) patients compared to BKA (7/113, 6.19%) and AKA patients (4/127, 3.15%), p=0.113. Stump wound problems not requiring revision surgery were also most commonly seen in TKA patients.

Rehabilitation Potential

At discharge from the hub hospital, 151/262 (57.6%) patients were suitable to start specialist prosthetic rehabilitation. Commencement of rehabilitation was delayed to beyond point of discharge in 20/262 (7.63%) patients due to on-going wound problems, and in 46/262 (17.6%)

patients for medical problems. Therefore only 217 (82.8%) patients experienced functional survival post-MLA. With the exclusion of the 14 (5.34%) of patients who died in hospital, the remaining 31/262 (11.8%) patients were deemed unsuitable for prosthetic rehabilitation on post-operative physiotherapy assessment and therefore did not progress to specialist rehabilitation. Unsuitability for rehabilitation was most commonly seen in AKA (21/127, 16.5%) compared to TKA (2/22, 9.1%) and BKA (8/113, 7.1%) patients, p=0.071.

Length of Stay

The median time from admission to MLA surgery was 5 [2-13] days, from MLA to discharge (excluding those who died) was 17.5 [10-28] days and for the total LOS was 26.5 [16-40] days.

There were no significant differences in median LOS by amputation level. However, a trend observed was that higher amputation levels were associated with shorter LOS in the pre-amputation period. Post-amputation length of stay was similar (17-20 days) for all amputation levels. The greatest variation was observed in total LOS. The median total stay (in days) for AKA was 23 [14-37] compared to 34 [18-47] for TKA and 28 [17-43] for BKA patients, p=0.856.

	Total (262)	%	AKA (127)	%	TKA (22)	%	BKA (113)	%	P value
Any Complications	105	40.1	42	33.1	7	31.8	38	33.6	0.985
Died in Hospital	14	5.34	7	5.51	2	9.09	5	4.42	0.668
Cardiac	9	3.44	3	2.36	0	0	6	5.31	0.298
Pulmonary	14	5.34	9	7.09	0	0	5	4.42	0.334
Renal	9	3.44	4	3.15	0	0	5	4.42	0.563
Gastrointestinal	10	3.82	7	5.51	0	0	3	2.65	0.319
Stroke	4	1.53	3	2.36	1	4.55	0	0.00	0.159
Delirium	5	1.91	2	1.57	0	0	3	2.65	0.657
Psychiatric	3	1.15	2	1.57	0	0	1	0.88	0.767
Stump Wound	27	10.3	13	10.2	3	13.6	11	9.73	0.859
Stump Revision	24	9.16	4	3.15	3	13.6	7	6.19	0.113
Contralateral Limb Loss	22	8.40	2	1.57	0	0	4	3.54	0.451
Rehabilitation Status at Discharge									
Ready to Commence Rehabilitation	151	57.6	67	52.8	11	50.0	73	64.6	0.135
Delay due to Wound Problems	20	7.63	7	5.51	3	13.6	10	8.85	0.338
Delay due to Medical Problems	46	17.6	25	19.7	4	18.2	17	15.0	0.639
Unsuitable for Rehabilitation	31	11.8	21	16.5	2	9.09	8	7.08	0.071
Discharge Destination									
Home	69	26.3	32	25.2	7	31.8	30	26.5	0.807
Rehabilitation Centre	29	11.1	10	7.87	2	9.09	17	15.0	0.200
Spoke Hospital	136	51.9	70	55.1	10	45.5	56	49.6	0.565
Nursing Home	14	5.34	8	6.30	1	4.54	5	4.42	0.800
Median Length of Stay (days)									
Pre-amputation	5 [2-13]		4 [2,10]		7 [3,10]		9 [2,15]		0.377
Post-amputation	17.5 [10-28]		17 [10,27]		20 [12,40]		19 [11,28]		0.702
Total	26.5 [16-40]		23 [14,37]		34 [18-47]		28 [17, 43]		0.856

Table 18: Complications, rehabilitation status, discharge destination and LOS post-MLA surgery by amputation level.

5.1.3.6 Univariate Analysis for Functional Survival

Pre-operative patient variables underwent univariate analysis to assess the strength of possible associations with functional survival (**Table 19**).

Age showed a strong association. Those aged over 75 years were significantly less likely to experience functional survival [OR 0.418, 95% CI 0.217-0.805, p=0.008]. There were also some gender-related differences. Female patients were more likely to experience functional survival, although not statistically significant [OR 0.450, 95% CI 0.191-1.06, p=0.063].

MLA level was indicative of functional survival, with BKA being associated with better outcome [OR 2.10, 95% CI 1.05-4.23, p=0.034]. Conversely AKA patients fared worse [OR 0.509, 95% CI 0.263-0.985, p=0.043], while no significant association was seen for TKA patients.

A few comorbidities were associated with poor functional survival. Congestive cardiac failure [OR 0.378, 95% CI 0.151-0.946, p=0.032], active malignancy [OR 0.230 95% CI 0.0973-0.542, p<0.001], and pre-operative delirium [OR 0.281 95% CI 0.0947-0.835, p=0.016]. Frailty also showed an association with poor functional survival. Patients with an MFI-5 score above 2 had significantly poorer outcomes [OR 0.391 95% CI 0.203-0.752, p=0.003]. Patients who experienced functional survival were less likely to have had a stroke, although this was not statistically significant.

Trends showed that patients who fared worse had higher rates of psychological problems, although not statistically significant. Having social problems was associated with poor functional survival, such as pre-amputation functional dependency [OR 0.335 95% CI 0.164-0.682, p=0.002] or being a vulnerable adult [OR 0.402 95% CI 0.181-0.893, p=0.022].

Those who failed to achieve functional survival had more deranged pre-operative haematological markers such as serum WCC over 10 10^9/L [OR 0.420 95% CI 0.186-0.950, p=0.033], urea above 10mmol/L [OR 0.485 95% CI 0.235-1.00, p=0.047] and albumin under

15g/L [OR 0.358 95% CI 0.152-0.840, p=0.015]. Anaemia also showed this trend although not statistically significant.

Aetiology was also associated with functional survival. ALI patients had the best rates of functional survival [OR 3.46 95% CI1.02-11.7, p=0.035] while no significant association was seen for acute-on-chronic CLTI [OR 0.796 95% CI 0.353-1.79, p=0.581] or CLTI patients [OR 1.19 95% CI 0.610-2.32, p=0.610]. Patients presenting with diabetic foot sepsis fared the worst [OR 0.506 95% CI 0.257-0.998, p=0.047].

	Functional survival				Univariate OR		p value
	Yes (217)		No (45)				
	No.	%	No.	%	OR	95% CI	
Age>75	62	28.6	22	48.9	0.418	0.217-0.805	**0.008**
Sex							
Male	154	71.0	38	84.4	2.22	0.942-5.24	**0.063**
Female	63	29.0	7	15.6	0.450	0.191-1.06	**0.063**
Emergency	182	85.8	40	88.9	0.758	0.277-2.08	0.589
Amputation Level							
BKA	100	46.1	13	28.9	2.10	1.05-4.23	**0.034**
TKA	18	8.29	4	8.89	0.927	0.298-2.88	0.896
AKA	99	45.6	28	62.2	0.509	0.263-0.985	**0.043**
Co-morbidities							
Ischaemic Heart Disease	93	43.9	25	55.6	0.625	0.327-1.19	0.153
Hypertension	154	72.6	38	84.4	0.489	0.207-1.16	**0.098**
Atrial Fibrillation	39	18.4	9	20.0	0.902	0.402-2.02	0.802
Congestive Cardiac Failure	16	7.37	8	17.8	0.378	0.151-0.946	**0.032**
Hypercholesterolaemia	43	20.3	10	22.2	0.891	0.409-1.94	0.770
Diabetes Mellitus	112	52.8	25	55.6	0.896	0.469-1.71	0.739
Renal failure							
eGFR>30	175	85.0	38	86.4	0.891	0.348-2.29	0.811
30<eGFR<15	12	5.53	3	6.67	0.845	0.228-3.13	0.801
eGFR<15	18	8.29	3	6.67	1.31	0.368-4.65	0.677
Chronic Obstructive Pulmonary Disease	40	18.4	10	22.2	0.791	0.362-1.73	0.556
Stroke	29	13.7	9	20.0	0.634	0.277-1.45	0.278
Active Malignancy	15	6.91	11	24.4	0.230	0.0973-0.542	**<0.001**
Frailty (MFI-5>2)	63	29.0	23	51.1	0.391	0.203-0.752	**0.003**
Pre-operative Delirium	9	4.15	6	13.3	0.281	0.0947-0.835	**0.016**
Psychosocial History							
Any Psychiatric Hx	38	17.5	13	28.9	0.523	0.251-1.09	**0.079**
Mood/Anxiety	22	10.1	8	17.8	0.522	0.216-1.26	0.142
Psychosis	3	1.38	1	2.22	0.617	0.0627-6.07	0.676
Cognitive Dysfunction	14	6.45	5	11.1	0.552	0.188-1.62	0.273
Any Social Problem	149	68.7	32	71.1	0.890	0.440-1.80	0.746
Vulnerable adult	25	11.5	11	24.4	0.402	0.181-0.893	**0.022**
Drug Misuse	144	66.4	31	68.9	0.891	0.446-1.78	0.743
Functional dependency	104	47.9	33	73.3	0.335	0.164-0.682	**0.002**
Deprivation Score (IMDD<6)	73	37.1	15	42.9	0.785	0.379-1.63	0.515
Haematological Markers							
Haemoglobin<10g/L	149	73.4	37	86.0	0.447	0.179-1.12	**0.079**
White Cell Count>10 (10^9/L)	138	66.0	37	82.2	0.420	0.186-0.950	**0.033**
Urea>10 mmol/L	38	18.4	14	31.8	0.485	0.235-1.00	**0.047**
Sodium mEq/L	137 [134-139]		137 [134-140]				0.303
Potassium mEq/L	4.55 [4.20-5.00]		4.60 [4.10-5.00]				0.630
Albumin<15g/L	19	10.1	10	23.8	0.358	0.152-0.840	**0.015**
CRP>100mg/L	95	48.5	24	54.5	0.784	0.407-1.51	0.466
Acute Kidney Injury	11	5.5	4	9.5	0.553	0.167-1.83	0.326
Aetiology of MLA							
ALI	43	19.8	3	6.67	3.46	1.02-11.7	**0.035**
Acute on chronic CLTI	36	16.6	9	20.0	0.796	0.353-1.79	0.581
CLTI	86	39.6	16	35.6	1.19	0.610-2.32	0.610
Diabetic Foot Sepsis	51	23.5	17	37.8	0.506	0.257-0.998	**0.047**

Table 19: Univariate analysis for predictors of functional survival post-MLA.

5.1.3.7 Post-operative Complications and Failure of Progression to Rehabilitation

The association between post-operative complications and failure of progression to rehabilitation was also tested (**Table 20**). Due to small event rates, confidence intervals for associations were generally large, therefore limiting the inferences that could be made. Those suffering a post-operative stroke had a trend towards poorer progression to rehabilitation (OR 5.0 [95% CI, 0.6-36.5], p=0.079). Patients suffering acute confusion post-operatively appeared less likely to progress to rehabilitation (OR 21.1 [95% CI, 2.3-193], p<0.001).

	Functional Survival						
	Yes (217)	%	No (45)	%	OR	[95% CI]	Univariate p value
Cardiac	9	4.15	0	0.00	0.23	[0.01-4.2]	0.164
Pulmonary	10	4.61	4	8.89	2.04	[0.6-6.8]	0.245
Renal	6	2.76	3	6.67	2.51	[0.6-10.4]	0.191
Wound Infection	22	10.1	5	11.1	1.14	[0.4-3.1]	0.845
Gastro-intestinal	9	4.15	1	2.22	0.57	[0.1-4.3]	0.540
Stroke	2	0.92	2	4.44	5.01	[0.6-36.5]	0.079
Delirium	1	0.46	4	8.89	21.1	[2.3-193]	**<0.001**
Psychiatric	2	0.92	1	2.22	2.42	[0.2-27.5]	0.455
Same admission revision	10	4.61	4	8.89	2.04	[0.6-6.8]	0.245
Same admission contralateral amputation	5	2.30	1	2.22	0.964	[0.1-8.5]	0.973

Table 20: Post-MLA complications and odds of progressing to rehabilitation.

5.1.3.8 Long-term Survival

During the entire study, 140 (53.4%) patients died. The median overall survival was 50.4 months [IQR 40.4-65.7 months].

Survival by Amputation Level

Kaplan Meier survival analysis was performed to identify differences in survival by MLA level (**Figure 14**). Median survival was significantly longer in patients who had a BKA (74.5 months), compared to those who had a TKA (33.1 months) or an AKA (39.4 months), p=0.014.

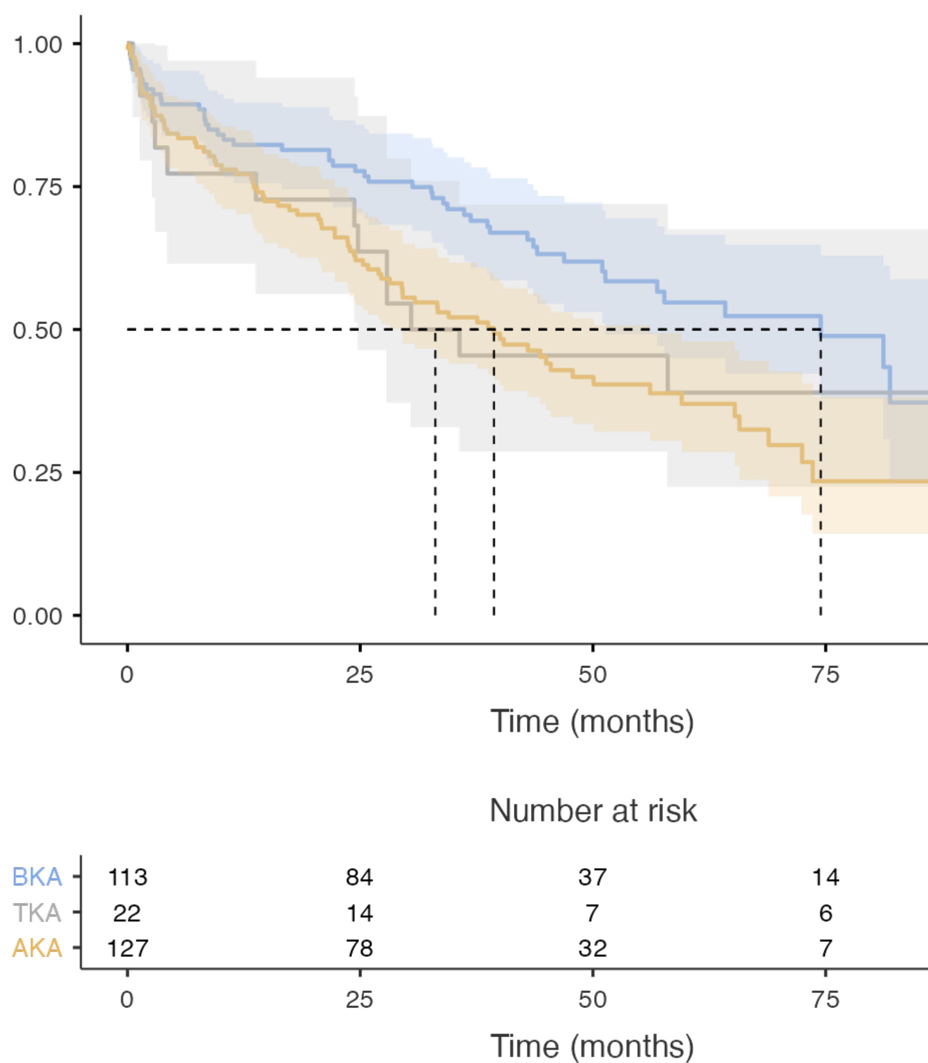

Figure 14: Kaplan-Meier survival analysis post-MLA by amputation level.

Survival by Rehabilitation Status

Kaplan Meier survival analysis was performed to identify differences in survival by rehabilitation potential in patients who survived their admission for amputation (**Figure 15**). There were significant differences in the median survival of patients who were ready to commence rehabilitation (65.7 months), compared to those who had significant delays to rehabilitation due to either medical or surgical problems (46.9 months) and those who were deemed unsuitable for rehabilitation (29.5 months), p=0.019.

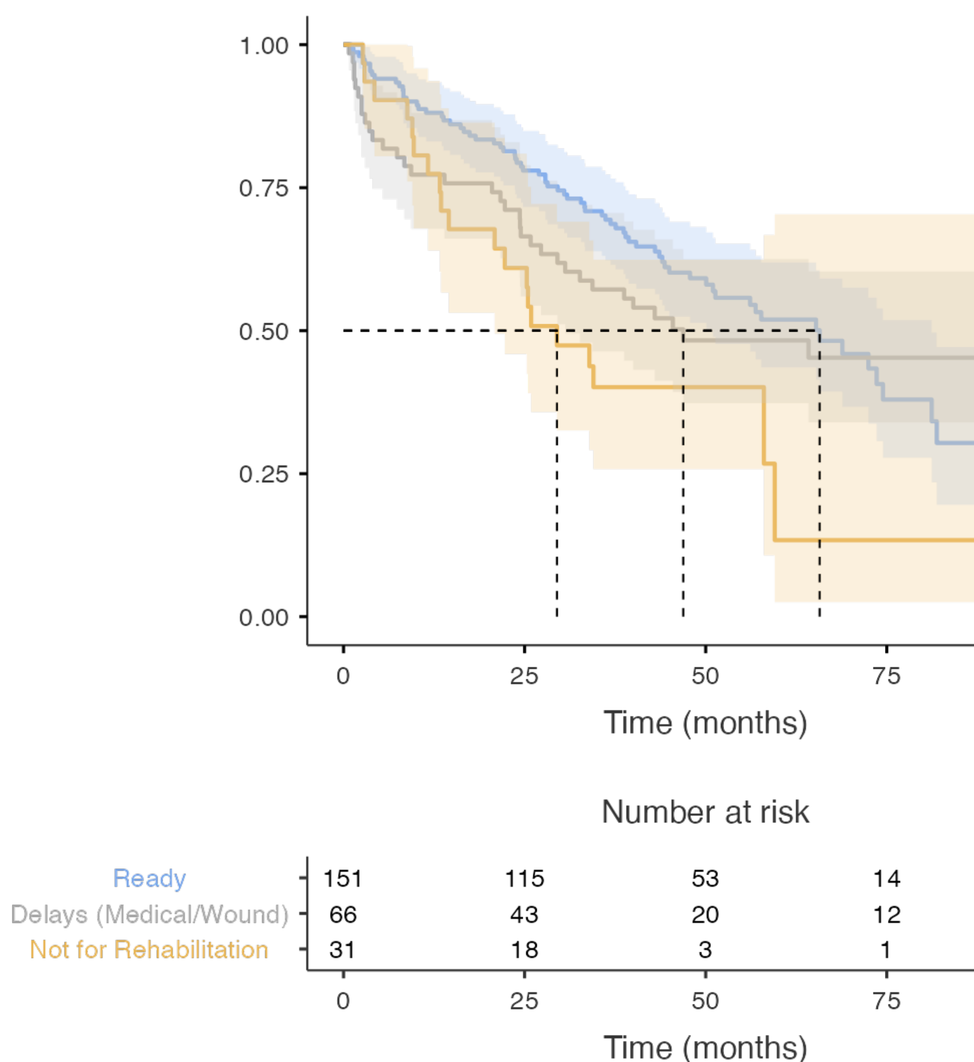

Figure 15: Kaplan-Meier survival analysis post-MLA by rehabilitation status at time of discharge.

5.1.4 Discussion

There is a distinct cohort of amputees who fail to achieve functional survival following their amputation due to in-patient death or unsuitability for rehabilitation on post-operative functional assessment. This chapter identified variables associated with this important and previously unreported parameter of functional outcome, the prediction of which was incorporated in the decision-making aid (Chapter 8).

In this study, 17.1% of patients either died in the same admission or were unsuitable for rehabilitation. This is a disappointingly important statistic. This study has also identified patient characteristics such as MLA level, demographics, comorbidities, and social problems, as being important factors in the failure of progression to rehabilitation. The substantial proportion of cases failing functional survival has implications on surgical decision-making, and provision of rehabilitation and palliative care services.

Moreover, rehabilitation potential on post-amputation assessment was a strong predictor of long-term survival. Those that progressed to rehabilitation without delays survived on average approximately 1.4 times longer than those who experienced medical or wound-related complications and over twice as long as those unsuitable for rehabilitation. It is likely that older and comorbid patients had poorer rehabilitation potential, and therefore confound this association between rehabilitation potential and survival. Nevertheless, rehabilitation potential at discharge from acute surgical care may be utilised as a surrogate marker of long-term survival and consequently this may be used in pre-operative discussions with patients and families to appropriately manage expectations.

Approximately a third of patients experienced a post-operative complication in the same admission, consistent with literature (211–213). Most medical complications in order of decreasing rates seen were pulmonary, gastrointestinal, cardiac, and renal problems. Stump wound problems were particularly prevalent in TKA, which provides an explanation for the disproportionately higher rates of revision surgery and longer length of stay for this MLA group. Post-operative complications led to significant delays in commencement of

rehabilitation and only 57.6% of patients were ready to start rehabilitation at time of discharge from the acute inpatient stay at the tertiary hub hospital.

Studies have shown the superior outcomes of rehabilitation achieved in inpatient rehabilitation services and in early commencement of prosthetic therapy (214,215). It is therefore pertinent to streamline rehabilitation pathways as centralisation of vascular services continue across the country.

Due to the hub and spoke model of vascular service provision, our multidisciplinary networks encourage the local delivery of vascular and endovascular care for less complex lower limb arterial disease. The care of more complex medical and surgical lower limb patients is undertaken by the tertiary hub. This offers one explanation for the larger proportion of higher-level amputations reported in this dataset compared to national rates.

Markers of complexity such as advanced age, more acute ischaemia, significant comorbidities, and deranged blood results were found to be more common in higher MLA level patients. Higher level amputees were older by median of ten years compared to BKA and had more comorbidities such as cerebrovascular disease and active malignancy. Aetiology also played an important role in the level of amputation with more acute ischaemia in AKAs and diabetic foot disease in BKAs. Pre-operative blood tests revealed evidence of chronic disease and frailty (anaemia and hypoalbuminaemia) for all amputation groups but raised inflammatory markers were more often seen for higher amputation levels.

There has been little focus on the testing of psychosocial parameters in previous studies which investigated predictors of poor outcome in amputation surgery. This study showed that pre-existing psychiatric and social problems were prevalent among lower limb patients undergoing an amputation. Mood and anxiety disorders were the predominant psychiatric problems and considerable number of patients were vulnerable adults, had a history of substance misuse or pre-amputation functional dependence. Being a vulnerable adult was associated with poorer functional survival. Psychosocial factors are commonly overlooked in the provision of patient-centred care in lower limb patients in the acute setting.

This was a retrospective single centre study and follow-up of patients to assess the long-term success of the subsequent rehabilitation stage was not undertaken. Therefore, as a stand-alone experiment, this study is not able to report rates of successful prosthetic mobility and patient independence in those who progressed to rehabilitation, as this process occurred out of hospital (rehabilitation centres, community settings, spoke hospitals, etc). In-depth characterisation of other patient-reported outcomes, such as quality of life, is also recommended for amputees, especially for the subgroups with the least desirable clinical outcomes such as those identified in this study.

Chapter 5.2: Impact of cancer on outcomes of major amputation: a supplementary study

5.2.1 Introduction

The previous experimental chapter highlighted an association between cancer and failure of progression to rehabilitation and this novel finding prompted a more in-depth analysis of the same study sample. The association between outcomes of lower limb arterial disease and cancer is poorly described compared to that of venous thromboembolic events (VTE) and cancer (216,217). Some studies have focussed on outcomes of limb revascularisation in cancer patients where cancer prevalence has been reported to be between 10 and 20% (218,219).

Rates of occult cancers, which may be as high as 16% in ALI (220), makes the true prevalence of cancer in lower limb arterial patients a challenge to ascertain. Cancer has been shown to be a significant predictor of mortality after revascularisation (218,221,222). However, less is known about its effects on outcomes after MLA, approximately 3000-5000 of which are performed each year for patients with lower limb arterial disease, in the UK (17).

The previous chapter reported all-cause mortality of 5.3%, 14.5% and 20.6% at 30-day, 6 month and 1 year, respectively. In literature, however, all-cause mortality after major amputation is as high as 44%, 66% and 85% after 1, 3 and 5 years, respectively (223). Poor outcomes have been attributed to increasing age, cardiovascular disease burden and frailty. In recent years, the incidence of malignancy in the over-65 group has increased 11-fold compared to younger adults, and this is expected to rise as populations age (224). With lower limb arterial disease predominantly affecting the elderly population, there is a clinical necessity to understand outcomes of amputation in patients with active cancer.

The aim of this study was to characterise patients with cancer who underwent an MLA and compare outcomes of amputation by nature and chronicity of the cancer. A secondary aim was to compare survival of cancer patients undergoing amputation with that of patients undergoing primary palliation for their unsalvageable limb.

5.2.2 Methods

The methods of this experimental chapter are described in Chapter 2. In brief, an in-depth-analysis of patients with active malignancy and its association with outcomes following MLA surgery was performed using the same dataset as that of Chapter 5.1.

5.2.3 Results

Patient characteristics and presentations of the unsalvageable limb are presented in **Table 21**.

5.2.3.1 Patient Characteristics

During the study period, 262 patients underwent 304 MLAs, the ratio of male to female was 3:1 and the median age was 71.0 [26-100] years. Of these, 42/262 (16.0%) had a diagnosis of cancer; 26/262 (9.92%) had active cancer and 16/262 (6.11%) had historic cancer. Of those with an active cancer, 14/26 (53.8%) had a known diagnosis and 12/26 (46.2%) were new cancers diagnosed at the time of amputation.

Overall, the groups were matched for comorbidities and frailty. Although not statistically significant, rates of ischaemic heart disease and chronic kidney disease in the new cancer group (16.7% and 16.7%, respectively) were approximately half of those in the other groups who underwent amputation.

5.2.3.2 Foot Presentation

ALI was the dominant cause of limb loss in patients with a new cancer diagnosis, with 6/12 (50.0%) of presentations being ALI compared to 0/14 (0%) in the established cancer group, 4/16 (25.0%) in patients with historic cancers, and 36/220 (16.4%) in the non-cancer group, p=0.006. Acute-on-chronic CLTI was more common in the established cancer group (6/12, 50.0%) than in new cancer (3/12, 25.0%), historic cancer (6/16, 37.5%) and non-cancer (29/220, 13.2%) groups, p<0.001. In contrast, CLTI presentations in the new cancer group were infrequent (1/12, 8.33%) compared to established (5/14, 35.7%), historic (2/16, 12.5%) and non-cancer (94/220, 42.7%) groups, p=0.013. There were no significant differences in rates of diabetic foot sepsis by cancer status.

	New Cancer (12)		Established Cancer (14)		Historic Cancer (16)		Non-cancer (220)		Palliation Group (18)		P value
		%		%		%		%		%	
Age	67.5 [63-75.3]		77.5 [72.5-82]		69 [61-81.3]		70.5 [61-78]		77.5 [68.8-84.5]		**0.003**
Emergency	12	100	13	92.9	13	81.3	184	83.6			0.413
Male	10	83.3	11	78.6	14	87.5	157	71.4	11	61.1	0.410
Coronary Arterial Disease	2	16.7	7	50.0	8	50.0	101	45.9	6	33.3	0.238
Hypertension	6	50.0	12	85.7	10	62.5	164	74.5	5	27.8	**0.097**
Atrial Fibrillation	0	0	2	14.3	2	12.5	44	20.0	3	16.7	0.285
Congestive Cardiac Failure	0	0	2	14.3	0	0	22	10.0	4	22.2	0.207
Hypercholesterolaemia	1	8.33	1	7.1	3	18.8	48	21.8	3	16.7	0.447
Diabetes Mellitus	4	33.3	8	57.1	6	37.5	119	54.1	7	38.9	0.252
Chronic Kidney Disease	2	16.7	4	28.6	5	31.3	70	31.8	2	11.1	0.314
COPD	3	25.0	2	14.3	2	12.5	43	19.5	10	55.6	**0.007**
Stroke	1	8.33	3	21.4	1	6.25	33	15.0	3	16.7	0.754
Smoking History	**6**	50.0	6	42.9	7	43.8	118	53.6	8	44.4	0.815
MFI-5	1 [1-2.25]		2 [2-3]		1.5 [0.75-2]		2 [2-3]		2 [1-2.8]		0.280
Foot Presentation											
ALI	6	50.0	0	0	4	25.0	36	16.4	7	38.9	**0.002**
Acute on Chronic CLTI	3	25.0	7	50.0	6	37.5	29	13.2	6	33.3	**<0.001**
CLTI	1	8.33	5	35.7	2	12.5	94	42.7	2	11.1	**0.002**
Diabetic foot sepsis	2	16.7	2	14.3	4	25.0	60	27.3	3	16.7	0.629

Table 21: MLA patient characteristics by cancer type.

5.2.3.3 Cancer Patients and Vascular Surgery

A variety of cancers were seen among the active cancer patients with some differences in their distribution between new and established cancers (**Table 22**).

The new cancers were predominantly gastrointestinal (4/12, 33.3%) and lung (3/12, 25%). In contrast, the established cancers were mainly haematological (6/14, 42.9%) and urogenital (5/14, 35.7%). All twelve new cancer diagnoses were made within four months of amputation, and half of these were diagnosed in the same admission as the amputation. Duration of cancer diagnoses in the established cancer group ranged from one to eight years.

Four patients had metastases, of which three were in the new cancer group, therefore metastatic at presentation. Seven patients were on chemotherapy, six (85.7%) of which were platinum-based agents. A further three patients were on adjuvant therapy when amputation was performed.

Overall, 14/26 (53.8%) of the active cancer patients had a medical or surgical revascularisation attempt prior to amputation, which comprised of 6/12 (50%) of the new cancer group and 8/14 (57.1%) of the established cancer group (**Table 23**).

As presentations were predominantly acute (ALI and acute-on chronic CLTI) in the new cancer group, revascularisation methods were predominantly thrombolysis and embolectomy. One patient had iloprost infusion in combination with anticoagulation without surgical or endovascular intervention. In contrast, revascularisation methods for the established cancer group were commonly angioplasties, stenting or bypass procedures to manage CLTI. In the newly diagnosed cancer group the diagnoses had been made 1-3 months prior to limb ischaemia and revascularisation in four patients and the remaining two patients were diagnosed with cancer post-revascularisation.

The median time from revascularisation attempt to subsequent amputation was 2.6 [0.5 – 8] weeks in the new cancer group and 5.4 [3 – 16] weeks in established cancer group, p=0.043.

Patient	Cancer Type	Duration of Cancer Diagnosis prior to Amputation	Confirmed Metastasis	On Chemo/Adjuvant Therapy at Time of Amputation
Amputated New Cancer Patients				
1	Bladder[$]	Same admission	No	No
2	Renal	2 months	No	No
3	Adrenal[$]	Same admission	No	No
4	Tongue	1 month	No	Docetaxel, Cisplatin, 5FU
5	Oesophageal	3 months	No	Epirubicin, Cisplatin, Capecitabine
6	Oesophageal	4 months	Yes	Capecitabine
7	Cholangiocarcinoma/Pancreatic[$]	Same admission	Yes	No
8	Lung	1 month	No	Etoposide, Carboside
9	Lung	Same admission-	Yes	Carboplatin, Paclitaxil
10	Lung (Recurrence)[$]	Same admission	No	No
11	Breast	Same admission[*]	No	Tamoxifen^
12	Rectal	4 months	No	Oxaliplatin
Amputated Established Cancer Patients				
1	Multiple myeloma	4 years	No	Cyclophophamide
2	Myelodysplasia	5 years	No	No
3	Myelodysplasia	6 years	No	No
4	Chronic Lymphocytic Leukaemia	4 years	No	No
5	Chronic Lymphocytic Leukaemia	5 years	No	No
6	Thrombocythemia	2 years	No	Anagrelide^
7	Breast	1 year	No	Tamoxifen^
8	Rectal	4 years	Yes	None-slowing growing metastases
9	Hepatic	3 years	No	No
10	Bladder	4 years	No	No
11	Prostate	7 years	No	No
12	Prostate	8 years	No	No
13	Prostate	2 years	No	No
14	Bladder and Supraglottic	2 years	No	No

[$] = Radiological diagnosis only. [*] = Cancer diagnosis made after amputation. ^ = Adjuvant therapeutic agent.

Table 22: Cancer type in new versus established cancer patients undergoing MLA.

Presentation	Recent Limb Salvage Attempt	Vessels Treated	Limb salvage attempt Pre/Post Ca Diagnoses	Time to Amputation in Weeks	Cancer Type	Metastasis	Chemo	Dead/Alive at End of Follow-up	Time from Amputation to Death
				New					
ALI[$]	Iloprost with anticoagulation	5 days of Iloprost 22/12/14	Post (3 months)	3	Oesophageal	No	Yes	Dead	3 months
ALI	Thrombolysis	Femoro-popliteal	Post (1 month)	0.5	Tongue	No	Yes	Alive	4 years
ALI	Embolectomy	Femoral	Post (3 months)	4	Oesophageal	Yes	Yes	Dead	1 month
Acute on Chronic CLTI	Stent	Femoral	Post (1 week)	1	Lung Ca	Yes	Yes	Dead	10 months
CLTI	Bypass	Femoral to Femoral	Pre	2	Lung Ca Recurrence	No	No	Alive	2 years
DFS	Angioplasty	Crural	Pre	8	Renal	No	No	Dead	8 months
				Established					
CLTI	Angioplasty	Femoral		3	Thrombocythemia	No	Yes	Dead	8 months
CLTI	Angioplasty	Femoral		5	Breast	No	Yes	Dead	3 months
CLTI	Angioplasty	Femoro-popliteal		16	Prostate	No	No	Dead	12 months
DFS	Angioplasty	Crural		3	Hepatic	No	No	Dead	2.5 years
CLTI	Stent	External Iliac		4	Multiple myeloma	No	Yes	Alive	5 years
CLTI	Bypass	Femoral to Peroneal		12	Prostate Ca	No	No	Alive	3 years
CLTI	Bypass	External Iliac to Popliteal		4	Bladder and Supraglottic	No	No	Dead	1 month
CLTI	Angioplasty	Femoral to Popliteal		16	Rectal Ca	Yes	No	Dead	1 year

Table 23: Revascularisation attempts in the new and established cancer patients undergoing MLA.

5.2.3.4 Palliation Subgroup

In the same study period, 18 patients with active cancer received palliation instead of amputation for their unsalvageable limb (**Table 21**). Their age and frailty scores were similar to the amputation group with established cancers. The palliated group had a significantly higher rate of chronic obstructive pulmonary disease (10/18, 55.6%) compared to the MLA groups, where rates ranged from 12.5 to 25.0%, p=0.008. Compared to the MLA subgroups, a higher rate of congestive cardiac failure was also seen in the palliation group, although not statistically significant. The most common foot presentations in the palliation group were ALI (7/19, 38.9%) and acute-on-chronic CLTI (6/18, 33.3%), a similar pattern to that seen in the MLA group with new cancers.

Lung cancer was the most common cancer type in the palliated group (6/18, 33.3%), another similarity with the amputated group with new cancers (**Table 24**). The rate of metastatic disease was high (9/18, 50.0%) and advanced cancer burden was the primary reason for palliation over amputation in 8/18, (44.4%) patients. Only one patient had a revascularisation attempt (an iliac stent).

Palliated Cancer Patients (No Amputation)					
Patient	Cancer Type, Reason for Palliation	Duration of Cancer Diagnosis prior to Palliation	Revascularisation Attempt	Metastasis	On Chemo/Adjuvant Therapy
1	Lung (Recurrence). Reason: advanced Ca.	5 years	No	Yes	No
2	Lung. Reason: advanced Ca and frail.	1 year	No	Yes	No
3	Lung. Reason Frail.	New	No	No	No
4	Lung. Reason: Frail.	New	No	No	Carboplatin
5	Lung. Reason: frail.	3 years	No	No	No
6	Lung. Reason: advanced Ca and frail.	1 year	No	Yes	Carboplatin, Etoposide
7	Lung. Reason: frail.	New	No	Yes	No
8	Melanoma. Reason: frail.	5 years	Iliac Stent	No	No
9	Melanoma. Reason: advanced Ca	1 year	No	Yes	Ipilinumab
10	Chronic Lymphocytic Leukaemia. Reason: not fit.	10 years	No	No	No
11	Myelodysplasia. Reason Frail.	6 years	No	No	No
12	Colon: Reason: advanced Ca	3 years	No	Yes	No
13	Colon. Reason. Reason: Frail.	8 years	No	No	No
14	Prostate. Reason: Frail.	10 years	No	No	No
15	Bladder. Reason: advanced Ca and frail.	New	No	Yes	No
16	Vulva. Reason: advanced Ca.	2 years	No	Yes	No
17	Renal. Reason: Frail.	New	No	No	No
18	Unknown Primary. Reason: Advanced Ca.	3 years	No	Yes	No

Table 24: Characterisation of cancer in patients receiving palliation for unsalvageable limbs.

5.2.3.5 All-cause Mortality

Cumulative mortality rates were higher for the new and established cancer groups compared to historic cancer and non-cancer groups (**Table 25**). The difference became statistically significant at 12 months at which point mortality rates were 50.0% for new cancer and 28.6% for established cancer groups in contrast to 18.8% for historic and 17.9% for non-cancer patients, p=0.005. In contrast, all patients in the palliation group, died within three months after commencement of palliation with the majority (70.6%) dying in the first month.

	New Cancer (12)		Established Cancer (14)		Historic Cancer (16)		Non-cancer (220)		Palliation (18)		P value
		%		%		%		%		%	
					Cumulative Mortality						
1-month	0	0	0	0	1	6.25	13	5.91	12	70.6	0.675
2-month	0	0	1	7.14	2	12.5	20	9.09	12	70.6	0.621
3-month	2	16.7	1	7.14	2	12.5	26	11.9	18	100	0.719
6-month	3	25.0	2	14.3	2	12.5	31	14.2			0.467
9-month	4	33.3	3	21.4	2	12.5	37	17.0			0.196
12-month	6	50.0	4	28.6	3	18.8	39	17.9			**0.003**
24-Month	7	58.3	6	42.9	3	18.8	54	24.8			**0.002**
36-Month	8	66.7	9	64.3	3	18.8	68	31.2			**<0.001**

Table 25: Cumulative all-cause mortality for MLA patients by cancer status.

5.2.3.6 Survival by Cancer Status

Kaplan-Meier survival analysis (**Figure 16**) demonstrated that the median survival post-amputation for new vs. established cancer and new cancers were 11.7 and 20.9 months respectively ($p<0.001$). In contrast, non-cancer patients survived a median of 65.8 months after amputation. The palliation group survived 0.5 months.

Patients with metastases had a shorter median survival (11.4 months) compared to active cancer patients with no metastasis (20.9 months), $p=0.069$ (**Figure 17**).

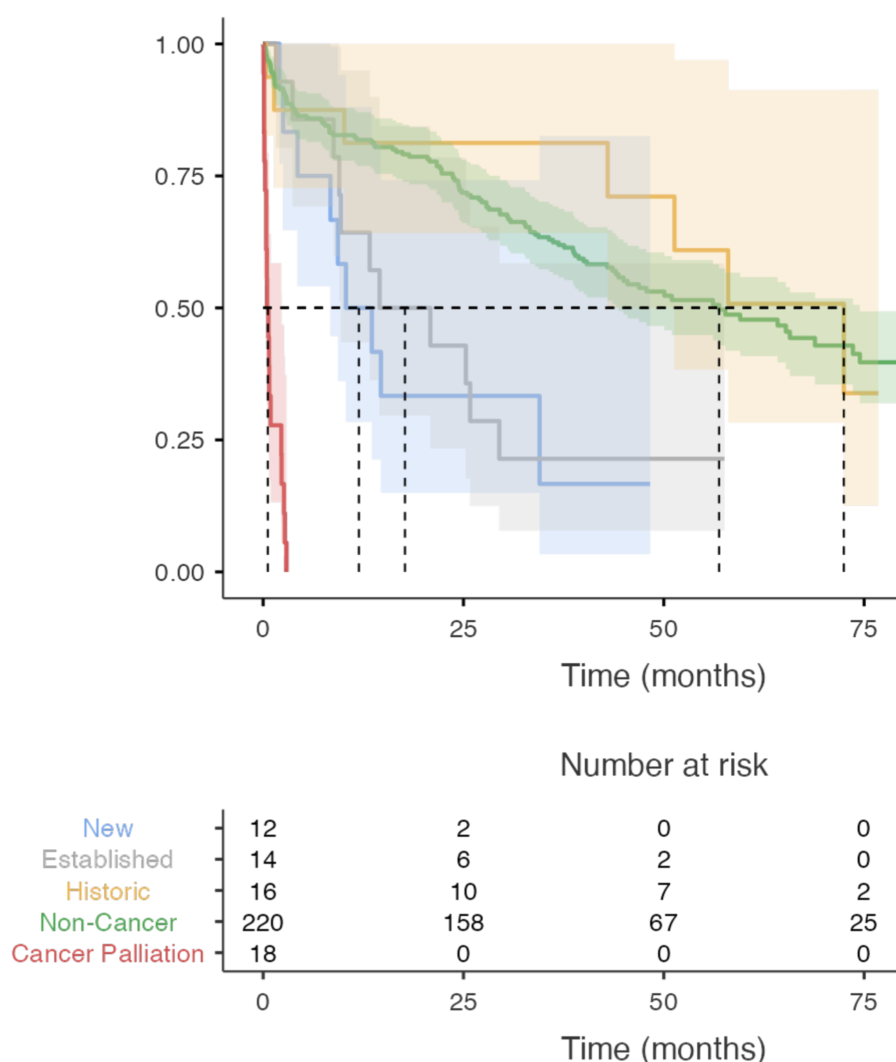

Figure 16: Kaplan-Meier survival analysis for MLA and palliation patients by cancer status.

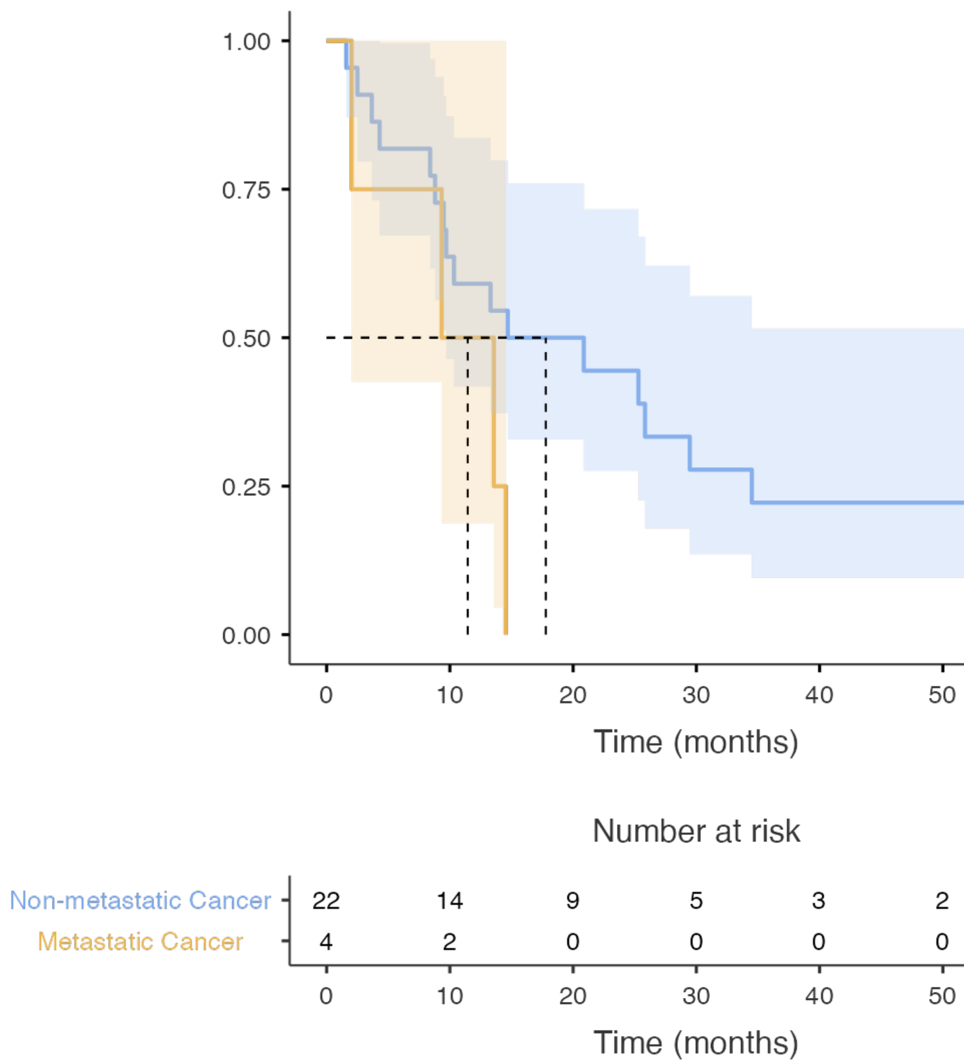

Figure 17: Kaplan-Meier survival analysis for MLA patients by metastasis status.

5.2.3.7 Post-operative Complications

Overall, the rate of complications was similar when compared by cancer status; 5/12 (41.7%) in new, 5/14 (35.7%) in established, 5/16 (31.3%) in historic and 90/220 (40.9%) in the non-cancer groups, p=0.812. Gastro-intestinal bleeding complications were only observed in new cancer patients and although statistically significant, the numbers were low (three patients). The primary lesion in these new cancers were renal, lung and breast.

Stump wound complications were seen more frequently in established (4/14, 28.6%) compared to new (1/12, 8.33%), historic (0%) and non-cancer (22/220, 10.0%) patients, p=0.073. In the follow-up period, stump revision surgery was performed in a total of 24 patients with no significant difference in rates by cancer status. Similarly, a total of 22/262 (8.40%) patients had contralateral MLA with no differences seen by cancer status (**Table 26**).

	New Cancer (12)		Established Cancer (14)		Historic Cancer (16)		Non-cancer (220)		P value
		%		%		%		%	
Amputation Level									
BKA	7	58.3	4	28.6	8	50	115	52.3	0.358
AKA	5	41.7	10	71.4	8	70	105	47.7	
Post-amputation Complications									
Any Complications	5	41.7	5	35.7	5	31.3	90	40.9	0.812
Died in Hospital	0	0	1	7.14	2	12.5	11	5.00	0.315
Cardiac	0	0	0	0	0	0	9	4.09	0.619
Pulmonary	2	16.7	1	7.14	1	6.25	10	4.45	0.329
Renal	0	0	0	0	1	6.25	8	3.63	0.721
Gastro-intestinal	3	25.0	0	0	0	0	7	3.18	**0.001**
Stroke	0	0	0	0	1	6.25	3	1.36	0.421
Delirium	0	0	1	7.14	0	0	4	1.82	0.457
Psychiatric	0	0	1	7.14	0	0	2	0.909	0.181
Stump Wound	1	8.33	4	28.6	0	0	22	10.0	0.073
Stump Revision	0	0	1	7.14	0	0	23	10.5	0.987
Contralateral Limb Loss	1	8.33	1	7.14	1	6.25	19	8.64	0.343

Table 26: Post-MLA complications compared by cancer status.

5.2.3.8 Length of Stay, Rehabilitation Status and Destination of Discharge

Median LOS was longer for new [30 (19.3-48.8) days] and established cancer [33.5 (19.5-39.8) days] patients compared to historic [26 (16.3-43) days] and non-cancer [26 (16-38.5 days] patients, p=0.847 (**Table 27**). A total of 14/262 (5.34%) patients died in the same admission after MLA, with no statistical differences compared by cancer status. Rehabilitation was commenced at discharge for a total of 151/262 (57.6%) patients, with a significantly lower proportion seen in the established-cancer group (2/14, 14.2%) compared to new-cancer (6/12, 50.0%), historic (12/16, 75.0%) and no-cancer groups (131/220, 59.5%), p=0.003. Delays to commencement of rehabilitation (due to medical or wound complications) were seen more frequently in cancer patients, in particularly the new cancer group.

A significantly higher proportion of established cancer patients (9/14, 64.3%) were deemed unsuitable for rehabilitation after amputation compared to new (1/12, 8.33%), historic (2/16, 12.5%) and non-cancer (19/220, 8.64%) groups, p<0.001. There was variation in destination of discharge, with a greater proportion of established-cancer patients (4/14, 28.6%) going to a nursing home compared to new (0%), historic (0%) and non-cancer group (10/220, 4.54%), p=0.013.

Length of Stay	New Cancer (12)	%	Established Cancer (14)	%	Historic Cancer (16)	%	Non-cancer (220)	%	P value
Pre-amputation	7.5 [2.75-12.6]		7 [1.25-12.8]		3 [1.75-12]		5 [2-13]		0.854
Post-amputation	23 [11.8-30.8]		20 [12-34.5]		23.5 [14-29]		17 [10-27]		0.682
Total Stay	30 [19.3-48.8]		33.5 [19.5-39.8]		26 [16.3-43]		26 [16-38.5]		0.847
Rehabilitation Status at Discharge post-amputation									
Rehabilitation commenced	6	50.0	2	14.3	12	75.0	131	59.5	**0.004**
Rehabilitation delayed	6	50.0	2	14.3	0	0	59	25.2	**0.003**
Medical-related	5	41.7	0	0	0	0	41	18.6	**0.010**
Wound-related	0	0	2	14.3	0	0	18	8.18	0.350
Unsuitable for Rehabilitation	1	8.33	9	64.3	2	12.5	19	8.64	**<0.001**
Died in Hospital	0	0	1	7.14	2	12.5	11	5.00	0.315
Destination of Discharge									
Home	6	50.0	4	28.6	3	18.8	56	25.5	0.255
Nursing Home	0	0	4	28.6	0	0	10	4.54	**<0.001**
Rehabilitation Centre	1	8.33	0	0	5	31.3	23	10.5	**0.036**
Repatriation to Spoke Hospital	5	41.7	5	35.7	6	37.5	120	54.5	0.270

Table 27: LOS, rehabilitation status and destination of discharge post-MLA by cancer status.

5.2.4 Discussion

The aim of this supplementary study was to examine the presentation, underlying factors, and outcomes from patients with cancer and unsalvageable limbs as cancer was strongly associated with poor functional survival in the previous study (Chapter 5.1).

The key findings were that patients with new cancers appeared more likely to present with ALI in the setting of solid organ malignancy. This contrasted with those with more established cancers, which were often haematological, who had deterioration of CLTI. This may be because of the hypercoagulable nature related to some acute malignancies or paraneoplastic syndromes leading to the development of acute limb ischaemia. In some cases, this may have been related to the use of platinum-based chemotherapeutic agents which were commonly observed in patients with a new cancer and ALI patients, and this relationship has previously been suggested (225,226).

The overall outcomes were poor for patients with a malignancy and unsalvageable limb disease, with the median survival being less than a year in those with new cancers, and less than two years in those with more established cancers. Although only four patients had metastatic cancer, the median survival after amputation was approximately half that of those with no metastasis, with all four dying by 14 months.

In successfully treated cancers, patients appeared to revert towards a baseline risk of non-cancer patients with both LOS and mortality rates being equivalent to non-cancer patients. This further supports the concept of hypercoagulability in the setting of active (new or established) cancer patients leading to limb ischaemia that then reverts once a cancer is successfully treated over the longer-term.

One unexpected finding was around the provision of full amputee rehabilitation in patients with active cancer in the context of their overall outcome. There was no difference in the hospital LOS in these two groups (30 days v 33 days). The new cancer group had considerably higher death rates than the established cancer group, approaching double, at every time point until three years post-amputation by which time the rates were similar between the

two groups (66.7 v 64.3% mortality). Conversely, patients with new cancers were far more likely to commence rehabilitation immediately (50%), or after a short delay (41.7%), than patients with established cancers in whom 64.3% were deemed unsuitable for rehabilitation. Half of these were discharged from hospital to a nursing home. In the new cancer group only 8.3% were deemed unsuitable for rehabilitation, and 50% were discharged directly home, yet had a median survival of under a year. It is apparent that a greater level of understanding is required on this point as, with 60% of patients with established cancer living for two years or more after amputation, it may be that some patients are not benefitting from the full range of rehabilitation services, and some patients with active cancer may be being referred for rehabilitation with unrealistic expectations.

In common with other case series on revascularisation in the face of malignancy (216,220,222,226–228), the results were short-lived in this cohort that required eventual MLA. Revascularisation was attempted in 14/26 cancer patients in our study. Median time to amputation after the revascularisation attempt was 5.4 weeks in the established cancer group and 2.6 weeks in new cancer group. A more detailed study is required to determine the overall current success levels of revascularisation in patients with limb threatening ischaemia with active new or established cancers, and to determine in whom revascularisation should be attempted, who should have a primary amputation, and who may be most suitable for palliation. These data only allow the analysis of the outcomes of some of these patient groups. It was clear that some patients were determined to be unfit for surgery and died within two weeks. Patients with new cancers and limb ischaemia had a median survival of under a year, roughly half that of those with more established malignancies.

The potential for clinician bias is present in this study because decisions around revascularisation, amputation and palliation are likely to be surgeon dependent, and this emphasises the importance of a functioning MDT in making these decisions. It is suggested that in the face of malignancy this team is expanded to include the input of oncologists, palliative care, and rehabilitation clinicians to individualise decisions for patients.

The main limitation of this study was the number of patients in the cancer groups, and this group consisted of a wide variety of cancers. This challenge is consistent with other studies,

all of which are single institutional studies. Despite this, the key messages in this study broaden the current evidence base by approaching the issue of limb ischaemia and amputation from the perspective of patients undergoing MLA rather than those presenting with limb ischaemia. Ultimately a key decision to amputate or palliate must be made in every patient if measures to restore or maintain limb perfusion fail. These data begin to provide a framework to support such decision-making by understanding the longer-term outcomes and functional results.

Chapter 6: Prosthetic mobility after major amputation

6.1 Introduction

Patients with unsalvageable limb disease secondary to ischaemia or diabetes face uncertainty over their functional outcomes. Typically less than half of patients undergoing MLA maintain a satisfactory level of mobility and independence (229–233) and poor mobility has been shown to be the main determinant in the poor quality of life reported by amputees (32,234). Therefore, being able to predict mobility is clinically relevant for appropriate procedural consent and shared decision-making.

A recent systematic review on predictive tools in amputation surgery identified only two tools for prediction of mobility after MLA (79). Clinically useful prediction tools such as the Blatchford Allman Russel Tool (BLART) and the AMPREDICT tools reporting high levels of model discrimination have certain limitations (26,235). Both tools predict mobility at one year, by which time up to a fifth of their study populations were no longer alive. The BLART tool included non-vascular aetiologies of limb loss who are likely to be a younger and healthier population group, thus limiting the specificity of the model for vascular patients. The AMPREDICT tool included trans-metatarsal amputees, a very different amputee group in comparison to higher-level amputees. Moreover, neither model account for the patient group failing functional survival, a parameter of outcome described in Chapters 5.1 and 5.2. Such idiosyncrasies of datasets, together with the large number of predictor variables included in their regression models lead to overfitting of models and loss of their generalisability.

The primary aim of this study was to find predictors of independent prosthetic mobility which would then be used in the construction of a prediction model for this functional outcome (addressing the limitations of the models above) achieved after rehabilitation in a vascular cohort of MLA patients. The Special Interest Group in Amputation Medicine (SIGAM) score was used as a basis for this model due to a good test-retest reliability (97,236). Other parameters of mobility were also analysed, including timed-up-and-go (TUG) and 2-minute distance, which served as supplementary steps for predicting mobility and assessing the criterion validity of the variables included in the dichotomised SIGAM prediction model, which are discussed in Chapter 8. A secondary aim was to confirm if independent prosthetic mobility was a surrogate marker of long-term survival.

6.2 Methods

The methods of this experimental chapter are described in Chapter 2. In brief, a retrospective analysis of prospectively collected data was performed to identify predictors of independent prosthetic mobility.

6.3 Results

6.3.1 Patient Characteristics

The baseline characteristics of the study population by SIGAM grade at end of the active therapy period is described in **Table 28**. There were 807 amputations, of which 36 (4.5%) were excluded as they were simultaneous bilateral procedures. This left 771 patients undergoing rehabilitation for unilateral MLA for analysis.

The majority (582/771, 75.5%) of patients were aged under 75 years, and the male to female ratio was approximately 3:1. Most (474/771, 61.5%) MLAs were BKAs, with TKAs constituting a small fraction (33/771, 4.3%) and the rest (263/771, 34.1%) being AKAs. Six (0.8%) of patients had a revision of a BKA to an AKA. The weight of the patients varied between 33.0kg to 160kg, with a mean of 77.0 (SD 19.3) kg. However, it is important to note that these were post-MLA weights.

The study population demonstrated a high burden of cardiovascular disease, with 414/771 (53.7%) having PAD, 485/771 (62.9%) having DM and 398/771 (51.6%) having hypertension. Cardiopulmonary disease was prevalent with 249/771 (32.3%) having ischaemic heart disease, 107/771 (13.9%) having atrial fibrillation, 66/771 (8.6%) having congestive cardiac failure and 119/771 (15.4%) having chronic obstructive pulmonary disease. Cerebrovascular disease was also common, with 107/771 (13.9%) having had a previous stroke.

Renal failure was not prevalent, with only 120/771 (15.6%) having chronic kidney disease of any severity and only 33/771 (4.3%) having end-stage renal failure. Moreover, small numbers of patients had an active malignancy (48/771, 6.2%) or cognitive impairment (19/771, 2.5%).

A large number (230/771, 29.8%) of patients had a prior history of a psychiatric problem. Area derivation deciles ranged from 1-10 with a mean decile of 6.9 (SD 2.4).

	Total (N=771)	Independent SIGAM D-F (N=385)	Dependent SIGAM A-C (N=386)	OR 95% CI for Independent Mobility	Test statistic p value
Age Over 75	189 (24.5%)	46 (11.9%)	143 (37.0%)	0.231 [0.159-0.334]	**< 0.001[1]**
Sex					**< 0.001[1]**
Female	180 (23.3%)	49 (12.7%)	131 (33.9%)	0.284 [0.197-0.409]	
Male	591 (76.7%)	336 (87.3%)	255 (66.1%)	3.52 [2.44-5.08]	
AKA	263 (34.1%)	77 (20.0%)	186 (48.2%)	0.273 [0.199-0.376]	**< 0.001[1]**
TKA	33 (4.28%)	14 (3.64%)	19 (4.92%)	0.729 [0.360-1.48]	0.378[1]
BKA	474 (61.5%)	293 (76.1%)	181 (46.9%)	3.61 [2.65-4.91]	**< 0.001[1]**
Revision	6 (0.778%)	0 (0%)	6 (1.55%)	0.076 [0.004-1.35]	**0.014[1]**
Peripheral Arterial Disease	414 (53.7%)	188 (48.8%)	226 (58.5%)	0.676 [0.508-0.898]	**0.007[1]**
Diabetes Mellitus	485 (62.9%)	261 (67.8%)	224 (58.0%)	1.52 [1.13-2.04]	**0.005[1]**
Hypertension	398 (51.6%)	189 (49.1%)	209 (54.1%)	0.817 [0.615-1.08]	0.160[1]
Ischaemic Heart Disease	249 (32.3%)	111 (28.8%)	138 (35.8%)	0.728 [0.538-0.986]	**0.040[1]**
Atrial Fibrillation	107 (13.9%)	44 (11.4%)	63 (16.3%)	0.662 [0.437-1.00]	**0.049[1]**
Congestive Cardiac Failure	66 (8.56%)	27 (7.01%)	39 (10.1%)	0.671 [0.402-1.12]	0.125[1]
Cerebrovascular Disease	107 (13.9%)	34 (8.83%)	73 (18.9%)	0.415 [0.269-0.641]	**< 0.001[1]**
Chronic Kidney Disease	120 (15.6%)	49 (12.7%)	71 (18.4%)	0.647 [0.436-0.961]	**0.030[1]**
ESRF	33 (4.28%)	11 (2.86%)	22 (5.70%)	0.487 [0.233-1.02]	**0.051[1]**
Chronic Obstructive Pulmonary Disease	119 (15.4%)	55 (14.3%)	64 (16.6%)	0.839 [0.567-1.24]	0.378[1]
Active Smoking	200 (25.9%)	96 (24.9%)	104 (26.9%)	0.901 [0.653-1.24]	0.525[1]
Active Malignancy	48 (6.23%)	17 (4.42%)	31 (8.03%)	0.529 [0.288-0.973]	**0.038[1]**
Cognitive Impairment	19 (2.46%)	4 (1.04%)	15 (3.89%)	0.260 [0.085-0.790]	**0.011[1]**
Psychiatric History	230 (29.8%)	113 (29.4%)	117 (30.3%)	0.955 [0.702-1.30]	0.771[1]
Weight post-MLA					**0.002[2]**
Mean (SD)	77.0 (19.3)	79.9 (18.5)	73.5 (19.8)		
Range	33.0 - 160.0	42.0 - 160.0	33.0 - 138.0		
Index of Multiple Deprivation Decile					0.565[2]
Mean (SD)	6.9 (2.4)	6.9 (2.3)	6.8 (2.5)		
Range	1.0 - 10.0	1.0 - 10.0	1.0 - 10.0		

1=Pearson's Chi-squared test, 2=Linear Model ANOVA

Table 28: Characteristics of MLA rehabilitation patients by prosthetic mobility.

6.3.2 Therapy-related Variables

Therapy-related factors by SIGAM grade at end of therapy are described in **Table 29**. Common medications among all patients were statins (499/771, 64.7%), antihypertensives (240/771, 31.1%) and antiplatelet agents such as aspirin (326/771, 42.3%) and clopidogrel (200/771, 25.9%). Anticoagulation medications were also prevalent with 79/771 (10.2%) being on Warfarin and 74/771 (9.6%) being on a NOAC or a DOAC. Among the diabetic patients, 230/485 (47.4%) were on an oral antidiabetic medication and 235/485 (48.5%) were on insulin. Antidepressant use was also high, with 229/771 (29.7%) being on a single or multiple agents.

The ratio of outpatient to inpatient therapy was approximately 3:2. The wait for therapy from time of amputation ranged between 0-42.3 months, with a mean of 3.0 [SD 3.4] months. The majority (521, 67.6%) of patients reported good EWA engagement in the period between amputation and therapy commencement.

The vast majority (712/771, 92.3%) of patients were compliant with prosthesis training during their rehabilitation. Prosthetic types varied depending on MLA level and other factors. Prosthetic use was significantly more frequent among below knee amputees 452/474 (95.4%) compared to through knee 29/33 (87.9%), above knee 231/264 (87.5%) and bilateral amputees 31/36 (86.1%), $p<0.001$.

The duration of therapy ranged between 0-8.1 months with a mean of 1.5 (SD 0.9) months. The mean number of physiotherapy sessions varied greatly between 1-117 sessions with a mean of 22.9 (SD 13.1) sessions. Distance from place of residence to rehabilitation centre also varied greatly [1.3-419.7km, with a mean of 35.5 (SD 37.8)] because the centre accepts national as well as regional referrals.

	Total (N=771)	Independent SIGAM D-F (N=385)	Dependent SIGAM A-C (N=386)	OR 95% CI for Independent Mobility	Test statistic p value
Antihypertensives	240 (31.1%)	125 (32.5%)	115 (29.8%)	1.13 [0.835-1.54]	0.423[1]
Statin	499 (64.7%)	265 (68.8%)	234 (60.6%)	1.43 [1.07-1.93]	**0.017[1]**
Aspirin	326 (42.3%)	164 (42.6%)	162 (42.0%)	1.03 [0.771-1.37]	0.860[1]
Clopidogrel	200 (25.9%)	101 (26.2%)	99 (25.6%)	1.03 [0.747-1.42]	0.853[1]
Warfarin	79 (10.2%)	37 (9.61%)	42 (10.9%)	0.871 [0.546-1.39]	0.561[1]
NOAC/DOAC	74 (9.60%)	36 (9.35%)	38 (9.84%)	0.945 [0.585-1.53]	0.816[1]
Oral DM Medication	230 (47.4%)	118 (45.2%)	112 (50.0%)	0.825 [0.577-1.18]	0.292[1]
Insulin	235 (48.5%)	134 (51.3%)	101 (45.1%)	1.28 [0.898-1.84]	0.170[1]
Antidepressant	229 (29.7%)	119 (30.9%)	110 (28.5%)	1.12 [0.824-1.53]	0.464[1]
Place of Therapy					**0.029[1]**
Inpatient	295 (38.3%)	162 (42.1%)	133 (34.5%)	1.38 [1.03-1.85]	
Outpatient	476 (61.7%)	223 (57.9%)	253 (65.5%)	0.724 [0.541-0.969]	
Early Walking Aid Use Prior to Therapy	521 (67.6%)	309 (80.3%)	212 (54.9%)	3.34 [2.42-4.60]	**< 0.001[1]**
Prothesis Use During Rehabilitation	712 (92.3%)	381 (99.0%)	331 (85.8%)	15.8 [5.68-44.1]	**< 0.001[1]**
Distance to Therapy (km)					**0.065[2]**
Mean (SD)	35.5 (37.8)	38.1 (41.5)	33.0 (33.7)		
Range	1.3 - 419.7	1.4 - 419.7	1.3 - 355.1		
Time to Therapy (months)					**< 0.001[2]**
Mean (SD)	3.0 (3.4)	2.3 (2.4)	3.6 (4.0)		
Range	0.0 - 42.3	0.0 - 32.0	0.0 - 42.3		
Therapy Duration (Months)					**0.016[2]**
Mean (SD)	1.5 (0.9)	1.4 (0.8)	1.5 (0.9)		
Range	0.0 - 8.1	0.2 - 8.1	0.0 - 6.3		
Physiotherapy Sessions					0.339[2]
Mean (SD)	22.9 (13.1)	23.3 (11.1)	22.4 (14.8)		
Range	1.0 - 117.0	4.0 - 77.0	1.0 - 117.0		
Physiotherapy Sessions per Month					**< 0.001[2]**
Mean (SD)	16.3 (5.3)	17.7 (4.5)	14.9 (5.7)		
Range	1.3 - 38.6	1.8 - 38.6	1.3 - 37.5		
Suspension Type					**< 0.001[1]**
Auxiliary	396 (51.6%)	157 (40.8%)	239 (62.4%)		
External Sleeve	242 (31.5%)	182 (47.3%)	60 (15.7%)		
None	59 (7.65%)	4 (1.04%)	55 (14.4%)		
Other	71 (9.21%)	42 (10.9%)	29 (7.51%)		

1= Pearson's Chi-squared test, 2= Linear Model ANOVA

Table 29: Medical and therapy factors for MLA rehabilitation patients by prosthetic mobility.

6.3.3 Rehabilitation Outcomes

Therapy outcomes by SIGAM grade are presented in **Figure 18**. No amputee achieved normal SIGAM mobility (grade F) at end of active therapy. The most common grade was D (387/771, 49.0%), followed by C (270/771, 35.0%), A (84/771, 10.9%), B (32/771, 4.2%) and E (7/771, 0.9%), respectively. When dichotomised, the rates of good (grades D-F) and poor (grades A-C) mobilisers were 49.9% and 50.1%, respectively.

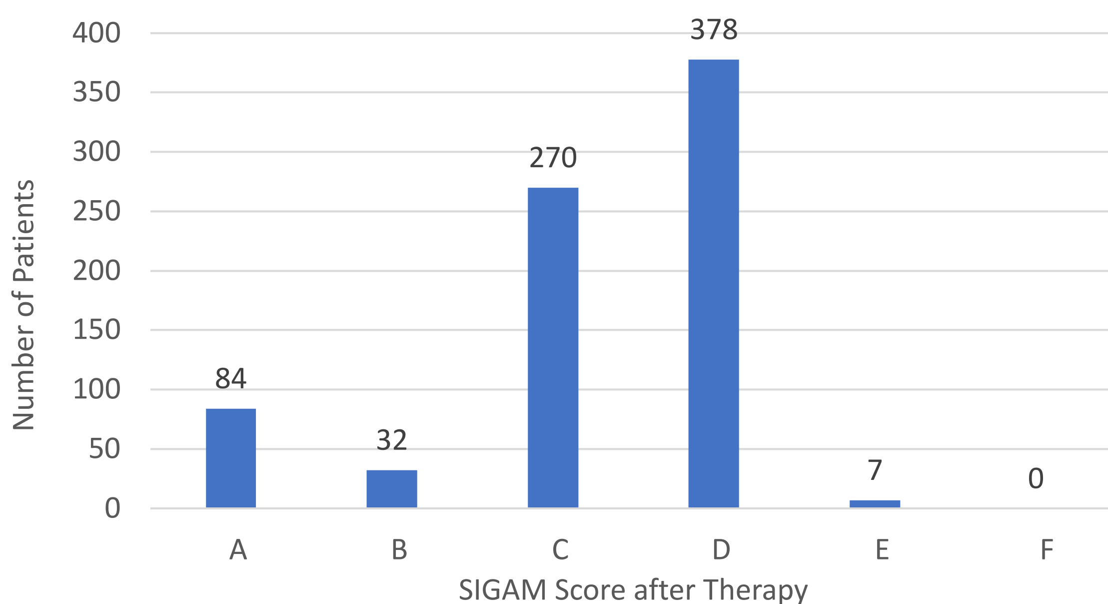

Figure 18: SIGAM scores after rehabilitation therapy.

TUG time, 2-minute distance, follow-up compliance and death during rehabilitation are reported in **Table 30**. The mean TUG time was 30.6 [SD 20.5] seconds and mean 2-minute distance was 63.7 [SD 33.0] meters. A total of 42 (5.4%) patients died during the six-month rehabilitation follow-up period after the end of active therapy. Death was more commonly recorded among dependent mobilisers (32/386, 8.29%) compared to independent mobilisers (10/385, 2.60%), $p<0.001$.

Non-compliance with follow-up in the rehabilitation clinic was high after the active therapy period. Of those who remained alive during rehabilitation clinic follow-up, only 296/771

(38.4%) attended both follow-up appointments, while 298/771 (38.7%) missed one follow-up and 176/771 (22.9%) missed both follow-up appointments. Non-compliance was significantly worse in the dependent mobiliser group with 118/386 (30.6%) of dependent mobilisers missing both clinic follow-up appointments compared to only 58/385 (15.1%) of independent mobilisers, p<0.001.

	Total (N=771)	Independent SIGAM D-F (N=385)	Dependent SIGAM A-C (N=386)	OR 95% CI for Independent Mobility	Test statistic p value
TUG Time (seconds)					**< 0.001[2]**
Mean (SD)	30.6 (20.5)	19.3 (8.0)	47.1 (22.0)		
Range	6.8 - 152.0	6.8 - 51.8	10.5 - 152.0		
2-minute Distance (metres)					**< 0.001[2]**
Mean (SD)	63.7 (33.0)	82.0 (27.7)	36.6 (18.6)		
Range	7.7 - 175.0	8.2 - 175.0	7.7 - 145.2		
Follow-up Appointment Compliance					**< 0.001[1]**
Missed none	296 (38.4%)	177 (46.0%)	119 (30.9%)		
Missed one f/u	298 (38.7%)	150 (39.0%)	148 (38.4%)		
Missed both f/u's	176 (22.9%)	58 (15.1%)	118 (30.6%)		
Death During Active Follow-up	42 (5.45%)	10 (2.60%)	32 (8.29%)		**< 0.001[1]**

1= Pearson's Chi-squared test, 2= Linear Model ANOVA

Table 30: Outcomes at six-months after MLA rehabilitation by prosthetic mobility.

6.3.4 Univariate Analyses for Independent Prosthetic Mobility

Predictors of functional outcome on univariate analysis are reported in **Table 28**.

The following variables showed a significant negative association with independent prosthetic mobility (SIGAM D-F): age over 75 years [OR 0.231 95% CI 0.159-0.334, p<0.001], being female [OR 0.284 95% CI 0.197-0.409, p<0.001], AKA [OR 0.273, 95% CI 0.199-0.376, p<0.001], revision surgery [OR 0.076 95% CI 0.004-1.35, p=0.014], PAD [OR 0.676 95% CI 0.508-0.898, p=0.007], DM [OR 1.52 95% CI 1.13-2.04, p=0.005], IHD [OR 0.728 95% CI 0.538-0.986, p=0.040], AF [OR 0.662 95% CI 0.437-1.00, p=0.049], cerebrovascular disease [OR 0.415 95% CI 0.269-0.641, p< 0.001], CKD [OR 0.647 95% CI 0.436-0.96, p=0.030], ESRF [OR 0.487 95% CI 0.233-1.02, p=0.051], active malignancy [OR 0.529 95% CI 0.288-0.973, p=0.038] and cognitive impairment [OR 0.260 95% CI 0.085-0.790, p=0.011]. Post-operative weight was also a significant factor, with independent mobilisers weighing on average approximately 6kg more than dependent mobilisers [p=0.002].

These variables underwent multivariate analysis for variable selection during model construction and validation reported in Chapter 8.

Therapy-related variables also underwent univariate analysis as reported in **Table 29**. These variables were not included in the model construction as only variables that would be known prior to MLA surgery were to be included. Nevertheless, their univariate analyses did shed light into important associations between therapy factors and outcome of rehabilitation.

Negative therapy-related predictors of independent prosthetic mobility were: an absence of statin use [OR 0.697 95% CI 0.518-0.938, p=0.017], receiving outpatient rather than inpatient therapy [OR 0.724 95% CI 0.541-0.969, p=0.029], disengagement with EWA use [OR 0.297 95% CI 0.199-0.391, p<0.001], disengagement with prosthesis use during therapy [OR 0.063 95% CI 0.023-0.176, p<0.001], a longer wait for start of therapy [p<0.001], prolonged therapy duration [p=0.016] and fewer physiotherapy sessions per month [p<0.001].

6.3.5 Univariate Analyses for TUG and 2-minute Walk Tests

Univariable linear regression analyses were performed for TUG (for falls risk) and 2-minute walk tests (for exercise tolerance) are shown in Table 31 and Table 32. It was evident that the patterns of variables which showed a significant association with SIGAM prosthetic mobility, TUG time and 2-minute distance were highly similar. Multivariate analysis for TUG and 2-minute tests are reported in Chapter 8 as part of the criterion validation for the risk prediction model on independent prosthetic mobility as per SIGAM scoring mentioned above.

	TUG time (seconds)			2 Minute distance (metres)		
Variable	Yes	No	p value	Yes	No	p value
Age>75?	39.1 [23.5-53.4]	21.0 [15.0-34.0]	**<0.001**	39.7 [27.0-63.0]	66.7 [40.7-90.9]	**<0.001**
Female?	31.4 [20.5-49.9]	21.3 [15.0-35.9]	**<0.001**	40.0 [27.6-67.5]	65.4 [41.0-90.1]	**<0.001**
Unilateral AKA?	37.8 [27.1-53.9]	18.9 [14.3-28.7]	**<0.001**	38.3 [26.9-54.1]	74.9 [49.8-95.4]	**<0.001**
Unilateral TKA?	35.1 [23.0-51.7]	22.7 [15.8-39.7]	**0.005**	51.3 [29.0-63.0]	60.7 [36.0-86.7]	**0.022**
Unilateral BKA?	18.3 [14.2-27.1]	37.6 [26.0-53.6]	**<0.001**	76.2 [52.0-96.7]	38.8 [27.0-55.9]	**<0.001**
Bilateral?	22.6 [14.4-42.6]	23.0 [15.9-40.8]	0.500	60.2 [34.8-86.9]	59.8 [35.8-85.9]	0.988
Revision to AKA?	99.5 [73.3-126]	23.0 [15.9-40.9]	**0.049**	27.7 [27.7-27.7]	60.0 [35.8-86.3]	0.234
Peripheral arterial disease?	25.9 [17.8-43.3]	20.3 [14.5-35.5]	**<0.001**	53.1 [32.9-78.9]	70.7 [43.9-94.0]	**<0.001**
Diabetes?	21.0 [14.7-35.7]	27.5 [18.5-46.0]	**<0.001**	67.8 [41.2-92.5]	50.0 [31.3-74.5]	**<0.001**
Hypertension?	25.7 [17.0-43.1]	21.2 [15.0-37.2]	**0.003**	56.1 [35.2-80.9]	65.8 [36.3-92.1]	**0.002**
Hyperlipidaemia?	21.1 [15.0-34.2]	23.9 [16.0-42.0]	**0.075**	64.0 [44.6-85.4]	58.2 [34.2-86.2]	**0.099**
Ischaemic heart disease?	27.0 [17.1-45.7]	21.6 [15.3-35.6]	**0.002**	50.8 [33.0-82.6]	63.8 [38.9-87.2]	**0.005**
Atrial fibrillation?	34.0 [20.0-49.9]	21.8 [15.8-37.6]	**<0.001**	47.7 [29.3-76.1]	61.9 [36.7-87.1]	**0.003**
Heart Failure?	31.2 [19.1-51.5]	22.7 [15.8-39.2]	**0.011**	45.7 [27.7-72.6]	61.3 [36.6-86.9]	**0.007**
Cerebrovascular disease?	38.9 [18.6-51.4]	21.8 [15.7-36.6]	**<0.001**	41.3 [29.0-73.5]	62.3 [38.2-87.0]	**<0.001**
Chronic kidney disease?	23.0 [16.7-47.5]	23.1 [15.8-40.4]	0.361	56.0 [32.9-85.0]	60.5 [36.0-86.7]	0.383
Chronic Lung Disease?	25.6 [18.0-44.0]	23.0 [15.6-40.9]	0.120	57.8 [31.1-77.0]	60.5 [36.0-87.2]	**0.047**
Smoker?	23.4 [16.0-42.6]	23.0 [15.8-40.3]	0.295	56.3 [34.5-82.4]	61.1 [36.5-87.2]	0.277
Active malignancy?	27.3 [14.8-40.5]	23.0 [15.9-41.0]	0.803	58.9 [31.6-84.2]	60.2 [35.8-86.1]	0.556
Cognitive impairment?	37.2 [18.8-64.3]	23.0 [15.9-40.8]	0.135	40.2 [22.8-55.8]	60.5 [35.8-86.4]	**0.067**
Excess alcohol?	19.1 [14.6-33.3]	23.5 [16.0-41.3]	**0.088**	69.0 [38.9-88.3]	58.9 [35.6-85.2]	0.265
Psychiatric problem?	21.8 [15.2-36.9]	24.0 [16.0-41.9]	0.258	64.7 [38.1-87.0]	58.8 [35.3-85.1]	0.293
Frailty Score$	0.084 [0.009-0.159]		**0.029**	-0.067 [-0.142-0.009]		**0.086**
Post-amputation Weight$	-0.190 [-0.292--0.084]		**<0.001**	0.262 [0.158-0.360]		**<0.001**

$= Spearman rank correlation

Table 31: Univariate analysis of patient-related variables for TUG time and 2-minute distance.

	TUG time (seconds)			2 Minute distance (metres)		
Variable	Yes	No	p value	Yes	No	p value
Antihypertensive?	22.8 [16.0-40.7]	23.1 [15.9-41.2]	0.960	62.3 [36.4,82.1]	58.2 [35.4,88.0]	0.695
Statin?	21.8 [15.4-38.0]	25.5 [16.8-45.1]	**0.020**	63.2 [38.2,87.0]	55.1 [32.6,81.6]	**0.026**
Aspirin?	23.1 [15.8-37.4]	23.0 [16.0-43.1]	0.694	59.7 [38.2,84.0]	60.1 [34.8,86.6]	0.943
Clopidogrel?	22.8 [16.5-41.4]	23.1 [15.8-40.5]	0.875	63.9 [35.1,84.5]	59.4 [35.8,87.0]	0.870
Warfarin?	28.2 [18.5-44.9]	22.7 [15.6-40.1]	**0.040**	50.8 [32.7,77.2]	60.5 [35.9,87.0]	**0.033**
NOAC/DOAC?	27.8 [16.9-49.3]	22.5 [15.9-39.3]	**0.066**	50.1 [30.9,70.3]	61.9 [35.8,87.0]	**0.025**
Diabetes – Oral?	21.1 [15.3-40.4]	20.1 [14.0-34.9]	**0.098**	63.8 [38.4,87.6]	72.5 [44.5,97.1]	**0.050**
Diabetes – Insulin?	20.0 [14.0-35.6]	22.1 [15.0-37.4]	**0.091**	74.4 [43.1,97.5]	63.5 [39.5,86.2]	**0.038**
Antidepressant?	21.7 [15.5-35.6]	24.6 [16.0-43.2]	0.121	65.2 [39.6,83.7]	58.4 [35.0,87.0]	0.344
Inpatient Therapy?	20.4 [14.3-35.8]	25.1 [17.2-42.8]	**<0.001**	67.7 [38.4,94.9]	56.1 [34.1,80.0]	**0.004**
EWA Engagement?	21.0 [15.0-36.0]	28.5 [19.6-47.3]	**<0.001**	65.1 [39.9,90.0]	47.5 [31.4,75.3]	**<0.001**
DNA	25.0 [16.3-43.6]	21.7 [15.2-35.1]	**0.013**	55.3 [32.5,80.9]	67.8 [42.5,91.7]	**<0.001**
Prosthesis Fitted?	23.1 [15.9-41.1]	18.3 [15.8-24.2]	0.343	59.6 [35.5,86.3]	74.8 [70.3,80.4]	0.325
Deprivation Rank$	0.049 [-0.029,0.126]		0.218	-0.050 [-0.127,0.028]		0.213
Distance (km)$	0.075 [-0.003,0.151]		**0.058**	-0.051 [-0.128,0.026]		0.196
Time to Therapy (months)$	0.232 [0.159,0.302]		**<0.001**	-0.220 [-0.291,-0.220]		**<0.001**
Therapy Duration (months)$	0.142 [0.067,0.216]		**<0.001**	-0.173 [-0.246,-0.098]		**<0.001**
Physiotherapy Sessions (number)$	0.066 [-0.011,0.142]		**0.092**	-0.090 [-0.166,-0.013]		**0.022**
PT Sessions/Month$	-0.183 [-0.257,-0.108]		**<0.001**	0.193 [0.117,0.267]		**<0.001**

$= Spearman rank correlation

Table 32: Univariate analysis of therapy-related variables for TUG time and 2-minute distance.

6.3.6 Survival by Functional Status

The median survival for the entire population was 73.3 [69.1-79.2] months. Comparison of survival by prosthetic function after active rehabilitation confirmed an important difference between the two groups (**Figure 19**). Independent mobilisers (SIGAM D-F) had a median survival of 93.7 [80.7-105.3] months, whereas dependent mobilisers (SIGAM A-C) did significantly worse with a median survival of 56.6 [48.5-66.7] months, p<0.001.

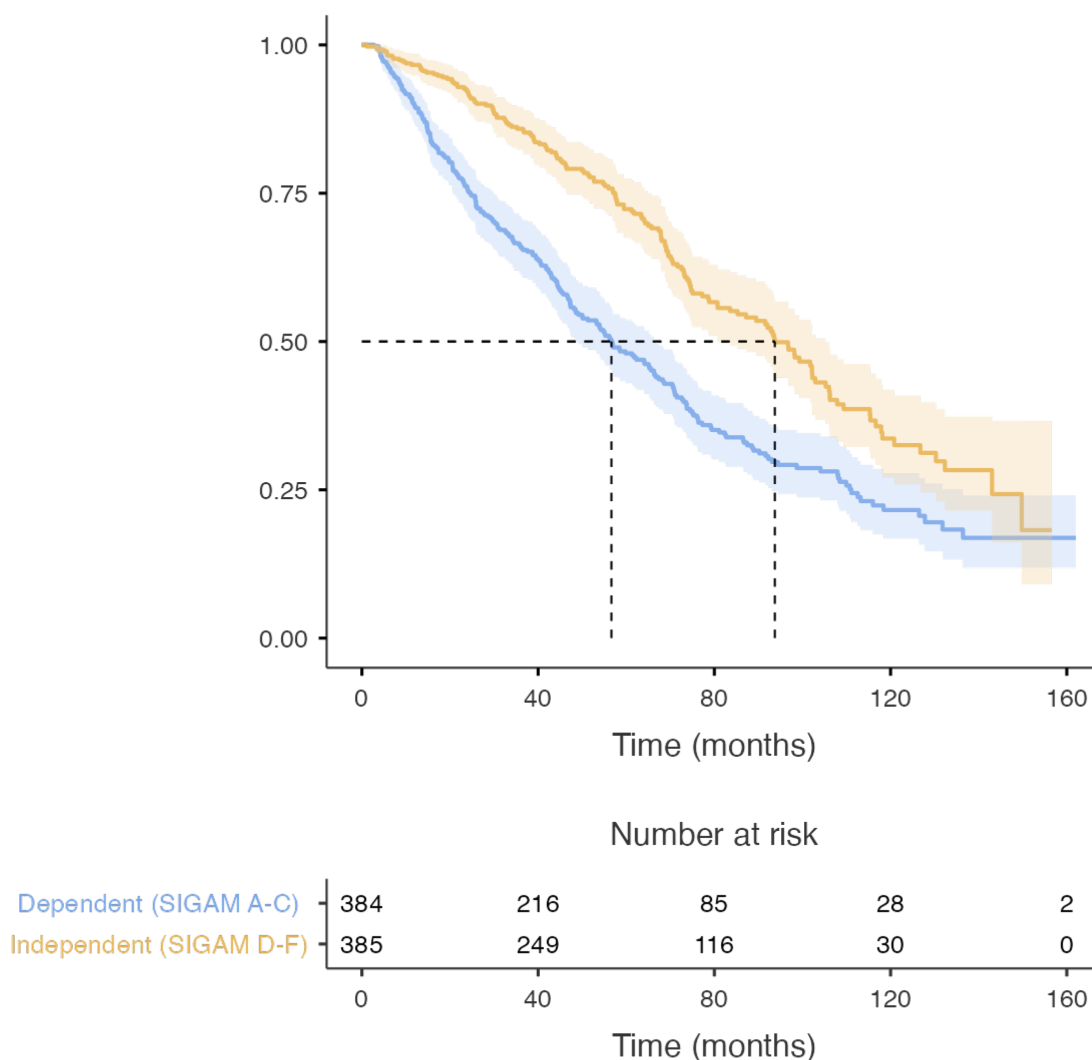

Figure 19: Survival of MLA rehabilitation patients by functional status at end of active therapy.

6.4 Discussion

This study has identified specific patient and therapy-related factors predictive of functional outcome of specialist rehabilitation following MLA.

Overall functional outcomes were poor, with less than half of patients entering the rehabilitation pathway achieving good levels of prosthetic mobility. In chapter 5.1, it was highlighted that only 82.9% of patients who underwent MLA progressed to rehabilitation. Therefore, amputees endure considerable peri-operative mortality, post-operative functional regression and if survive the MLA, go on to have poor prosthetic ambulation rates after specialist rehabilitation. Moreover, rates of non-attendance in follow-up clinics and mortality were significantly higher among poor mobilisers, compounding the challenges of long-term optimisation in this complex patient group.

Due to the heterogeneity in methods for assessing functional outcome in literature, evidence on gender differences in functional outcomes after amputation has not been conclusive. Female patients have been reported as being less likely to be fitted with a prosthesis at discharge than males (237) and less likely to adjust socially to amputation and prosthetic use (238). In contrast, male patients have been shown to perform significantly worse than female patients in a walking test (239). In this study, female patients performed consistently worse in all three parameters of mobility (prosthetic use, dynamic stability, and exercise tolerance).

The impact of prehabilitation on functional outcomes is poorly understood in amputation. A systematic review identified only two studies (a quantitative and a qualitative) on this subject (240). The evidence from this study supports the need for a biopsychosocial model of care in the pre-amputation period. Cardiovascular health was shown to be a predictor of functional outcome in our study, a finding strongly supported in literature (241,242). A potential target for prehabilitation, identified by our study was statin use. The beneficial impact of long term statin use on multiple parameters of functional activity, in patients with PAD, has been previously demonstrated (243).

There was a high prevalence of pre-existing psychiatric problems among our study population. Studies have shown that anxiety increases with social isolation (244) and that patients are more likely to go home after rehabilitation rather than other locations if they have protective sociological factors such as having a partner, less depression, and better mobility (242,245,246). Although it has be suggested that positive affect falls during rehabilitation, a stronger goal pursuit pre-amputation leads to better outcomes (247).

An association between female gender and higher levels of anxiety and depression after lower limb amputation has also been reported (60). This finding and those of previous experimental chapters may explain the gender-related differences in functional performance post-MLA. Furthermore, balance confidence has been shown to be associated with mobility capability and performance and social activity (248,249), offering support for the role of pre-MLA functional optimisation.

Therapy-related variables also proved to be of importance in functional outcomes. To ensure that selection bias was not a factor in superior outcomes, therapy-related variables that were significant on univariate analysis underwent multivariate analysis by adjusting for age, demographics, and comorbidities. Although therapy-related variables were not included in the risk prediction models (Chapter 8), they gave valuable insights into how rehabilitation may be optimised. Multivariate analysis showed that certain therapy-related factors remained independent predictors of SIGAM, TUG and 2-minute tests (**Supplementary Figure 1**).

In-patient specialist rehabilitation was associated with better prosthetic mobility. Post-operative in-patient rehabilitation has been associated with reduced mortality, re-amputation, and improved rates of prosthetic use, medical stability and QoL (250,251). Specialised amputee rehabilitation has also demonstrated superior outcomes of survival, prosthesis use, and home discharge over generalised rehabilitation services, regardless of timing and clinical complexity (214,252,253).

Early walking aid compliance, reduced wait to therapy, greater prosthesis use during therapy and greater intensity of therapy were predictors of outcome after adjustment for patient

characteristics and amputation level. Short peri-operative hospital stays and timely prosthesis fitting have been shown to be associated with better functional outcome and shorter rehabilitation stay (254–256).

The population included this study were patients who were successfully discharged from acute post-operative care and received rehabilitation. Patients who died in the acute post-operative period and a severely comorbid subgroup who were deemed to have no rehabilitation potential were not referred to, or were not accepted into, rehabilitation. This introduces a selection bias to the overall rates of prosthetic use, mobility, and survival, and it is envisaged that the outcomes among an entire amputee cohort would likely be worse than those reported here. To address these limitations, prediction of prosthetic mobility needs to be complemented with the prediction of functional survival as performed in this thesis (Chapter 5.1).

Chapter 7: Palliation for the unsalvageable limb

7.1 Introduction

For completeness, a decision aid for MLA must contain information on the outcomes of non-surgical management of the unsalvageable limb. With an ageing population and rising rates of diabetes, surgeons may be faced with greater incidence of advanced limb ischaemia or DFD requiring either amputation or palliation. Surgery on comorbid patients carries a high risk of peri-operative morbidity and mortality (257). Thirty-day mortality following MLA has been reported to be as high as 17.5% (210). The National Confidential Enquiry into Patient Outcome and Deaths 2014 report on lower limb amputation highlighted the need to make thoughtful decisions against operation for some patients (18).

Good palliative care involves fulfilment of patients' wishes such as dying at home, addressing chronic pain, psychological distress and social problems (258,259). Palliation for unsalvageable limbs is often recommended to patients who refuse an amputation, have poor pre-morbid quality of life or are deemed to be too high an anaesthetic risk (260). However, end-of-life care in this patient group is poorly understood. Transfer of care to the palliative care team ensures that patients receive optimal end-of-life care, but no formal follow-up from the surgeon's perspective leaves the surgeon uncertain about palliative care outcomes. Knowledge on questions such as likely length of survival and place of death are crucial in providing the patient with the adequate information required for decision-making between MLA and palliation.

Understanding the course of palliation in patients with an unsalvageable limb is therefore important in informing the shared decision-making process undertaken by the patient and the MDT to provide the highest standard of humane end-of-life care. This study characterises the end-of-life care in patients who received palliation instead of MLA for an unsalvageable ischaemic limb. Through this process, this experimental chapter aimed to provide vital palliative care outcome data to be incorporated in the decision aid.

7.2 Methods

The methods of this experimental chapter are described in Chapter 2. In brief, this was a cohort study aimed at understanding the fate of patients undergoing palliation for their unsalvageable limb.

7.3 Results

7.3.1 Patient Characteristics

Table 33 describes the characteristics of the palliated population by aetiology of the unsalvageable limb. The median age was 83 [74.3-86.0] years, and the ratio of male to female was 1:1. The rate of DM and known PAD in the study population was high at 42.4% and 54.6%, respectively. Cardiopulmonary comorbidities were prevalent: rates of ischaemic heart disease, congestive cardiac failure, atrial fibrillation, and COPD were 27/66 (40.9%), 19/66 (28.8%), 23/66 (34.8%) and 27/66 (40.9%), respectively. A large proportion of patients (11/66, 16.7%) had a prior history of cognitive impairment, mainly dementia. Active malignancies were prevalent at 18/66 (27.3%).

The median frailty (MFI-5) score was 2 [2-3], with 48.5% of patients being dependent adults prior to their admission. Rates of psychiatric diagnoses and social problems were low, at 5/66 (7.6%) and 14/66 (21.2%), respectively.

During the same admission episode, 16 (24.3%) patients had ipsilateral limb salvage surgery prior to being palliated. They had rest had either a minor amputation (4/66, 6.1%), or a revascularisation attempt (12/66, 18.2%) prior to commencement of their palliation.

Comparison of these variables by aetiology revealed differences. Ischaemic heart disease was more prevalent in acute-on-chronic CLTI (6/9, 66.7%) and CLTI (10/19, 52.6%) patients compared to ALI (8/28, 28.6%) and DFS (3/10, 30.0%) patients, p=0.121. Atrial fibrillation was predictably more common in ALI patients compared to the other aetiologies. Chronic kidney disease was more prevalent in the DFS patient group. Active malignancy was more prevalent in acute presentations of CLTI. Minor amputations were performed most often in DFS patients. Revascularisation was least attempted in ALI patients.

	Total (66)	%	ALI (28)	%	Acute-on-chronic CLTI (9)	%	CLTI (19)	%	DFS (10)	%	p-value
Age	83 [74.3-86.0]		84 [79.5-88]		83 [71-86]		80 [73-84.5]		79 [75.8-85]		0.439
Male	33	50.0	10	35.7	7	77.8	11	57.9	5	50.0	0.136
Diabetes Mellitus	28	42.4	6	21.4	5	55.6	7	36.8	10	100	**<0.001**
Peripheral Arterial Disease	36	54.6	9	32.1	6	66.7	11	57.9	10	100	**0.002**
Ischaemic Heart Disease	27	40.9	8	28.6	6	66.7	10	52.6	3	30.0	0.121
Congestive Cardiac Failure	19	28.8	9	32.1	2	22.2	5	26.3	3	30.0	0.939
Atrial Fibrillation	23	34.8	12	42.9	2	22.2	6	31.6	3	30.0	0.656
Cerebrovascular Disease	14	21.1	5	17.9	2	22.2	4	21.1	3	30.0	0.883
Chronic Obstructive Pulmonary Disease	27	40.9	12	42.9	5	55.6	9	47.4	1	10.0	0.163
Chronic Kidney Disease	14	21.1	6	21.4	1	11.1	3	15.8	4	40.0	0.392
Hypertension	40	60.0	18	64.3	5	55.6	11	57.9	6	60.0	0.957
Hyperlipidaemia	12	18.2	6	21.4	2	22.2	1	5.30	3	30.0	0.338
Contralateral Limb Disease	17	25.8	9	32.1	2	22.2	4	21.1	2	20.0	0.789
Active Malignancy	18	27.3	6	21.4	5	55.6	4	21.1	3	30.0	0.211
Dementia	11	16.7	6	21.4	1	11.1	2	10.5	2	20.0	0.740
mFI-5 Score	2	[2-3]	2	[1-3]	2	[2-3]	2	[2-2.5]	2.5	[2-3]	0.330
Dependent Mobility	32	48.5	13	46.4	3	33.3	9	47.4	7	70.0	0.434
Psychiatric Diagnoses	5	7.60	3	10.7	0	0	1	5.30	1	10.0	0.715
Social Problems	14	21.2	5	17.9	4	44.4	2	10.5	3	30.0	0.183
Index of Multiple Deprivation	7	[5.25-9]	7	[5-9]	8	[6-8]	8	[6-9]	6	[3.75-7.75]	0.498
Pre-palliation Surgery											
None	47	71.2	25	89.3	7	77.8	11	57.9	4	40.0	**0.011**
Minor amputation	4	6.06	0	0	0	0	1	5.26	3	30.0	**0.003**
Revascularisation	12	18.2	3	10.7	2	22.2	5	26.3	2	20.0	0.131

Table 33: Characteristics of palliated patients by aetiology of unsalvageable limb.

Blood results at commencement of palliation are presented in Table 34. Deranged laboratory parameters were very common such as anaemia, leucocytosis, uraemia, low eGFR and elevated CRP. Comparison by aetiology revealed that DFS patients were significantly more anaemic, had a higher platelet count and lower albumin compared to other aetiologies. They also had higher CRP levels although this did not reach statistical significance.

	Total	ALI	Acute-on-chronic CLTI	CLTI	DFS	Difference
Haemoglobin (g/L)	103 [88.3-117]	115 [101-138]	99 [92-117]	100 [88-107]	86.5 [84-92.8]	**0.003**
White Cell Count (10^9/L)	13.6 [9.8-18.9]	13.6 [8.88-18.3]	11.5 [9.6-13.6]	14.3 [10.5-20.3]	15.9 [13.8-22.7]	0.196
Platelets (g/L)	289 [199-430]	238 [148-321]	242 [222-342]	332 [224-466]	395 [314-478]	**0.031**
Sodium (mEq/L)	138 [134-141]	138 [134-140]	137 [133-141]	139 [138-142]	138 [134-141]	0.652
Potassium (mEq/L)	4.65 [4.20-5.10]	4.80 [3.98-5.20]	4.40 [4.30-4.9]	4.30 [4.10-4.95]	4.95 [4.82-5.10]	0.342
Urea (mmol/L)	9.15 [6.43-13.1]	8.45 [6.57-12.4]	8.60 [5.70-11.1]	8.30 [5.60-14.8]	14.1 [8.57-17.3]	0.396
Creatinine mmol/L	95.5 [75.5-150]	95.5 [76.5-137]	90.0 [75.0-107]	90.0 [73.0-123]	144 [96.8-308]	0.349
eGFR (ml/min/1.73 m²)	52 [34.3-60]	48.5 [35.8-60]	60 [56-60]	60.0 [37-60]	35.5 [16-52.5]	0.120
Albumin (g/L)	23.0 [19.0-29.0]	27.0 [22.7-31.0]	26.0 [18.0-31.0]	22.0 [18.3-23.8]	19.5 [16.3-23.8]	**0.012**
C-reactive Protein (mg/L)	111 [39.0-242]	107 [41.5-243]	57.5 [16.5-154]	115 [60-243]	177 [73-282]	0.412

Table 34: Haematological markers of palliated patients by the aetiology of unsalvageable limb.

7.3.2 Length of Stay and Survival

LOS by aetiology is shown in **Table 35.** The median LOS from admission to commencement of palliation was 4 [1-10.5] days, LOS from onset of palliation to death was 14.5 [7-38.5] days and total LOS was 11.5 [5-19] days. Comparison of these time points by aetiology showed that onset of palliation was significantly faster in ALI patients compared to other aetiologies. ALI patients died significantly faster than other aetiologies and total LOS was significantly shorter. These time points for DFS patients were significantly longer than for the other aetiologies.

Time Points (days)	Total	ALI	Acute-on-chronic CLTI	CLTI	DFS	Difference
Admission to Palliation	4.0 [1.00-10.5]	1.0 [0.750-5.25]	3.0 [2.00-17.0]	5.0 [4.00-20.5]	6.5 [2.25-24.3]	**0.005**
Palliation to Death	14.5 [7.00-38.5]	9.5 [3.00-20.3]	14.5 [9.50-38.0]	19.5 [11.0-118]	50.0 [27.0-80.3]	**0.013**
Admission to Death	7.0 [2.00-20.5]	5.50 [2.00-12.8]	5.0 [1.75-17.0]	7.5 [4.25-85.0]	34.5 [7.50-55.0]	0.172
Length of Stay	11.5 [5.00-19.0]	7.5 [3.00-12.3]	12.0 [10.0-17.0]	13.0 [9.00-28.0]	15.5 [12.0-32.0]	**0.013**

Table 35: Time periods for palliation by aetiology of the unsalvageable limb.

When comparing by surgery type, LOS (days) was significantly longer if a minor amputation 13 [11-18.8], a revascularisation 25 [10.8-40.8] or a combination of both procedures 19 [17.5-28] was performed compared to no surgery 10 [4.5-13], p=0.024 (**Figure 21**).

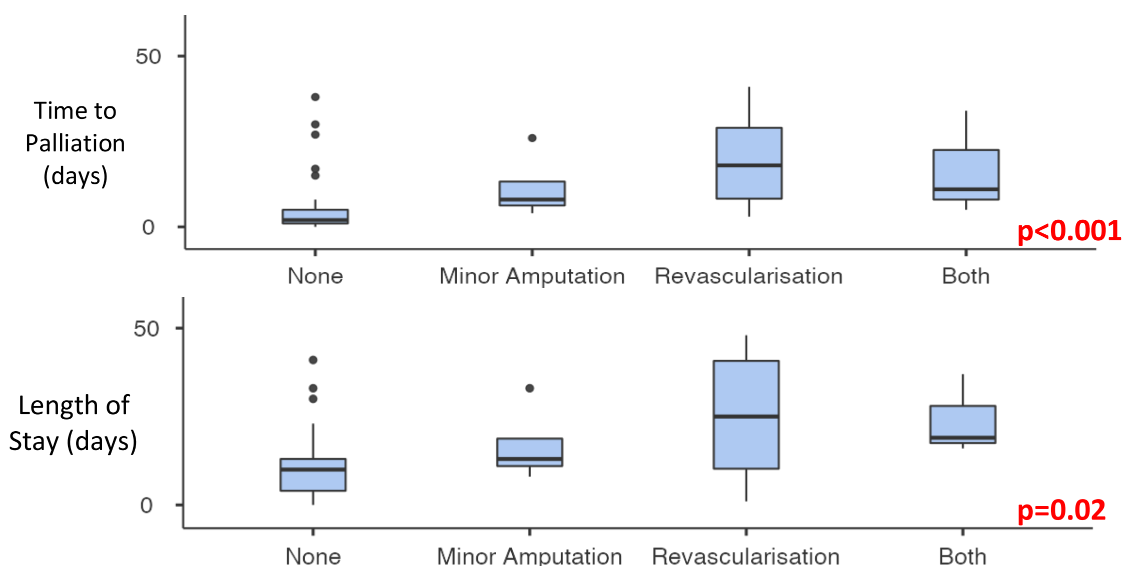

Figure 20: Time to palliation and LOS by type of ipsilateral surgery prior to palliation.

Overall mortality rates at one, two and four weeks were 16/60 (26.7%), 30/30 (50%) and 42/60 (66.7%), respectively. These differences in trends of survival can also be visualised by the Kaplan-Meier analysis in **Figure 20**. Median survival for the entire cohort from time of palliation was seven [2-20.5] days. Six patients (9.09%) survived for longer than three months, of whom three (4.55%) survived longer than one year.

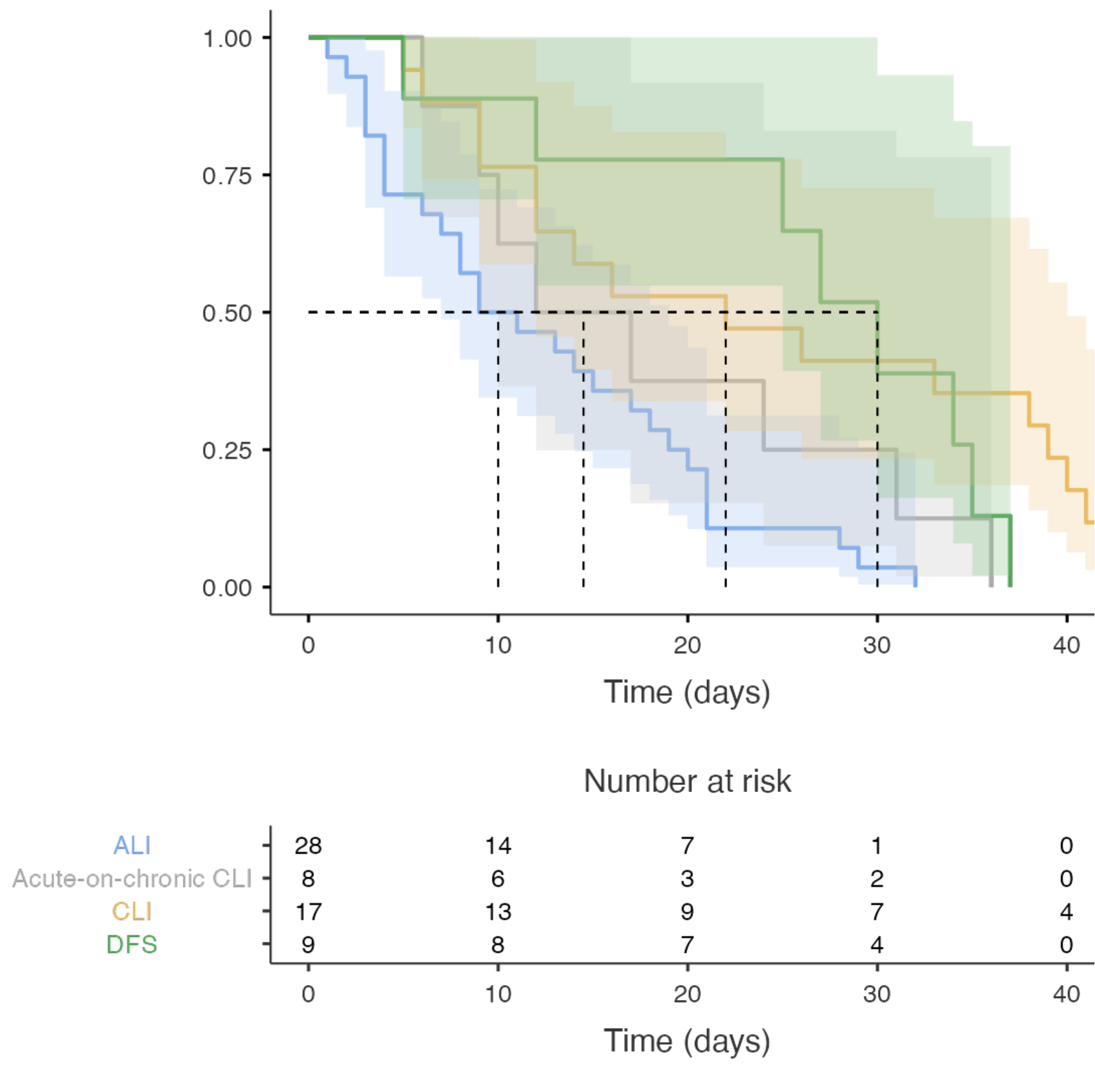

Figure 21: Survival trends of palliated patients by aetiology of the unsalvageable limb.

7.3.3 Place of Death

Discussion regarding each patient's preferred place of palliative care was deemed appropriate for 36 patients, of whom 18 (50%) preferred home, 8 (22.2%) preferred hospice, 4 (11.1%) preferred care home and 6 (16.7%) preferred hospital.

Seven patients remained alive at end of the study period. Place of death was not discussed with 42/66 patients due to their physical or psychological or cognitive state. It was deemed appropriate to discuss preferred place of death for 24 patients, of whom 6 (25%) preferred home, 9 (37.5%) preferred hospice, 4 (16.7%) preferred care home and 5 (20.8%) preferred hospital. The pattern of actual place of death in the 59 patients who died during follow-up was different to that of the preferred place of death: 9/59 (15.3%) died at home, 8/59 (13.6%) died in hospice and 42/59 (71.2%) died in hospital (**Figure 22**). No significant differences were seen when comparing by aetiology.

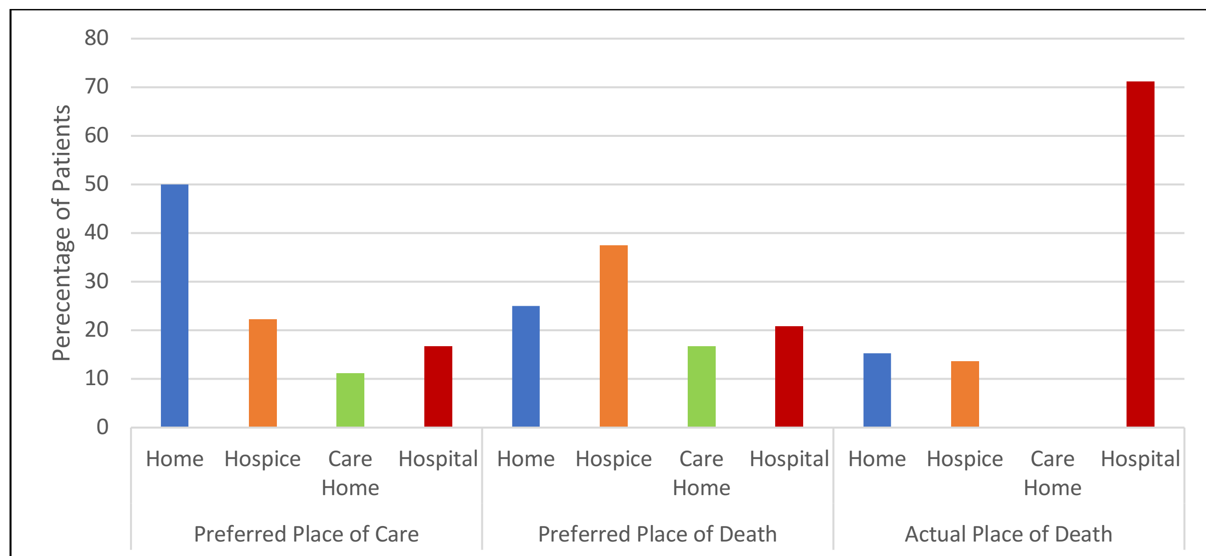

Figure 22: Preferred place care, preferred place of death and actual place of death for palliated patients.

7.4 Discussion

This study presented a single institution's experience of palliation in patients with limb ischaemia and in whom revascularisation options were exhausted or not possible, and in whom the option of MLA was excluded. A total of 77 patients were palliated in the same period as 262 patients undergoing an MLA. Therefore 22.7% of all unsalvageable limbs were palliated.

The information in this study can be used to inform future discussion with patients, relatives, and palliative care specialists about likely timeframes. It also demonstrated that currently we are poor at meeting patients' preferences for where they wish to die, and this should be addressed.

A literature review identified one similar study, by Campbell et al 2000 describing a cohort of 30 patients receiving palliation for advanced limb ischaemia (261). In their study, survival after decision to palliate ranged from <24 hours to 42 days, with a median of 3.5 days, which was considerably shorter than that seen in our study (7 [2-20.5] days). The ratio of acute to chronic rest pain to chronic tissue loss ischaemia groups are similar between the two studies. A possible explanation may be that our population cohort was younger (median age of 83) than in the Campbell study (median age of 87).

Nevertheless, there is paucity of data on reporting the natural history of patients receiving palliation for an unsalvageable limb. Our study has shown that outcomes of palliation can vary significantly when comparing different subgroups of patients. Identifying factors associated with outcomes such as length of stay and survival after palliation can better guide the surgical and palliative management of this challenging patient group.

In our study, the DFS group had the longest survival after commencement of palliation indicating a slow deterioration in overall health with this aetiology. CLTI patients survived longer than more acute presentations such as acute-on-chronic CLTI and ALI. A possible factor affecting this may be differences in age and comorbidity between the groups, with a greater proportion of the CLTI patients being younger diabetic foot patients. The CLTI group also had

the longest length of stay and were more likely to undergo ipsilateral minor amputation or attempted revascularisation in the same admission prior to palliation. When comparing length of stay by surgery type, it was shown that surgery, in particular revascularisation, was associated with a significantly longer time to palliation and length of stay. This may have important implications on the quality of the end-of-life care provided to such patients.

Our study showed that although patients' preferred place of death was outside of the hospital (home in most cases), the majority of the patients died in hospital. Longer inpatient stay and delayed time to palliation, partly due to limb salvage attempts, may lead to physiological decompensation and unsuitability for community palliation. Better patient selection for limb salvage surgery may therefore improve QoL in the palliation period for patients unsuitable for MLA or those who refuse it. This is supported by findings in the Mestral et al 2019 study on end-of-life care following major leg amputation (262). The authors showed that compared to non-amputees receiving palliation, amputees were less likely to die at home, more likely to die in hospital, had higher end-of-life healthcare costs and greater length of stay in hospital.

Despite having the largest series of vascular patients included in a study on palliation outcomes of unsalvageable limbs, as per a literature search, the major limitation of this study was that subgroup analyses relied on small patient groups. Predictive modelling for time to death and place of death was therefore not possible. The study also failed to capture patients who died prior to being seen by the palliative care team. Although all 66 patients received a palliative care team review within 24 hours of referral, rapid or out-of-hours deaths remain unaccounted for.

In conclusion, the results show that times to death can be lengthy in this cohort and dependent on aetiology of the unsalvageable limb, and as such the formal involvement of palliative care team is vital. This study sheds new light on this understudied patient population in vascular surgery and further research can better inform shared decision-making for patients and surgeons when faced with an unsalvageable limb. The large proportion of patients being palliated under these circumstances, necessitates such research and for robust pathways to be developed to appropriately manage them.

Chapter 8: Construction and validation of the decision aid

8.1 Introduction

Decision aids are a part of a shared decision-making process, encouraging active participation by patients, as well as providing valuable predictive clinical information for the clinicians in intervention-related decisions.

There is strong evidence that patients want to take part in decision-making. A recent systematic review of 115 studies found that in 63% of studies, patients preferred shared decisions with clinicians. There was also a temporal trend highlighting that the wish of patients to participate in shared decision-making appears to have increased over time (50% of studies before year 2000 versus 71% of studies after year 2000 (263).

The aim of this chapter was to report the construction of an online and app-based decision aid for patients considered for MLA, to be used by patients and clinicians. Findings from previous chapters highlighted the importance of distinguishing functional survival as a separate entity of functional outcome. Therefore, the decision aid will consist of two components: one predicting functional survival and the other predicting independent prosthetic mobility. A key part of any predictive model is its validation. Therefore, internal validation of both models and criterion validation of the second model were performed and reported here.

8.2 Methods

The methods of this descriptive chapter are described in Chapter 2. In brief, this chapter reports on the construction and validation of the risk prediction models generated from experimental Chapters 5.1 and 6 and the palliation outcome data from Chapter 7. Model 1 (generated from Chapter 5.1) was for the prediction of functional survival following MLA. Model 2 (generated from Chapter 6) was for the prediction of independent prosthetic mobility (using SIGAM scoring) after rehabilitation. Internal validation was performed using bootstrapping for both models.

Criterion Validation for the Model 2 was performed using prediction of TUG time and 2-minute distance. Outcome data for patients receiving primary palliation for unsalvageable limb disease were included as narratives within the decision aid. Risk calculators were built using variable coefficients from the logistic regression equations generated by each model and incorporated into a web-based application.

8.3 Result

8.3.1 Model 1: Prediction of Functional Survival

Pre-operative patient variables that showed a significant univariate association with post-MLA functional survival (survival of surgery and suitability for rehabilitation) underwent multivariate logistic regression analysis (**Table 36**). Factors that were negative predictors of functional survival were: age over 75 years, being male, aetiology of MLA (where ALI was used as the reference level because it was associated with the best outcome), MLA level (BKA used as reference level because it was associated with the best outcome), active malignancy congestive cardiac failure and hypoalbuminaemia (stratified into levels of severity).

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	6.226	1.101	5.65	< .001	505.7	58.4	437
Age over 75 years	-1.17	0.433	-2.71	**0.007**	0.309	0.132	0.721
Male Gender	-1.07	0.536	-1.99	**0.046**	0.343	0.120	0.981
Aetiology of MLA (ALI used as reference level)							
Acute-on-chronic CLTI	-1.67	0.787	-2.13	**0.033**	0.187	0.040	0.874
CLTI	-1.49	0.742	-2.01	**0.045**	0.225	0.053	0.964
DFS	-2.91	0.828	-3.51	**< .001**	0.055	0.011	0.276
MLA Level (BKA used are reference level)							
TKA	-1.16	0.803	-1.44	0.149	0.314	0.065	1.514
AKA	-1.66	0.535	-3.11	**0.002**	0.189	0.066	0.540
Active malignancy	-1.71	0.569	-3.00	**0.003**	0.181	0.059	0.552
Congestive cardiac failure	-1.31	0.579	-2.26	**0.024**	0.271	0.087	0.841
Hypoalbuminaemia (>20 used as reference level)							
15<Albumin<20	0.281	0.492	0.570	0.569	1.324	0.505	3.473
Albumin <15	-1.57	0.565	-2.77	**0.006**	0.209	0.069	0.631

Table 36: Multivariate logistic regression analysis for functional survival.

The estimated coefficients for each variable were then incorporated into the logistic regression equation of Model 1 (Equation 2).

$$
\begin{aligned}
\boldsymbol{y} = \mathbf{6.226} - \mathbf{1.17}\ (\boldsymbol{Age} > \mathbf{75}) - \mathbf{1.07}\ (\boldsymbol{Male}) - \mathbf{1.67}\ (\boldsymbol{Ac.on.Chr.CLITI}) - \mathbf{1.49}\ (\boldsymbol{CLTI}) \\
- \mathbf{2.91}\ (\boldsymbol{DFS}) - \mathbf{1.16}\ (\boldsymbol{TKA}) - \mathbf{1.66}\ (\boldsymbol{AKA}) - \mathbf{1.71}\ (\boldsymbol{Active\ Malignancy}) \\
- \mathbf{1.31}\ (\boldsymbol{Congestive\ Cardiac\ Failure}) + \mathbf{0.281}\ (\mathbf{15} < \boldsymbol{Albumin} < \mathbf{20}) \\
- \mathbf{1.57}\ (\boldsymbol{Albumin} < \mathbf{15})
\end{aligned}
$$

Equation 2: Logistic regression equation for Model 1 (prediction of functional survival).

Tests of the predictive power of the model yielded high discrimination (AUC or C-Statistic of 0.819) and calibration (Hosmer-Lemeshow p<0.531) (Figure 23).

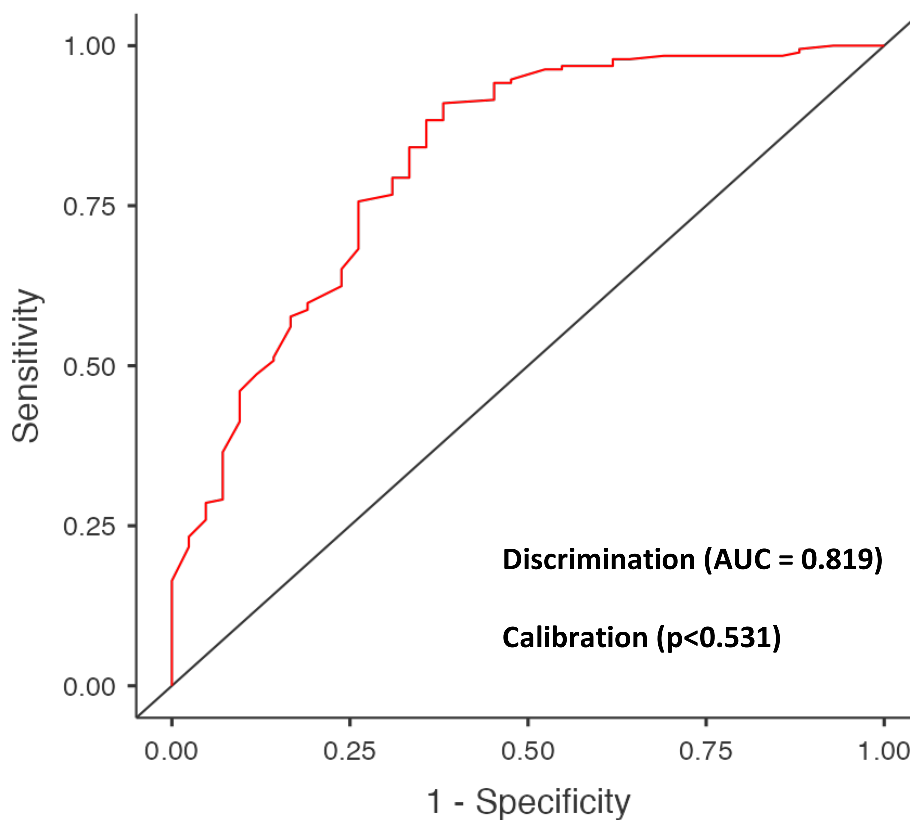

Figure 23: Sensitivity - specificity curve for Model 1 with discrimination and calibration.

8.3.2 Model 2: Prediction of Independent Prosthetic Mobility

Pre-operative patient variables that showed a significant univariate association with independent prosthetic mobility (on SIGAM assessment) underwent multivariate logistic regression analysis (**Table 37**). Factors that were negative predictors of this outcome were: age over 75 years, being female, MLA level (BKA used as reference level), active malignancy, cerebrovascular disease, end-stage renal failure (eGFR>30 used as reference level) and cognitive impairment.

Predictor	Estimate	SE	Z	p	Odds ratio	95% Confidence Interval	
						Lower	Upper
Intercept	1.405	0.142	9.91	< .001	4.077	3.087	5.383
Female Gender	-1.37	0.208	-6.57	**< .001**	0.255	0.170	0.384
Age over 75 years	-1.45	0.208	-6.97	**< .001**	0.235	0.157	0.353
MLA level (BKA used as reference level)							
AKA	-1.39	0.183	-7.59	**< .001**	0.249	0.174	0.356
TKA	-0.78	0.408	-1.92	**0.055**	0.457	0.206	1.017
Active malignancy	-0.846	0.352	-2.41	**0.016**	0.429	0.215	0.855
Cerebrovascular disease	-0.710	0.252	-2.82	**0.005**	0.492	0.300	0.806
Renal Failure (eGFR>30 used as reference level)							
15<eGFR<30	-0.368	0.265	-1.39	0.165	0.692	0.412	1.163
eGFR<15	-1.36	0.409	-3.32	**< .001**	0.257	0.115	0.572
Cognitive impairment	-1.55	0.629	-2.46	**0.014**	0.213	0.062	0.729

Table 37: Multivariable logistic regression analysis for independent prosthetic mobility.

The estimated coefficients for each variable were then incorporated into the logistic regression equation of Model 2 (**Equation 3**).

$$y = 1.405 - 1.45\,(Age > 75) - 1.37\,(Female) - 0.78\,(TKA) - 1.39\,(AKA) - 0.846\,(Active\ Malignancy) - 0.710\,(Cerebrovascular\ Disease) - 0.368\,(15 < eGFR < 30) - 1.361\,(eGFR < 15) - 1.549\,(Cognitive\ Impairment)$$

Equation 3: Logistic regression equation for Model 2 (prediction of independent prosthetic mobility).

Tests of the predictive power of the model yielded high discrimination (AUC or C-Statistic) of 0.819 and calibration (Hosmer-Lemeshow p<0.496) (Figure 24).

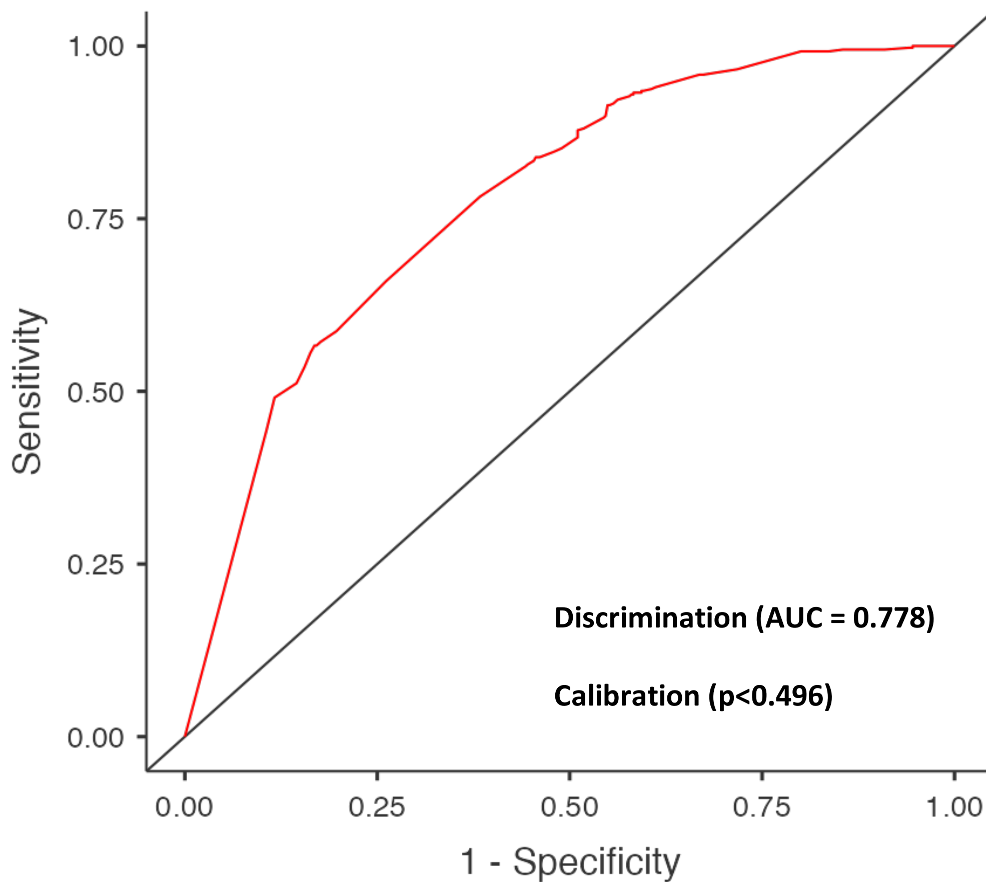

Figure 24: Sensitivity - specificity curve for Model 2 with discrimination and calibration.

8.3.3 Model 1 Internal Validation with Bootstrapping

Internal validation of all predictor variables was demonstrated with bootstrapping – yielding similar odds ratios with confidence intervals and significant p-values (Table 38). Bootstrapped AUC was 0.811 (Figure 25), which was similar to that of the original model (0.819), confirming minimal over-optimism in Model 1.

	Odds Ratio	5%	95%	P-value
Constant	447.749	59.540	3,367.115	0.000
Age>75	0.277	0.123	0.621	**0.002**
Sex (Male)	0.371	0.141	0.979	**0.045**
Level (BKA used as reference level)				
TKA	0.373	0.084	1.651	0.194
AKA	0.219	0.083	0.576	**0.002**
Active malignancy	0.186	0.062	0.558	**0.003**
Aetiology (ALI used as reference level)				
Acute-on-chronic CLTI	0.188	0.041	0.862	**0.031**
CLTI	0.197	0.047	0.816	**0.025**
DFS	0.053	0.011	0.257	**0.000**
Congestive cardiac failure	0.292	0.097	0.878	**0.028**
Hypoalbuminaemia (>20 used as reference level)				
15<Albumin<20	1.368	0.541	3.461	0.508
Albumin <15	0.216	0.075	0.624	**0.005**

Table 38: Bootstrap internal validation of Model 1.

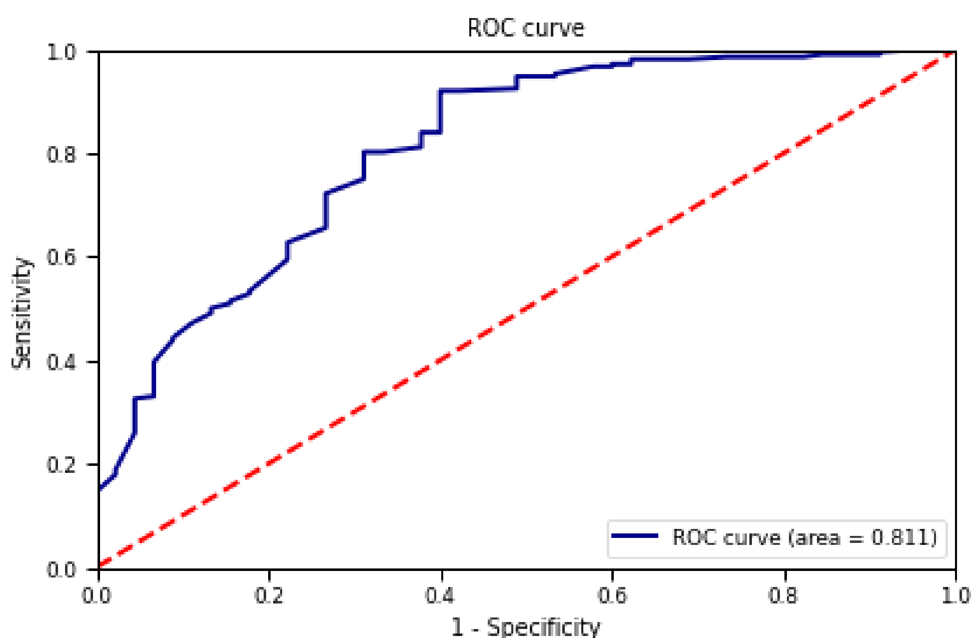

Figure 25:ROC for Bootstrap validation of Model 1.

8.3.4 Model 2 Internal Validation with Bootstrapping

Internal validation of all predictor variables was demonstrated with bootstrapping – yielding similar odds ratios with confidence intervals and significant p-values (**Table 39**). Bootstrapped AUC was 0.778 (**Figure 26**), which was equal to that of the original model, confirming no over-optimism in Model 2.

	Odds Ratio	5%	95%	P-value
Constant	4.077	3.087	5.383	0.000
Age Over 75	0.235	0.157	0.353	**<0.001**
Female	0.255	0.170	0.384	**<0.001**
MLA level (BKA used as reference)				
AKA	0.249	0.174	0.356	**<0.001**
TKA	0.457	0.206	1.017	**0.055**
Active malignancy	0.429	0.215	0.855	**0.016**
Cerebrovascular disease	0.492	0.300	0.806	**0.005**
Renal Failure (eGFR>30 used as reference level)				
15<eGFR<30	0.692	0.412	1.163	0.165
eGFR<15	0.257	0.115	0.572	**0.001**
Cognitive Impairment	0.213	0.062	0.729	**0.014**

Table 39: Bootstrap internal validation of Model 2.

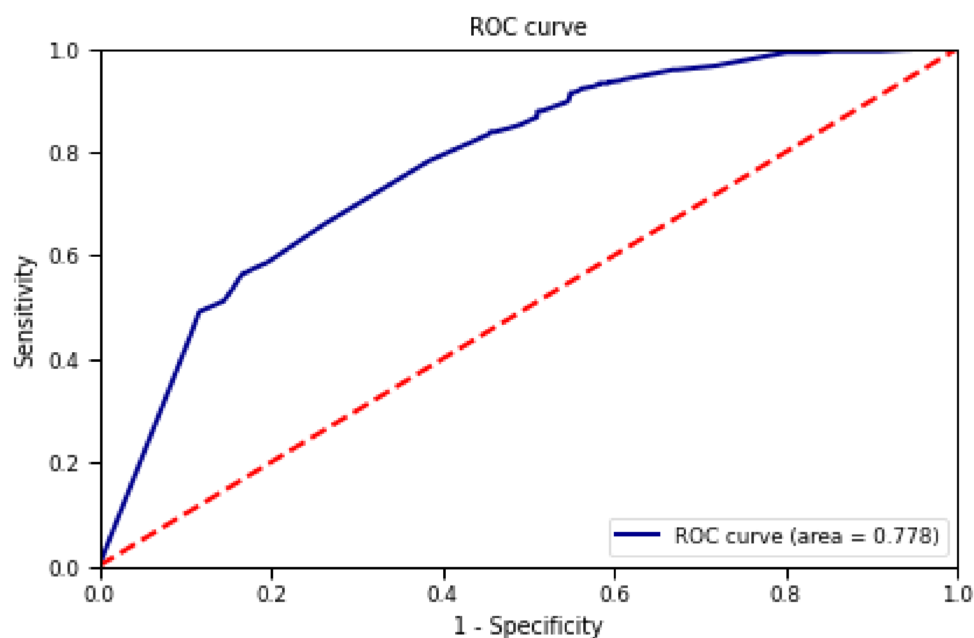

Figure 26: ROC for Bootstrap validation of Model 2.

8.3.5 Criterion Validation of Model 2

A three-way test for correlation was performed between SIGAM grades, TUG times and 2-minute distances. A density curve in **Figure 27** illustrates the change in the TUG time with SIGAM grade. Patients with the best grade (E) demonstrated the fastest median TUG time of 9.2 [8.3-10.2] seconds. As grades worsened to D, C and B, TUG times increased significantly to 17.4 [14, 22.9], 44.4 [29.9, 57.3] and 60.5 [60, 62] seconds, respectively, ($p<0.001$).

A similar relationship in test performance was observed when analysing the change in 2-minute distances with SIGAM grade (**Figure 28**). The median distance achieved halved with every decrement in SIGAM grade from E (152 [122, 152] metres) to B (17 [15, 22] metres), ($p<0.001$). Patients with the worst SIGAM grade (A) were unable to perform the TUG or the 2-minute tests.

There was a strong reciprocal relationship between TUG time and 2-minute distance, as illustrated by the scatter-density plot in **Figure 29**. As TUG time increased, there was an exponential fall in the 2-minute distance achieved, ($p<0.001$). The density curves on the outer edges of the scatter plot show a clear difference in distribution of TUG times and 2-minute distances between good and poor SIGAM grades.

The trend in change of SIGAM (blue), TUG (brown) and 2-minute (green) performance by number of predictor variables from Model 2 is shown as density curves in **Figure 30**. As the number of Model 2 predictors present increased, the prosthetic performance in all three tests deteriorated.

Figure 27

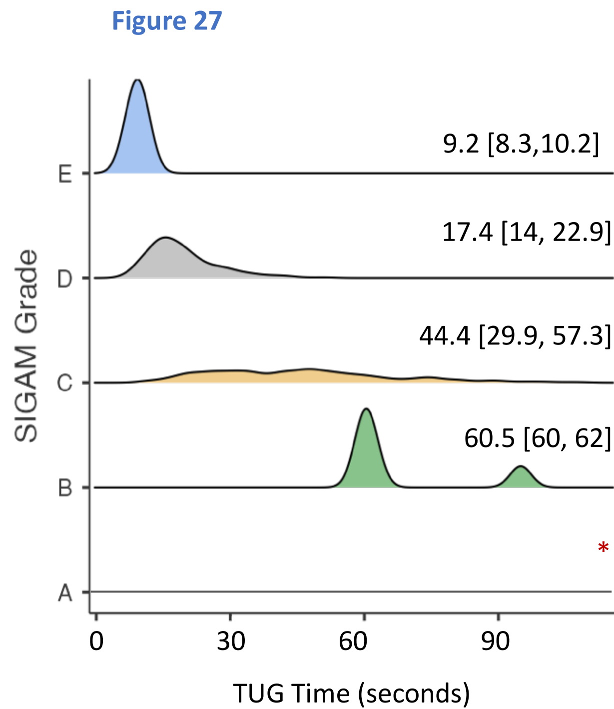

Figure 28

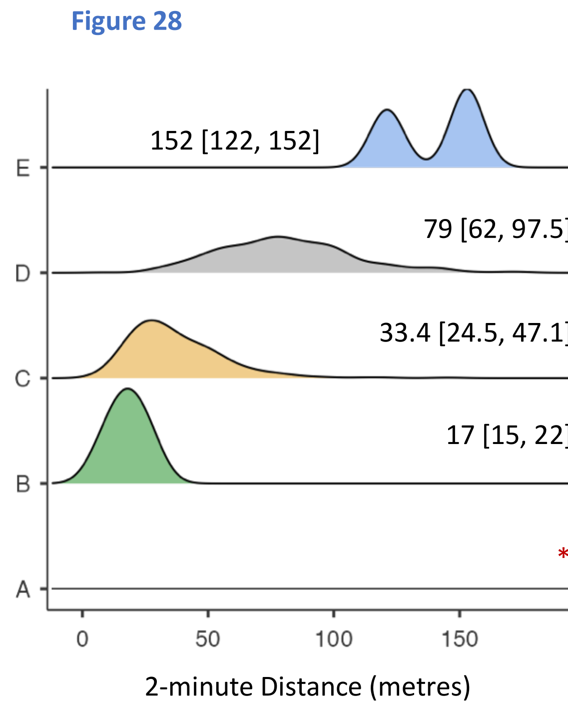

Figure 29

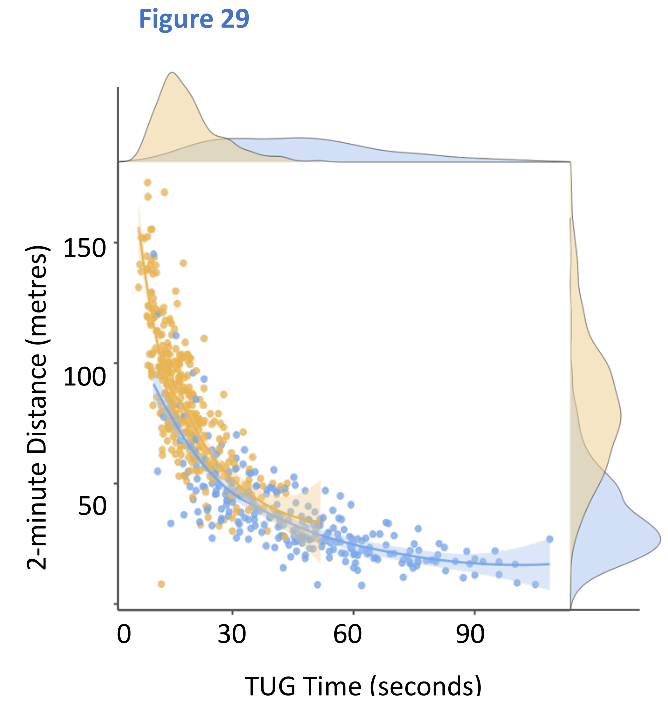

Figure 27: Density graphs of TUG time by SIGAM grade.

Figure 28: Density graphs of 2-minute distance by SIGAM grade.

Figure 29: Scatter plot of 2-minute distance by TUG time with density graphs for each parameter (SIGAM A-C in yellow and D-F in blue density curves).

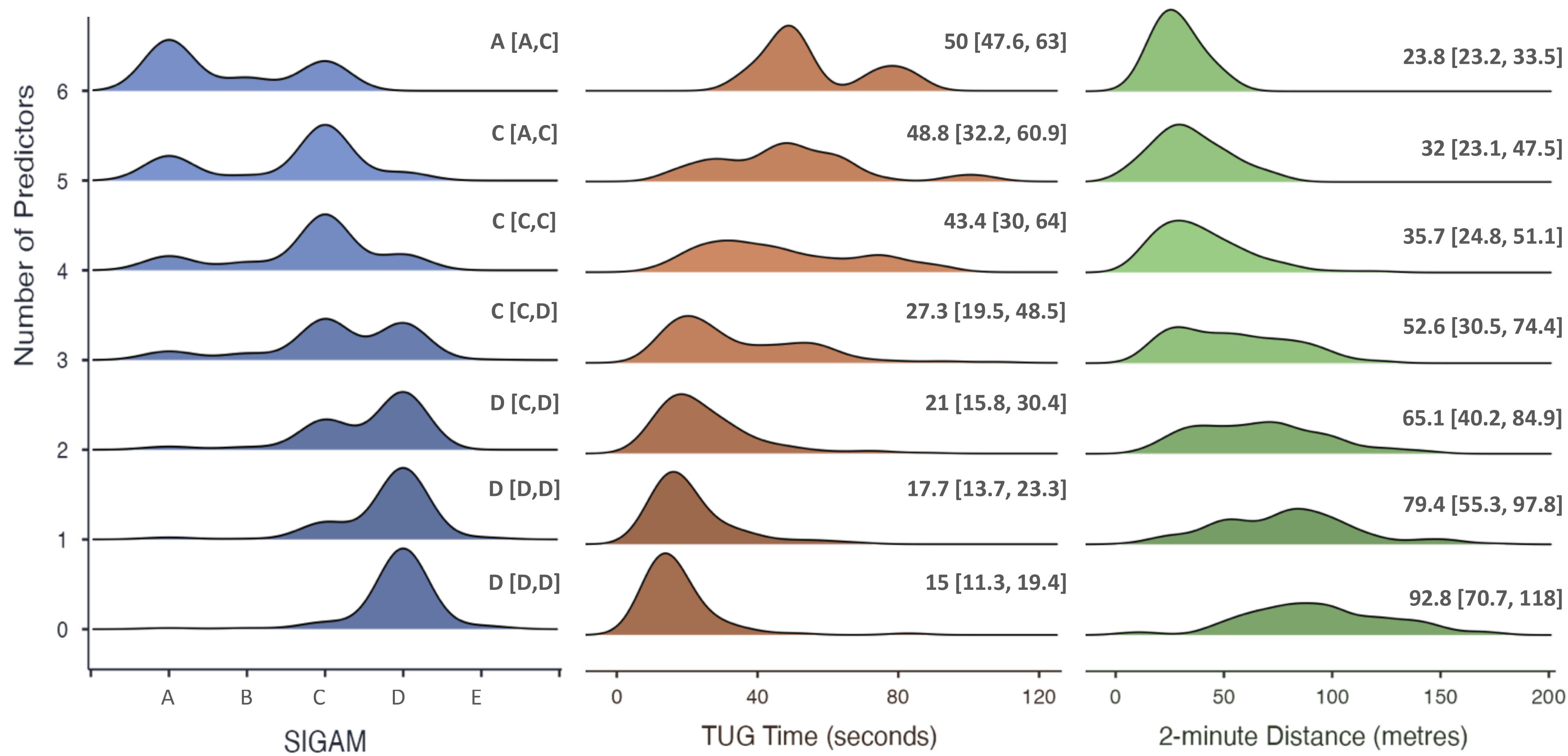

Figure 30: Density graphs for SIGAM, TUG time and 2-minute distance by number of predictors.

8.3.6 Multivariable Analysis for TUG time and 2-minute distance with Prosthesis

For TUG and 2-minute performance, factors with significant association in a stepwise multivariable linear regression analysis are shown in **Table 40** and **Table 41**, respectively. Difference in list of variables between this model and that of the SIGAM prosthetic mobility were that cardiac problems, (atrial fibrillation and congestive cardiac failure), rather than active cancer were significant for TUG. The strong similarities between these linear regression models and the logistic regression model (Model 2) for dichotomised SIGAM prediction provide support for the validity of Model 2.

Predictor	Estimate	SE	t	p	Effect size	95% CI	
Intercept [a]	1.220	0.013	95.62	**< .001**			
Female	0.124	0.020	6.24	**< .001**	0.474	0.325	0.623
Age Over 75	0.142	0.020	7.02	**< .001**	0.545	0.392	0.697
MLA level (BKA used as reference level)							
AKA	0.256	0.018	14.24	**< .001**	0.978	0.843	1.113
TKA	0.201	0.041	4.89	**< .001**	0.770	0.461	1.080
Atrial Fibrillation	0.067	0.024	2.77	**0.006**	0.258	0.075	0.440
Heart Failure	0.080	0.030	2.65	**0.008**	0.306	0.080	0.533
Renal failure (eGFR>30 used as reference level)							
15<eGFR<30	0.035	0.027	1.28	0.202	0.133	-0.071	0.337
eGFR<15	0.159	0.044	3.60	**< .001**	0.609	0.277	0.941
Cerebrovascular disease	0.067	0.024	2.73	**0.006**	0.255	0.072	0.439
Cognitive Impairment	0.144	0.061	2.37	**0.018**	0.549	0.095	1.004

Table 40: Stepwise linear regression analysis for TUG time (log-transformed).

Predictor	Estimate	SE	t	p	Effect size	95% CI	
Intercept [a]	1.905	0.013	145.27	**< .001**			
Female	-0.142	0.020	-6.99	**< .001**	-0.554	-0.709	-0.398
Age Over 75	-0.122	0.021	-5.87	**< .001**	-0.476	-0.635	-0.316
MLA level (BKA used as reference level)							
AKA	-0.231	0.019	-12.6	**< .001**	-0.899	-1.039	-0.758
TKA	-0.161	0.044	-3.69	**< .001**	-0.625	-0.958	-0.292
Atrial Fibrillation	-0.054	0.025	-2.17	**0.030**	-0.213	-0.405	-0.021
Heart Failure	-0.087	0.031	-2.81	**0.005**	-0.337	-0.573	-0.101
Renal failure (eGFR>30 used as reference level)							
15<eGFR<30	-0.018	0.028	-0.640	0.523	-0.069	-0.282	0.143
eGFR<15	-0.166	0.045	-3.65	**< .001**	-0.641	-0.986	-0.296
Cerebrovascular disease	-0.050	0.025	-1.99	**0.047**	-0.194	-0.386	-0.002
Cognitive Impairment	-0.140	0.062	-2.25	**0.025**	-0.542	-1.014	-0.069

Table 41: Stepwise linear regression analysis for 2-minute walk test (log-transformed).

8.3.7 Incorporation of Models in a Web-based Application

The risk calculating software (named the SGVI Amputee Risk Calculator) was created and presented in an application format. Screen shots of the application's interface are shown in **Figure 31**. The electronic form consists of all variables required to calculate each score and their respective questions are presented in a drop-down list format. The form takes approximately two to five minutes to complete. Upon submission of the selected variables, the software will present all risk values which will be used to inform clinician and patients during consenting and decision-making. In this prototype, estimation of TUG and 2-minute performance are also included, for which the validation is ongoing. Outcome data for patients receiving primary palliation for unsalvageable limb disease were included as narratives within the decision aid.

SGVI Amputee Risk Calculator

Age
Age > 75 years

Sex
Female

Urgency
Emergency

Amputation Level
Above Knee

Revision
Yes

Aetiology
Acute Limb Ischaemia

AF
Yes

CCF
Yes

CCF
Yes

CVA
Yes

Malignancy
Yes

Psych
Yes

Chronic Cognitive Problems
Yes

Function
Independent

Renal
Normal

Albumin
Normal

Delirium
Yes

Functional Survival
Likelihood of Progressing to Prosthetic Rehabilitation
77.8%

Independent Prosthetic Mobility
Likelihood of Independent Prosthetic Mobility
0.3%

TUG Time
Estimated TUG Time
125.6 seconds

2-Minute Distance
Estimated 2-minute Distance
11.9 meters

Figure 31: Prototype for SGVI Amputee Risk Calculator Application.

8.4 Discussion

The use of the validated models reported in this chapter can be used to aid discussions regarding the expectations of functional outcome post-amputation.

Locomotor tests during rehabilitation have been shown to be good indicators of prosthetic abandonment at twelve months (264). Both predictive models demonstrated good discrimination and calibration, with internal validation showing minimal over-optimism. The predictive ability of Model 2 (dichotomised SIGAM prediction) was further supported through criterion validation using prediction of TUG and 2-minute distance. Moreover, the strong three-way correlation between different objective parameters of mobility supported the assumption that there was an acceptably low inter- and intra-operator variability in their measurement by the physiotherapy team.

Given the differing aetiologies and acute physiologic derangements, risk stratification in MLA surgery presents a unique challenge. To address these, the risk calculators produced in this body of work met the following vital criteria:

1. the valid quantification of binary outcomes of interest in the vascular MLA population,
2. the use of readily obtainable objective data,
3. an early applicability of the tool prior to a surgical intervention,
4. an applicability in non-operative cases,
5. utility for auditing purposes,
6. an applicability to clinical practice.

When considering MLA surgery, clinicians and patients should begin by calculating the functional survival (surviving surgery and progression to rehabilitation) as well as the success of early prosthetic rehabilitation.

The initial estimates of prediction can then form the basis for a discussion that includes consideration of the burden and severity of other comorbidities, optimisation of risk-enhancing conditions and adherence to healthy lifestyle recommendations. In this discussion, patient health literacy and numeracy are important factors determining the depth and

breadth of the content. Other important factors include the patient's personal desire to proceed with surgery and succeed with prosthetic rehabilitation.

The predictive modelling was simplified as far as possible to improve its clinical utility in both the pre-amputation and rehabilitation period. However, it is important to note that other factors showed significant associations with functional outcomes on univariable analyses. Due to small numbers of certain patient factors, regression analyses yielded large confidence intervals and therefore these factors were omitted from the final model. It is anticipated that, with larger case numbers, such variables may also be important predictors of functional outcome (265).

The inclusion of weight in predicting mobility remains controversial. Obesity is included in the AMPREDICT and BLART tools for predictive functional outcome, yet studies focussing on this variable have suggested that the association is not significant (266,267). In this study, post-amputation weight was studied, which demonstrated strong collinearity with age and gender and therefore was excluded from the prediction model.

Quantitative risk scores for functional outcomes in MLA surgery will likely be improved in the future with advances in epidemiology, development of additional large and representative cohorts, consideration of novel risk markers, and advances in data analysis. Such data should allow for better risk estimation in segments of the population, including underrepresented minority groups and those with social deprivation, and may allow for more targeted risk assessment within diverse racial/ethnic groups. Future models may also allow for longitudinal risk assessment, with updating of predicted risk based on initiation of and response to rehabilitation. Following the successful construction of the risk calculator based on findings of this thesis, external validation of its predictive models is necessary. Work has commenced on submission of ethical approval for collection of more local and regional data for internal and external validation.

In conclusion, this risk prediction calculator can help to objectify the clinical triage process and to quantify probability of functional outcomes, in the pre-amputation setting. Thus, the tool can support informed consent and decision-making for both patient and clinician.

Chapter 9: Discussion of findings of this thesis

This thesis incorporated the prediction of two distinct parameters of functional outcome to address a pertinent issue pertaining to decision-making in the management of the unsalvageable limb. The first parameter was (short-term) functional survival, an outcome previously unreported because patients who do not enter the rehabilitation pathway due to post-operative death or unsuitability for rehabilitation are overlooked in studies. However, these patients comprised 17.1% of the MLA cohort in this body of work. The second parameter was independent prosthetic mobility, which from the findings of the systematic reviews and qualitative work undertaken in this thesis, was one of the chief, yet unaddressed, concerns for patients before and after limb loss.

9.1 Functional outcome is not the focus of care for the clinician in contemporary vascular surgery but was identified to be the chief concern of patients facing limb loss

The systematic review in Chapter 3 highlighted the discrepancies in the reporting of outcomes of MDT-led care of patients with threatened or unsalvageable limbs, providing an insight into current limitations and future potentials.

The focus of current literature is heavily biased on improving limb salvage rates, and although this remains crucial, an opportunity to simultaneously address other domains of patient health are being missed. A disproportionately small number of studies attempted to provide frameworks addressing medical and patient-centred outcomes including psychosocial health, QoL, and most relevant to this thesis, functional outcomes. Only one out of the thirty-eight studies on MDT-led care of lower limb arterial patients reported a functional outcome measure (ambulation) which was poorly defined. It should also be noted that MLA patients were poorly represented within these studies, emphasising a need for more research on this patient group.

The cross-sectional study in Chapter 4.1 identified the concerns of patients facing limb loss and characterised the prevalence of psychosocial problems. It showed that mobility remained the major concern both before and after amputation. Sociodemographic variables were also identified that may well have significant consequences on the health-related behaviours and general wellbeing of patients. There was a high rate of depression, anxiety and psychiatric medication use among female and younger patients. A large proportion of patients in this study lived alone, and social isolation secondary to a poor functional status was a commonly expressed concern.

In conclusion, Chapters 3 and 4.1 disproved the first null hypothesis: that there is no inconsistency between clinicians and patients in the prioritisation of functional outcome for their decision-making when facing MLA. The findings imply there is a need for utilising validated tools for predicting functional outcomes that will aid timely clinical decision-making and address a principal patient concern during multidisciplinary care of the threatened and unsalvageable limbs.

9.2 Functional outcome after limb loss has important implications on levels of social isolation which bears implications on general health and quality of life patients

As shown in the supplementary work in Chapter 4.2, evidence in literature signifies a strong association between poor mobility and social isolation in lower limb arterial patients, which in turn was associated with poorer clinical outcomes such as higher mortality rates. Furthermore, socio-demographic factors showing associations with poorer mental health, were identified.

Provision of psychosocial care and optimisation of mobility, which appear inter-related, should be standardised in multidisciplinary teams. Research into the development of tools predicting mobility (which may act as a surrogate marker of level of social isolation) after a major amputation is therefore important in vascular surgery. Patients at risk of poor mobility and isolation may be referred to physiotherapy, psychosocial therapy, and community-based social support schemes. Further research into how this can address treatment compliance, readmission rates, protracted hospital-stay and health costs is also desirable.

Socio-ecological framework modelling highlighted the interaction between the patient and their environment and how their lower limb problems affect their health-related behaviours. Thus, the use of socio-ecological frameworks may be beneficial in identifying patients at highest risk of psychological or social problems, as well introduce interventions aimed at optimising outcomes at all levels of influence (personal, interpersonal, economical, and health-related behavioural).

Findings of Chapters 3, 4.1 and 4.2 together highlight a broader implication on clinical decision-making. Clinicians may wish to focus more on the optimisation of mobility rather than limb salvage as their primary goal in the management of the threatened limb for more patients.

9.3 Functional survival should be an important consideration in decision-making for MLA

In the cohort study for Chapter 5.1, the concept of "functional survival" following major amputation was introduced.

Only 82.9% of patients experienced functional survival following major amputation. The other 17.1% of patients either died in the same admission or were unsuitable for rehabilitation on post-operative assessment. This substantial proportion of cases, underreported in amputation research, has implications on surgical decision-making, and provision of rehabilitation and palliative care services.

Moreover, rehabilitation potential on post-amputation assessment was a strong predictor of long-term survival and therefore may be utilised as a surrogate marker of long-term survival. Consequently, this may be used in pre-operative discussions with patients to manage expectations. This study has also identified patient characteristics, such as active malignancy and psychosocial problems, as being important factors in the failure of progression to rehabilitation.

9.4 Cancer has detrimental impact on outcomes after amputation

Findings from the supplementary cohort study in Chapter 5.2 suggest cancer is prevalent among vascular amputees, with a large proportion diagnosed coincidentally. The overall outcomes were poor for patients with a malignancy and unsalvageable limb disease, with the median survival being less than a year in those with new cancers, and less than two years in those with more established cancers, with even poorer prognoses with metastatic disease.

One unexpected finding was around the provision of full amputee rehabilitation in patients with active cancer in the context of their overall outcome. Patients with new cancers were far more likely to commence rehabilitation immediately, or after a short delay, than patients with established cancers who were more often deemed unsuitable for rehabilitation. Half of the latter patient group were discharged from hospital to a nursing home.

In the new cancer group only 8.3% were deemed unsuitable for rehabilitation, and 50% were discharged directly home, yet had a median survival of under a year. It is apparent that a greater level of understanding is required on this point as, with 60% of patients with established cancer living for two years or more after amputation, it may be that some patients are not benefitting from the full range of rehabilitation services, and some patients with active cancer being referred for rehabilitation with unrealistic expectations.

9.5 Functional outcome after amputation is poor in current practice

The cohort study in Chapter 6 has identified patient and therapy-related factors predictive of functional outcome in amputees following rehabilitation. Overall, functional outcomes were poor with less than half of patients entering the rehabilitation pathway achieving independent levels of prosthetic mobility outside the household. Moreover, rates of non-attendance with follow-up and mortality were significantly higher among amputees with poorer prosthetic function. There was a high prevalence of pre-existing psychiatric problems and female patients performed consistently worse in parameters of mobility assessing prosthetic use, falls risk and exercise tolerance.

Broadly, two time-points exists for interventions: in the pre-rehabilitation phase (in the pre-amputation period) and the rehabilitation phase (in the post-amputation period). Findings of strong associations between pre-operative comorbidities supports the need for a biopsychosocial model of care in the pre-amputation period. The impact of prehabilitation on functional outcome is poorly understood in amputation research. A potential target for prehabilitation, identified by our study was statin use and cardiovascular health has been shown to be an important determinant of functional outcome in literature. Factors such as EWA engagement, waiting time to start therapy, prosthesis use during therapy and intensity of therapy were shown to be predictive of functional outcome.

In conclusion, Chapters 5.1, 5.2 and 6 disprove the second null hypothesis: that it is not possible to predict function outcome after major amputation. A clear understanding of how patients can be optimised to achieve best possible functional outcomes is necessary in vascular surgery.

9.6 Understanding the outcomes of palliation over MLA is vital for decision-making

The cohort study in Chapter 7 shed a new light on an understudied patient population in vascular surgery and further research can better inform shared decision-making for high-risk patients and for surgeons when faced with an unsalvageable limb. The large proportion of patients being palliated for their unsalvageable limb was high (22.7%).

Outcomes of palliation can vary significantly by presentation of unsalvageable limb and identifying factors associated with outcomes such as length of stay and survival after palliation can better guide surgical and palliative management in this challenging patient group. When comparing length of stay by surgery type, it was shown that surgery, in particular revascularisation, was associated with a significantly longer time to palliation and length of stay. This may have important consequences on the quality of remaining life for certain patients.

Our study showed that although patients' preferred place of death was outside of the hospital (home in most cases), the majority of the patients died in hospital. Longer inpatient stay and delayed time to palliation, partly due to limb salvage attempts, may lead to physiological decompensation and unsuitability for community palliation. Better patient selection for limb salvage surgery may therefore improve quality of life in the palliation period for patients unsuitable for major amputation or those who refuse it.

Further research is required to better guide end-of-life care in this challenging population group and aid decision-making when faced with the prospect of major amputation.

9.7 Valid risk-prediction of function outcome will enhance decision-making for major amputation

Chapter 8 reported on the construction and validation of two risk-prediction models: one to predict functional survival and the other to predict independent prosthetic mobility. Both models performed with good accuracy and calibration. Internal validation with bootstrapping ensured that there was no over-optimism of the performance of the models. Criterion validity, performed as an additional step in the validation of the second model, was also

performed. The simplicity of the predictor variables chosen for the models ensures ease of use in the clinical setting as well as permit external validation. Findings of Chapter 8 disproved the third null hypothesis: that it is not possible to construct a valid decision aid based on the prediction of functional outcome after MLA.

9.8 Hurdles for the future of functional outcome research in amputation surgery

In a systematic review of forty studies on functional and quality of life assessment after major amputation, fourteen different tools for functional measures were identified, with only five being specific for major lower limb amputees (268). Although a dynamic outcome, most tools were not used at regular intervals for patients. Such heterogeneity in design and implementation of functional assessment tools complicate the process of understanding functional outcome research in amputees.

The necessity for amputation-specific tools predicting post-operative ambulation is evident. A systematic review on predictive tools in amputation research highlighted that only two tools based on a total of only 737 amputations cases exist for predicting successful ambulation rates after amputation (79). These were the Blatchford Allman Russell (BLART) and the AMPREDICT-Mobility tools, which predict prosthetic function at 12 months post-amputation (26,235).

Further limitations of such tools include the absence of robust external validation and inclusion of only the cohort of amputees that had been referred for prosthetic rehabilitation, which introduces selection bias and inflates the accuracy of predictive models.

Although there is growing recognition of the importance of functional outcomes, there remains barrier to their assessment, documentation, and interpretation. These barriers stem from the existence of different conceptual bases as well as technical and methodological problems with the tools themselves, lack of proper validation studies, issues with how they are administered and confusion from the multiplicity of tools. These are further complicated by external issues related to institutional inertia, resource constraints and training needs.

9.9 Conclusion

This thesis adopted a variety of experimental approaches to tackle the pertinent issue of functional outcome after major lower limb amputation. Findings of this thesis showed that it is possible to predict functional outcome reliably, thus addressing the chief concern of patients facing limb loss, and to use such prediction tools in aid of pre-operative decision making. Due to its broad nature as a topic, the assessment of functional outcome in this thesis was limited to certain parameters: functional survival (a fresh concept introduced in this thesis) and prosthetic mobility.

Recommendations for future research include 1) the evaluation of other parameters of functional outcome such as cognitive function (in all patients) and physical function in patients not using prosthetics (wheelchair- or bed-bound patients), 2) the simultaneous evaluation of other patient-centred outcomes such as quality of life. There are however many hurdles in research and clinical practice, and this undervalued topic in vascular surgery would benefit from a consensus on definitions, standardisation of functional outcome assessment, and long-term follow-up of amputees.

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Appendices

This section of the thesis includes the supplementary tables and figures mentioned in the main body of text.

Paper	Study Design	Participants	Interventions	Outcome of Interest	Setting, Geographical & Cultural	Reason for exclusion
Jeyaraman 2019 (269)	Retrospective, single-centre study, Multi-disciplinary Foot Clinic 2003-2015, Medical follow-up 5.8 years, Regression analysis	New patients aged>18 with DF, n=533, Indigenous=247, non-Ind =266, Mean age= 59.9 ± 12.3 years, M= 322 (62.8%), F= 191 (37.2%)	Wound management, not reporting revascularisation	Mortality	Outpatient clinic, Northern Australia	No comparison of impact of MDT vs no-MDT
Holscher 2018 (8)	Retrospective single-centre, Multidisciplinary diabetic foot service 2012-2017, Regression analysis	Admitted DF patients, n= 206, Age= 58.5%±12, M= 125 (60.7%), F= 81 (39.3%), White 78(37.9%), Black 122 (59.2%), Other 6 (2.9%)	Operative	30 Day Readmissions	Inpatient, Tertiary centre, USA	No comparison of impact of MDT vs no-MDT
Rhou 2015 (270)	Retrospective, single-centre, Multidisciplinary high-risk foot clinic, 2006-2010, Regression analysis	Patient with DFDs lasting minimum of 4 weeks, n=107, Age 65.6±12.6, M=81.3%, F=19.7%, Caucasian= 79.6%	Wound management, not reporting revascularisation	Wound healing	Outpatient clinic, Australia	No comparison of impact of MDT vs no-MDT
Kassaia in 2013 (271)	Prospective, single-centre, Multidisciplinary wound care, Descriptive and Survival analysis	DM patient with CLI, patients=46, n (no. of. limbs treated) = 50, Age= 64.34±14.75, M= 76%, F=24%	Angioplasty and Wound management	Wound healing, Mortality, MALE, MACE, Cerebral at 6 months	Diabetes clinic, Iran	No comparison of impact of MDT vs no-MDT
Hartmann 2017 (272)	Retrospective, single-centre, 2007, follow-up 6 month,	All DM patients with PAD, n= 122, Age= 71, M= 64.1%, F= 35.9%	Revascularisation	Mobility	Does not specify the setting, Germany	No comparison of impact of MDT vs no-MDT
Tennvall 2000 (273)	Cross-sectional, single-centre, 1998	All DFD patients known between 1995-1998, n= 457, Age= 67 (16-98), M= 64.3%, F= 35.7%	Foot care	QOL	Tertiary centre, Sweden	No comparison of impact of MDT vs no-MDT
Pedras 2018 (274)	Longitudinal, single centre, Mean follow-up 34.98 days	DFD patients, n=179, Age= 66 ±11.03, M=70.9%, F= 29.1%,	Unclear	Anxiety and Depression scores (HADS) pre- and post-amputation	Tertiary centre, Portugal	Compares anxiety pre- and post-surgery rather than MDT vs non-MDT. Interventions used were not clearly defined.
Pedras 2016 (275)	Cross-sectional, single-centre, 2013-2015	DFD inpatients who were referred for amputation surgery, n=206, Age= 66.1±10.88, M= 72.3%, F= 27.7%	Foot care	Sociodemographic, clinical and pain characterisation	, Tertiary centre, Portugal	No comparison of impact of MDT vs no-MDT
Hicks 2018 (276)	Retrospective review of prospectively maintained database, 2012-2017,	DFD inpatient and outpatients, n=277	Foot care	Wound healing	Tertiary centre, USA	No comparison of impact of MDT vs no-MDT

Supplementary Table 1: Characteristics of excluded studies for systematic review for Chapter 3.

		None (29)	%	Minor (25)	%	Pre-MLA (13)	%	Post-MLA (9)	%	p-value
Age		67.5 [55.7, 72.6]		59.6 [56.1, 71.3]		59.6 [53.2, 72.9]		73.0 [69.9, 77.1]		0.174
Male		21	72.4	21	84.0	7	50.0	6	66.7	0.167
Race	White British	23	79.3	16	64.0	10	71.4	7	77.8	0.523
	Asian British	1	3.45	3	12.0	0	0	0	0	0.447
	Black British	2	6.90	0	0	1	7.69	0	0	0.505
	Asian	2	6.90	0	0	0	0	0	0	0.746
	Afro Caribbean	1	3.45	1	4.00	3	21.4	1	11.1	0.142
	Eastern European	0	0	5	20.0	0	0	0	0	**0.014**
Language Problems		3	10.3	4	16.0	0	0	0	0	0.427
Home Type	House	23	79.3	16	64.0	12	85.7	5	55.6	0.382
	Flat	5	17.2	8	32.0	2	14.3	2	22.2	0.533
	Nursing Home	1	3.45	0	0	0	0	1	11.1	0.233
	Visiting from Abroad	0	0	1	4.00	0	0	0	0	0.618
Lives Alone		12	41.2	7	28.0	5	35.7	5	55.6	0.364
No Next of Kin		6	20.7	0	0	0	0	2	22.2	**0.012**
Comorbidities										
Hypertension		15	51.7	12	48.0	10	71.4	3	33.3	0.414
Hyperlipidaemia		8	27.6	7	28.0	3	21.4	3	33.3	0.884
Anaemia		2	6.90	4	16.0	1	7.1	2	22.2	0.400
Smoker		3	10.3	2	8.00	2	14.3	0	0	0.842
Previous Revascularisation		12	41.4	9	36.0	8	57.1	5	55.6	0.443
Ischaemic Heart Disease		5	17.2	7	28.0	2	14.3	3	33.3	0.484
Congestive Cardiac Failure		4	13.8	6	24.0	1	7.79	0	0	0.423
Atrial Fibrillation		4	13.8	4	16.0	0	0	0	0	0.382
Chronic obstructive pulmonary disease		4	13.8	2	8.00	0	0	2	22.2	0.245
Renal Failure		13	44.8	10	40.0	3	21.4	4	44.4	0.459
CVA		1	3.45	1	4.00	1	7.69	1	11.1	0.628
Chronic Pain		3	10.3	2	8.0	4	28.6	0	0	0.230

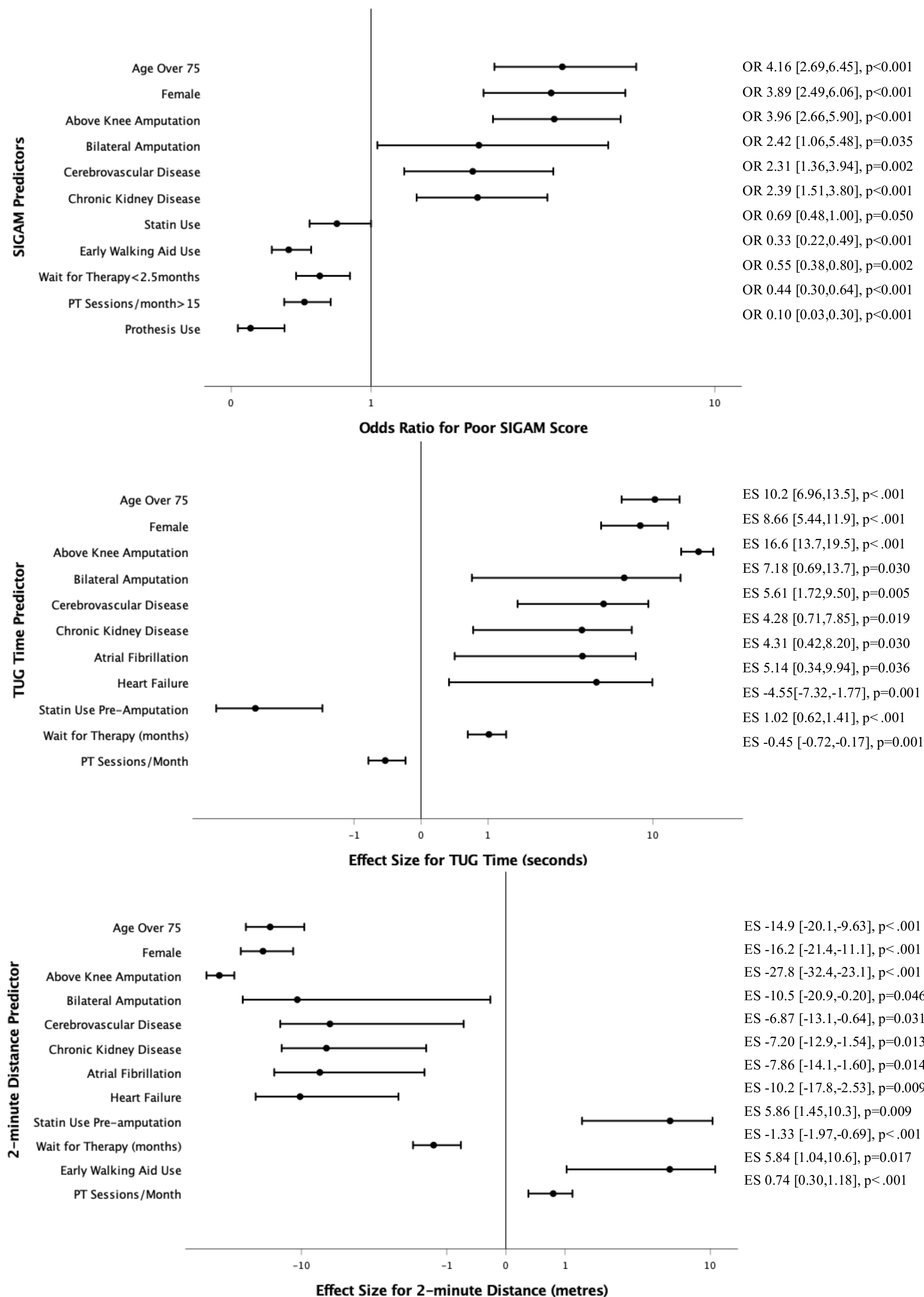
Supplementary Table 2: Comorbidities of DFD patients by amputation status for Chapter 4.1.

Yes/ No/ Unclear/ NA	Is there congruity between the stated philosophical perspective and the research methodology?	Is there congruity between the research methodology and the research question or objectives?	Is there congruity between the research methodology and the methods used to collect data?	Is there congruity between the research methodology and the representation and analysis of data?	Is there congruity between the research methodology and the interpretation of results?	Is there a statement locating the research culturally or theoretically?	Is the influence of the researcher on the research, and vice-versa, addressed?	Are participants, and their voices, adequately represented?	Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?
Galea 2017 (187) Score: 9	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Hallin 2002 (188) Score: 6	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No
Egberg 2012 (180) Score: 5	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes
Treat-Jacobson (181) 2002 Score: 6	Yes	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Wann-Hanson (182)2005 Score 10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palaya 2018 (189) Score: 9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Kinmond 2002 (190) Score: 8	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes

Supplementary Table 3: JBI QARI Critical appraisal of quantitative studies in Chapter 4.2.

Yes/ No/ Unclear/ NA	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate ?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Are all important confounding factors/subgroups/ differences identified and accounted for?	Were subpopulations identified using objective criteria?
Collins 2006 (162) Score 7/10	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Kusaslan 2018 (183) Score 8/10	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roumia 2017 (161) Score 9/10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Oka 2005 (184) Score 8/10	Yes	N	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pell 1993 (32) Score 8/10	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Thompson 1983 (185) Score 9/10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Wattanakit 2005 (186) Score 8/10	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Singh 2015 (165) Score 6/10	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No

Supplementary Table 4: JBI QARI Critical appraisal of qualitative studies in Chapter 4.2.



Supplementary Figure 1: Forrest plots for multivariate analysis of therapy variable for SIGAM, TUG and 2-minute tests.

Presentations

Title	Name and date of meeting
I was invited by Professor Greenhalgh to speak as a faculty member in Charing Cross 2021: Functional outcome after major lower limb amputation.	Charing Cross Symposium 2021 (London, UK)
I presented at the BJS National Prize Session in VS 2020: Functional outcome after major lower limb amputation in vascular surgery.	VSGBI 2020 (Virtual, UK)
Poor mobility, lack of statin-use and socio-economic deprivation is associated with worse survival after a major lower limb amputation: a 10 year prospective study from a rehabilitation centre.	Veith International Symposium 2019 (New York, USA)
Outcomes of rehabilitation after a major lower limb amputation; a 10-year experience.	Charing Cross Symposium 2020 (London, UK)
The psycho-social implications of surgical management in diabetic foot disease.	Vascular Society of Great Britain and Ireland, (Virtual, UK) 2020
Functional outcome after major lower limb amputation in vascular surgery.	Vascular Society of Great Britain and Ireland, (Virtual, UK) 2020
Psychosocial and demographic considerations in management in diabetic foot disease.	Charing Cross Symposium 2021 (London, UK)

Submitted for Publication

All articles submitted are in the peer-review process.

I was invited by Professor Stephen Black (Chief Editor) to write a review on "functional outcomes after major lower limb amputation" for the Vascular and Endovascular Review Journal.

"Psychosocial and demographic considerations in management in diabetic foot disease". Submitted to Journal of Vascular Surgery.

"Burden of social isolation in lower limb arterial disease". Submitted to Vascular.

"Failure of progression to rehabilitation following major lower limb amputation". Submitted to Annals of Surgery.

"Impact of cancer on outcomes of major lower limb amputation". Submitted to European Journal of Vascular and Endovascular Surgery.

Supplementary Reflection Report

I thank my examiners for allowing me to write a reflection piece on specific issues raised in my viva. As advised by my examiners, I intend to use this reflection to improve the write-up of my studies for publication purposes.

Impact of COVID on Thesis

In my fruitful first year of research, I was lucky enough to present some of my work at the Veith Symposium, New York, 2019. A few months after this, the pandemic was in full force, and all research halted. I worked a full clinical rota for approximately four months, after which research opportunities were slowly re-introduced. The loss of such a valuable period for research had the most considerable impact on my thesis, but it was not the only problem that COVID brought with it.

Working from home meant that the benefits of meeting people face-to-face, such as organising collaborations, discussing research strategies and networking, were lost. The productivity of meetings fell when relying on virtual meetings. It was also challenging to manage the people I was collaborating with, especially when meeting deadlines.

Resource utilisation was also affected. I no longer had full access to the university library or the classes offered, especially those on performing systematic reviews, qualitative studies, statistics and coding. I think that the acquisition of these skills required an even higher level of self-directed learning than what a PhD would have normally entailed. The psychological hurdles faced must also be highlighted. The anxiety of not being able to finish studies on time and publish work was constant. Issues in my personal life, such as the passing of a dear friend whom I could not visit due to restrictions, were a real blow to my morale. Moreover, I had to work on my application for specialty training during my PhD.

Lack of time, people, resources and personal life impacted the design and write-up of some aspects of my thesis. Initial ambitions on the quality of what was achievable therefore had to

be curtailed to some degree. Still, perseverance and resourcefulness were required to ensure that the scientific process of my research was protected.

Limitations and Strengths of Qualitative Studies

While my examiners commended me on some of the novelty of my qualitative work, certain limitations of methodology were discussed. The retrospective collection of data on psychosocial problems introduced risks of bias, including patient sampling and self-selection. Content analysis of clinical documentation to identify qualitative data such as "patient concerns" may introduce unintentional reporting bias. A rigorous process of thematic analysis was not comprehensively reported and, therefore, may be questioned by qualitative journals. While we agreed on the above points, the novelty of the work and other strengths should also be highlighted. Firstly, this was a pragmatic study designed to capture a broad patient group. While some findings may not be generalisable to all patients, interesting results on gender and other socio-demographic factors have the potential to open further avenues of research by generating new hypotheses.

The examiners recognised the novelty and resourcefulness of using content analysis of clinical documentation. The qualitative work involved collaboration with a clinical psychologist who is a dedicated member of the diabetic foot MDT. This service is a rare asset for an MDT and encourages new avenues of MDT-led interventions to promote holistic care. Utilisation of socio-ecological framework modelling isn't common in vascular surgery, yet my studies highlight its potential benefits on understanding health-related behaviours and future targets of psychosocial care of lower limb patients. Finally, it was recognised by the examiners that qualitative research has substantial value in line with the overarching aim of my thesis.

Limitations and Strengths of Systematic Reviews

The limitations of my systematic reviews were centred around the rigor of reporting methodology. A more comprehensive description of exact steps in the search and screening strategy, definitions and inclusion and exclusion criteria were required. Ensuring that the discussion of results focused on the research question was also identified as an area for

improvement. Despite particular limitations, each systematic review identifies a significant issue and its implications on how patient-centred care is provided and therefore is publishable, as highlighted by the examiners.

Limitations and Strengths of Retrospective Cohort Studies

The quantitative aspect of my thesis involved retrospective studies. This methodology immediately affects the overall level of evidence supporting my conclusions. Some cohort studies relied on small patient populations and subgroup analyses. Moreover, the importance of reporting missing data was highlighted. The hub and spoke model of care prevented some studies from making longer-term observations on rehabilitation in Chapter 5.1. I was also quizzed on how I obtained frailty scores retrospectively. I was able to justify that with the choice of frailty scoring that I could deduce from my data points, but I agreed that other frailty scores would have been helpful to calculate with more granular data.

The term "functional survival" and its definition were questioned as it appeared a little confusing to the examiners. This term is, of course, a new concept that I have thought of and introduced. After explaining its definition, its analogy to "amputation-free survival", and my justification for its existence, I believe I was able to defend this concept. However, the lesson that I took away was the importance of complete clarity in my writing when introducing new concepts.

Although the above limitations were noted, the examiners agreed that this reflects the broad evidence base in literature for my topic of choice and that there are valuable findings that contribute to new knowledge and new questions. Other strengths of my work included the overall granularity with which data was reported and the exploration of biopsychosocial factors. There was consistency on the findings of many studies within my thesis on issues such as gender differences in outcome, cancer, psychosocial problems and therapy factors impacting rehabilitation outcomes. Some datasets were extensive and of high quality, such as the prosthetic mobility study.

Generalisability of the Work

Considering limitations and strengths in the methodologies discussed, I believe that new knowledge-generated from many aspects of this thesis are generalisable. Two chapters are systematic reviews with overall valid methodology. There were interesting findings consistent with topical research on other vascular patient groups, such as gender-related differences, and my work shed a fresh light on this issue from the perspective of amputation surgery. Functional survival is essential to understand as it identifies a critical phase of recovery after amputation but one in which a significant proportion of patients do poorly.

Cancer and its impact on outcomes is a debated topic that has not been studied for amputation surgery and data was gathered to a very granular level. The study reporting outcome of prosthetic rehabilitation relied on excellent quality outcome data from a prestigious and well-resourced regional rehabilitation centre. Finally, the simplicity and validity of the risk prediction models, with care taken to limit overfitting, allows for external validation studies. My focus will now turn to improving my write up and to get this work published.

Future Studies

Below are potential avenues of research that I believe should be explored. I plan to focus on this line of research in my ongoing career.

Chapter 3 (Reporting of outcomes by MDTs):

- 1) Studies on the impact of MDT on medical, organisational and patient-centred outcomes. 2) Studies on improving MDT efficacy.

Chapter 4.1 (Psychosocial problems in lower limb patients):

- 1) Prospective PROMS post amputation 2) Socio-ecological framework modelling in lower limb patients 3) Prospective study on the impact of psychosocial interventions on health-related behaviours, clinical and patient-centred outcomes 4) Understanding temporal changes in psychosocial problems in lower limb patients.

Chapter 4.2 (Social isolation in lower limb arterial disease):

- 1) Prospective study on social isolation in lower limb patients, temporal trends, impact on health-related behaviour and clinical outcomes

Chapter 5.1 (Functional survival):

- 1) Making functional survival into a new avenue of research, exploring its validity as a concept through a Delphi consensus 2) Larger multi-centre datasets to predict functional survival and validation studies

Chapter 5.2 (Cancer and Amputation):

- Prospective study on the impact of cancer (by type and chronicity of cancer diagnoses) on amputation outcomes, larger datasets for subgroup analysis, HES data

Chapter 6 (Prosthetic rehabilitation):

- 1) Understanding and predicting other patient-centred outcomes (such as QoL, Pain scores) after amputation 2) Reporting the rate and quality of wheelchair utilisation. 3) Cox regression model construction for long term-survival

Chapter 7: (Palliation for the unsalvageable limb)

- 1) Larger and prospective palliation study 2) Understanding and predicting other patient-centred outcomes (such as QoL, Pain scores) in palliated patients 3) Prediction of survival in palliation to streamline patients towards best end-of-life care.

Chapter 8: (Construction of decision-aid)

- 1) Face validation via Delphi consensus 2) Study its impact on decision-making 3) External validation study of the risk prediction tool.