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EXPLORING THE RELATIONSHIP BETWEEN BODY COMPOSITION, SYSTEMIC INFLAMMATION, AND OUTCOMES IN VASCULAR SURGICAL DISEASE

By

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy
(PhD) to the University of Glasgow.

This thesis was written from research conducted in the Academic Department of Surgery,
Glasgow Royal Infirmary, via the College of Medical, Veterinary, & Life Sciences,
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AUTHOR'S DECLARATION

The work in the present thesis was conducted between October 2021 and October 2024 at the Academic Unit of Surgery, Glasgow Royal Infirmary. I, the author, declare that all of the work presented in this thesis was conducted by me, other than the following:

Miss Amy Walter contributed to several elements of the data collection in the AAA and CLTI cohorts featured in chapters 3, 5, 6, 7, 8, 9, 11, 13, and 14.

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2. Evaluation of the prognostic value of computed tomography-derived body composition in patients undergoing endovascular aneurysm repair. *J Cachexia Sarcopenia Muscle.* 2023 May 23. DOI: 10.1002/jcsm.13262. PMID: 37221439
3. The prognostic value of preoperative systemic inflammation-based scoring in patients undergoing endovascular repair of abdominal aortic aneurysm. *J Vasc Surg.* 2023 Apr 20;S0741-5214(23)01060-1. DOI: 10.1016/j.jvs.2023.04.018. PMID: 3708682
4. The relationship between computed tomography-derived body composition, systemic inflammation, and survival in patients with abdominal aortic aneurysm. *J Vasc Surg* 2023 Oct;78(4):937-944.e4. DOI: 10.1016/j.jvs.2023.06.012. PMID: 37385355
5. The Relationship between Clinical Frailty Score, CT-Derived Body Composition, Systemic Inflammation, and Survival in Patients with Chronic Limb-Threatening Ischemia. *Ann Vasc Surg* 2023 Jun 24;S0890-5096(23)00339-4. DOI: 10.1016/j.avsg.2023.06.012. PMID: 37356659
6. The prognostic value of clinical frailty and American Society of Anesthesiology score in patients with chronic limb threatening ischaemia. *Vasa* 2023 Sep;52(5):302-309. DOI: 10.1024/0301-1526/a001085. PMID: 37528752

7. CT-derived body composition: Differential association with disease, age and inflammation in a retrospective cohort study. *PLoS One*. 2024 Mar 21; 19(3):e0300038. DOI:10.1371/journal.pone.0300038. PMID: 38512880

8. A systematic review of the neutrophil to lymphocyte and platelet to lymphocyte ratios in patients with lower extremity arterial disease. *Vasa*. 2024 May;53(3):155-171. DOI: 10.1024/0301-1526/a001117. PMID 38563057.

9. Cardiopulmonary exercise testing, computed tomography-derived body composition, systemic inflammation and survival after elective abdominal aortic aneurysm repair: A retrospective cohort study. *Eur J Anaesthesiol*, 2024 Jul 1;41(7):490-499. DOI 10.1097/EJA.0000000000002004. PMID: 38757161.

10. A systematic review of the role of systemic inflammation-based prognostic scores in patients with abdominal aortic aneurysm. *Surgeon*. 2024 Aug 26:S1479-666X(24)00095-7. DOI: 10.1016/j.surge.2024.08.014. PMID: 39191632.

11. The relationship between peri-operative systemic inflammation and survival in patients with abdominal aortic aneurysm. *Ann Vasc Surg*. 2024 Oct 10:S0890-5096(24)00618-6. DOI: 10.1016/j.avsg.2024.08.024. PMID: 39395590.

12. The relationship between CT-derived cervical muscle mass and quality, systemic inflammation, and survival in symptomatic patients undergoing carotid endarterectomy. *BJS Open*. 2024 Sep 3;8(5):zrae114. DOI: 10.1093/bjsopen/zrae114. PMID: 39441694.

13. Longitudinal association between statins and changes in CT-body composition in patients with abdominal aortic aneurysm. *J Cachexia Sarcopenia Muscle*. 2025 Apr 9;16(2). DOI: 10.1002/jcsm.13565. PMID: 40204359.

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DEFINITIONS & ABBREVIATIONS

%1yrOS	% 1-year overall survival
%5yrOS	% 5-year overall survival
AAA	Abdominal aortic aneurysm
AJCC	American joint committee on cancer
ASA	American Society of Anaesthesiologists
AT	Anaerobic threshold
AUC	Area under the curve
BASIL-1	Bypass versus Angioplasty in Severe Ischaemia of the Leg 1 Trial
BEST-CLI	Best Endovascular versus Best Surgical Therapy in Patients with CLTI Trial
BMI	Body-mass index
BMT	Best medical therapy
C3	Cervical vertebra 3
C3 SMA	C3 skeletal muscle area
C3 SMD	C3 skeletal muscle density
C3 SMI	C3 skeletal muscle index
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcome Study
CEA	Carotid endarterectomy

CFS	Clinical frailty score
CHI	Community Health Index
CI	Confidence interval
CLTI	Chronic limb threatening ischaemia
COPD	Chronic obstructive pulmonary disease
CPEX	Cardiopulmonary exercise testing
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
CT-BC	Computed tomography-derived body composition analysis
CT-SS	CT-sarcopenia score
CVA	Cerebrovascular attack
CVD	Cerebrovascular disease
CYP3A4	Cytochrome P 450 3A4
DAFS	Data Analysis Facilitation Suite
DASI	Duke activity status index
DEXA	Dual energy X-ray absorptiometry
DNA	Deoxyribonucleic acid

eNOS	Endothelial cell nitric oxide synthase
ESVS	European society for vascular surgery
EVAR	Endovascular aneurysm repair
EWGSOP2	Second European working group on sarcopenia in older people
F/B-EVAR	Fenestrated/branched-endovascular aneurysm repair
FDA	Food and drug administration
GPS	Glasgow prognostic score
GVG	Global vascular guidelines
HMG-CoA	β -hydroxy β -methylglutaryl-coenzyme A
HR	Hazard ratio
HSC-PBPP	Public Benefit and Privacy Panel for Health and Social Care
HU	Hounsfield units
ICA	Internal carotid artery
IGF-1	Insulin-like growth factor 1
IHD	Ischaemic heart disease
IL-1 β	Interleukin-1-beta
IL-6	Interleukin 6
IQR	Interquartile range

hsCRP	High-sensitivity C-reactive protein
JAK-STAT	Janus kinase signal transducer and activator of transcription
L3	Lumbar vertebra 3
L3 dSMI	L3 derived skeletal muscle index
LDH	Lactate dehydrogenase
LDL	Low density lipoproteins
LEAD	Lower extremity arterial disease
LMI	Liver mass index
MACE	Major adverse cardiovascular event
MACLE	Major adverse cardiovascular and limb event
MALE	Major adverse limb event
MAPK	Mitogen-activated protein kinase
MCN	Managed clinical network
MeSH	Medical subject heading
METS	Metabolic equivalence of tasks score
mGPS	Modified Glasgow prognostic score
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging

MUST	Malnutrition universal screening tool
NF- κ B	Nuclear factor kappa-B
NHS	National health service
NICE	National institute for health and care excellence
NIH	National institutes of health
NLR	Neutrophil:lymphocyte ratio
NR	Not reported
NS	Not significant
OR	Odds ratio
OSR	Open surgical repair
PACS	Picture archiving and communicating system
PBPP	Public benefit and privacy panel
PCC	Pearson correlation coefficient
PIS	Post-implantation syndrome
PLR	Platelet:lymphocyte ratio
PMA	Psoas muscle area
PMI	Psoas muscle index
PMID	PubMed identifier

poGPS	Post-operative Glasgow Pro gnostic Score
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PTA	Percutaneous transluminal angioplasty
QoL	Quality of life
QUIPS	Quality in prognosis studies
rAAA	Ruptured abdominal aortic aneurysm
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SD	Standard deviation
SE	Standard error
SFA	Subcutaneous fat area
SFI	Subcutaneous fat index
SIG	Systemic inflammatory grade
SII	Systemic immune-inflammatory index
SIR	Systemic inflammatory response
SMA	Skeletal muscle area
SMD	Skeletal muscle density
SMI	Skeletal muscle index

SPSS	Statistical package for social sciences
SVS	Society of vascular surgery
TASC	Transatlantic inter-society consensus
TIA	Transient ischaemic attack
TNF- α	Tumour necrosis factor alpha
TNM	Tumour, node, metastasis
UK	United Kingdom
UK-COMPASS	UK complex aneurysm study
USA	United States of America
VCAM-1	Vascular cell adhesion molecule-1
VFA	Visceral fat area
VFI	Visceral fat index
VIF	Variance inflation factor
VO ₂	Volume of oxygen
WCC	White cell count
WIFI	Wound, ischaemia, foot, infection
WoSCAN	West of Scotland Cancer Network

List of definitions & abbreviations, in alphabetical order.

DEDICATION

To my wife Emilie, for her enduring patience and support throughout our marriage and during the completion of this work.

ABSTRACT

Cardiovascular disease remains the leading global cause of death, with a predicted increase in the future due to a range of demographic and social factors. Within this spectrum of illnesses, vascular surgical conditions are an important group of problems. The typical underlying pathophysiology is atherosclerosis, which has a well described risk factor profile. The disease entities which comprise the majority of vascular surgical practice are aortic aneurysm (AAA), chronic limb threatening ischaemia (CLTI), and cerebrovascular disease (CVD).

Sarcopenia, defined as a progressive loss of skeletal mass and function (EWGSOP2 definition), has recently emerged as an important factor associated with a range of chronic illnesses. It has been evaluated as a potential prognostic factor, with the largest amount of evidence coming from patients with cancer. CT-derived body composition analysis (CT-BC) is a technique used to quantify sarcopenia through measurement of cross-sectional tissue areas, allowing muscle and fat indices to be derived and quantitatively analysed.

A key aetiological factor in the development of both cardiovascular disease and sarcopenia is the systemic inflammatory response (SIR). The SIR can be quantified using inflammation-based prognostic scoring systems, such as the neutrophil:lymphocyte ratio (NLR), platelet:lymphocyte ratio (PLR), and modified Glasgow Prognostic Score (mGPS), both of which have been independently associated with inferior survival in patients with cancer.

In vascular surgical conditions, both sarcopenia as measured by CT-BC, and the SIR, are less widely reported than in other conditions. The aim of the present thesis was to describe the existing evidence base describing these factors, and evaluate their associations and potential prognostic value, in patients with AAA, CLTI, and CVD.

In chapter 2 the literature describing the potential prognostic role of CT-BC in patients undergoing elective endovascular repair (EVAR) of AAA was reviewed, and on meta-analysis a clear association between low skeletal muscle mass and inferior survival outcomes was observed, however the existing studies had limited methodology.

In chapter 3, CT-BC parameters were evaluated in a multicentre cohort of patients undergoing EVAR for AAA. There was an independent association between low skeletal muscle index (SMI) and inferior survival outcomes in this cohort.

In chapter 4 the literature describing the association between elevated NLR and PLR and outcomes in patients undergoing intervention for AAA was reviewed. Elevated NLR and PLR were generally associated with inferior long-term survival., despite limitations in methodology observed.

In chapter 5 the NLR and mGPS were combined into the systemic inflammatory grade (SIG), which aims to provide a more comprehensive assessment of the SIR. There was an independent association between increasing SIG and inferior survival outcomes in patients undergoing intervention for AAA.

In chapter 6 Combining the factors of interest from chapters 3 and 5 in chapter 6 allowed for a description of the combined potential prognostic value of both CT-derived sarcopenia (as measured through CT-SS, a novel observation in this patient group) and the SIR (as measured through SIG). There was a marked observation of significantly inferior survival in patients with both low skeletal muscle mass/density and elevated SIG.

In chapter 7 a possible association between sarcopenia and inferior physiological fitness as assessed by cardiopulmonary exercise testing (CPEX) was explored, with sarcopenia assessed using the CT-Sarcopenia Score (CT-SS), which combines muscle mass and density. There was no significant association between sarcopenia and CPEX parameters. When compared to CPEX parameters, CT-SS demonstrated greater association with survival.

In chapter 8 patients undergoing intervention for AAA were compared to patients undergoing resection for colorectal cancer (CRC). The magnitude of the SIR and low skeletal muscle density (SMD) were more prevalent in patients with CRC, and there was an association between increasing age and decline in CT-BC parameters in both patient groups.

In chapter 9 the post-operative SIR was examined in relation to survival following both elective and emergency repair of AAA. Elevated day 3 CRP was associated with inferior

survival outcomes in both the elective and emergency cohorts, though at different timepoints.

In chapter 10 the literature describing survival outcomes, disease severity, and technical success of intervention in patients with CLTI, in relation to NLR and PLR, was reviewed. Methodology was heterogenous in the 34 studies, however the majority of studies report an association between elevated NLR/PLR and the outcomes of interest.

In chapter 11 the effect of frailty (as measured by the clinical frailty score, CFS), CT-BC, and the SIR on survival in a cohort of patients with CLTI was described. CT-SS, mGPS, and CFS were independently associated inferior survival outcomes.

In chapter 12 the association between CT-BC, the SIR, and survival was described in a cohort of patients undergoing carotid endarterectomy for symptomatic carotid lesions. The SMD at C3 and elevated SIG were shown to be independently associated with inferior survival.

In chapter 13 the longitudinal change in CT-BC was investigated in patients undergoing intervention for AAA. A decline in both SMI and SMD was observed following intervention for AAA. The decline in SMD was of a greater magnitude than SMI. Statin therapy was associated with a lower risk of baseline low SMI.

In chapter 14 the cross sectional liver area was recorded in patients with AAA at baseline and at follow-up CT, and the association between survival and relationship to CT-BC parameters was tested. Low liver area was associated with inferior survival. There was a decline in liver area, but a preservation of liver density. CT-BC muscle parameters had a greater association with survival than liver parameters.

The present thesis reports a multitude of novel observations which demonstrate an association between CT-BC, the SIR, and survival, as well as their associations, in patients with vascular surgical conditions. These results support the work performed in different conditions, and highlight the possible role of these factors in clinical risk prediction and patient selection.

1 INTRODUCTION

1.1 CARDIOVASCULAR DISEASE

1.1.1 DISEASE BURDEN

Despite advances in medical management, screening, risk factor modification, and secondary prevention strategies, cardiovascular disease remains the leading worldwide cause of death, with a particularly marked increase in low/middle income countries^{1,2}. Worldwide, there are approximately 20 million deaths per year which are attributable to cardiovascular disease^{3,4}. Atherosclerotic cardiovascular disease forms the vast majority of the disease burden, with ischaemic heart disease (IHD) the most common manifestation and leading cause of death⁵. Both demographic (aging population, obesity epidemic) and geopolitical factors (climate crisis, cost of living crisis) factors are likely to contribute towards a further increase in the global burden of cardiovascular disease in the coming decades^{6,7}. Health promotion strategies, such as the implementation of strict controls (and subsequent phasing out of) tobacco smoking, may offer potential utility in reducing the incidence of cardiovascular disease^{8,9}. However, these measures are seldom observed in low/middle income countries and are likely to be offset by population aging and the increasing burden of chronic illnesses such as diabetes mellitus^{7,10}.

1.1.2 VASCULAR SURGICAL CONDITIONS

Vascular surgical conditions consist of a range of clinical entities, the vast majority of which involve arterial pathology. The predominant underlying pathophysiological entity is atherosclerosis, which is discussed in section 1.2, however non-atherosclerotic disease may also be encountered. This is perhaps most manifest in aneurysmal disease, however may also be observed in trauma, vasculitis, and acute embolic phenomena. This thesis predominantly describes patients with aneurysmal disease and conventional occlusive atherosclerotic disease, both of which share similar risk factors and patient demographics.

1.1.2.1 AORTIC ANEURYSM

“Aneurysm” refers to a pathological dilatation of an artery to over 1.5 times its normal anatomical diameter. Whilst aneurysms can be found at any anatomical location, the most common is an abdominal aortic aneurysm (AAA), which is defined as >3cm dilatation of the abdominal aorta. AAA may be below the level of the renal arteries (infrarenal AAA) or

involving the visceral segment of the aorta (juxta-/para-renal AAA). The iliac arteries may also become involved either in isolation or combined with AAA. Management of isolated iliac artery aneurysms follows similar principles to AAA, though with slight differences to the surgical approach. The estimated UK prevalence of AAA is 1.5%, rising to 1.9 – 4.0 % in males aged over 65¹¹. AAA is not caused by typical atherosclerotic obstructive arterial disease, rather due to atherosclerotic degeneration of the arterial wall resulting in dilatation. The resulting arterial wall damage appears to result in an imbalance of collagenase (the matrix metalloproteinase family, MMP), causing increased lysis of collagen and degenerative dilatation¹². Rarer causes of aortic aneurysm, such as following acute aortic dissection, or mycotic aneurysms due to infection of the arterial wall, are managed differently and are beyond the scope of the present thesis.

The natural history of AAA is to progressively enlarge at a variable rate over years or decades, with recent literature suggesting a modest growth rate of 0.19cm diameter increase per year¹³. In contemporary practice, diagnosis of AAA is most commonly as an incidental finding due to the large amount of cross-sectional imaging performed in modern healthcare. Additionally, in the UK, the AAA screening programme uses ultrasonography in males aged 65 to identify asymptomatic AAA. Those patients with aneurysms above a size where repair may be indicated are referred for assessment and consideration of repair, and those who have aneurysms below threshold undergo surveillance using ultrasound to monitor the progression of their AAA. Whilst the majority of AAA are asymptomatic, large aneurysms may cause symptoms such as abdominal pain, or obstruction of adjacent viscera due to mass effect, which may lead to hospital presentation and diagnosis. Finally, ruptured AAA (rAAA) is a catastrophic presentation of AAA, which carries up to 85% mortality and is inevitably fatal if left untreated¹⁴. The aim of management of AAA is to either prevent rupture (in the elective setting) or to repair rupture (in the emergency setting). The risk of progressing to rAAA is determined by the Law of Laplace; where tension in a vessel wall is proportional to the product of the luminal pressure and the radius ($T = P \times R$). Increasing wall tension (“T”) increases the risk of wall rupture. Optimisation of blood pressure (“P”) is therefore of paramount importance. There are, at time of writing, no lifestyle or pharmacological modalities to directly reverse, arrest, or slow rate of growth of AAA, therefore wall radius (“R”) must be managed surgically.

Repair of AAA consists, broadly, of two treatment strategies: either an open surgical repair (OSR) or endovascular aneurysm repair (EVAR). OSR requires surgical access to the retroperitoneum, typically achieved via midline laparotomy. Haemostatic control of the

aorta is obtained, the aneurysm incised, and a prosthetic graft sutured in place. In contrast, EVAR excludes the AAA from the systemic circulation through deployment of an impermeable stent-graft across the aneurysmal segment of aorta, with proximal and distal seals in healthy artery above and below the AAA. This is performed under angiographic guidance, and requires intra-arterial access, most commonly percutaneously via the femoral arteries. Juxta-/para-renal AAA require more complex stent-grafts with the capability to stent into visceral vessels (fenestrated or branched devices, F/B-EVAR). In general, OSR causes a more profound physiological insult than EVAR, and therefore requires greater physiological fitness to tolerate the procedure without complication. However, EVAR is more constrained by anatomical considerations, with some aneurysm morphologies not amenable to EVAR. Additionally, EVAR appears to have inferior longevity compared to OSR, with a much higher reintervention rate¹⁵. For this reason, typical practice is to perform surveillance imaging of patients who undergo EVAR, either through ultrasound or CT¹⁶. The key component of surveillance is the identification of endoleaks, defined as persistent perfusion of the residual aneurysm sac. In the context of an endoleak, the size of the residual aneurysm sac is important; increasing sac size may necessitate reintervention to ameliorate the risk of secondary rupture. In the majority of patients who undergo EVAR sac regression is seen, which is considered a reassuring finding and may indicate reduced risk of reintervention^{17,18}.

Several large trials performed in the 1990s and 2000s influence choice of OSR or EVAR^{19–21}. Generally, younger patients with a greater degree of physiological reserve will be offered OSR, whilst older patients will be offered EVAR²². Several techniques are available to attempt to quantify the degree of physiological fitness, such as echocardiography, pulmonary function tests, and cardiopulmonary exercise testing (CPEX). Each of these investigations offer different information, and their use varies between institutions. This selective practice is reflected in guidelines for pre-operative investigation of patients with AAA²². Finally, the benefit to elective repair must be considered in the context of the risk of intervention, and contemporary practice is heavily influenced by the UK Small Aneurysm Trial²³. Powell *et al* observed that, in 1090 patients enrolled between 1991 and 1995 who underwent OSR, there was no long-term survival benefit to repairing AAA below a threshold of 5.5cm diameter. These findings have culminated in a threshold for intervention of 5.5cm being widely adopted into guidelines and practice²². As mentioned previously, patients with AAA below 5.5cm are offered ultrasonographic surveillance, followed by referral to consider intervention when threshold is reached.

1.1.2.2 CHRONIC LIMB THREATENING ISCHAEMIA

Chronic limb threatening ischaemia (CLTI) is considered the most severe form of obstructive atherosclerotic disease affecting the peripheral arterial system. Lower extremity arterial disease (LEAD) encompasses a spectrum of presentations based on symptom burden, ranging from patients with asymptomatic atherosclerotic lesions to those with severe symptoms associated with significant morbidity and mortality. Whilst atherosclerotic disease may affect any limb, the lower limbs are affected far more than the upper limbs, and the disease process is often symmetrical²⁴. Symptoms are caused by compromised blood supply to peripheral tissues due to atherosclerotic plaque buildup, with the severity of symptoms proportional to the relative degree of ischaemia. The chronic atherosclerotic stenoses may deteriorate acutely, often due to plaque rupture and thrombosis of an already diseased vessel.

Impaired peripheral perfusion results in reduced aerobic respiration and increased dependency on anaerobic respiration, culminating in a buildup of metabolites (including adenosine triphosphate, lactate, free hydrogen ions) which induce a localised inflammatory cascade²⁵. These inflammatory mediators trigger a pain response through activation of peripheral nociceptors. In less severe disease, patients may experience symptoms only when tissue oxygen demand is increased through increased metabolic activity, such as during exercise (“intermittent claudication”). In more severe disease patients may become symptomatic when tissue oxygen demand is minimal, such as at rest or during sleep, and may culminate in tissue damage (necrosis and ulceration). Tissue loss may be spontaneous, or more commonly as a result of non-healing wounds from minor, often occult, trauma.

The 2019 Global Vascular Guidelines define the clinical presentation of CLTI as over 2 weeks of ischaemic rest pain, nocturnal pain, or tissue loss²⁶. Accurate diagnosis of CLTI is important in LEAD, as presence of CLTI is indicative of more severe disease with a high risk of limb loss if left untreated, and an associated poor prognosis due to the prevalence of comorbidities associated with atherosclerosis. Severity of disease can be quantified using several validated scoring systems based on clinical presentation; the Society of Vascular Surgery (SVS) Wound, Ischaemia, Foot, Infection (WIFI) Score is widely reported and appears to be associated with limb salvage rates^{27,28}. Patients who are asymptomatic or suffer with claudication alone are typically managed without intervention, receiving secondary prevention strategies as detailed previously, whereas those with CLTI may undergo intervention if appropriate. The primary management aim in CLTI is limb salvage,

achieved through revascularisation procedures, and secondarily surgical debridement of non-salvageable tissue to achieve wound healing is considered where required. Similarly to the repair of AAA, revascularisation in CLTI broadly follows 2 main treatment modalities; open surgical or endovascular reconstruction, and the same treatment principles regarding patient fitness and technical feasibility apply.

Contemporary practice is influenced by several large trials, with the widely cited BASIL-1 and BASIL-2 trials highlighting the complexity of decision making for open surgical bypass versus endovascular intervention depending on the location of the occlusive disease^{29,30}. The findings of BASIL-1 were corroborated by the recent Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia (BEST-CLI) trial³¹. There remains an element of heterogeneity in worldwide practice and subsequent follow-up trials which may influence practice are eagerly awaited. Prognosis in patients with CLTI remains poor; reported amputation-free survival rates are variable however may be as low as 70% at 1-year following presentation²⁶. Whilst the poor prognosis may be partially attributable to CLTI itself, the severity of the systemic atherosclerotic burden typically results in a clinical phenotype of multiple morbidity, and poor survival may be seen irrespective of limb salvage.

1.1.2.3 CEREBROVASCULAR DISEASE

Atherosclerotic disease affecting the cranial circulation is termed cerebrovascular disease (CVD). In contrast to CLTI, symptoms are not typically gradually produced by the degree of flow limitation as a result of stenosis, rather by acute rupture or ulceration of plaque causing distal embolisation to the intracranial vessels (termed atheroembolisation). Patients may be asymptomatic and have small vessel intracranial disease identified as an incidental finding on CT or magnetic resonance imaging (MRI), have temporary symptoms with complete resolution (transient ischaemic attack, TIA), or develop symptoms with permanent deficit (cerebrovascular attack / stroke, CVA). Symptoms are produced based on the anatomical location of arterial occlusion.

TIA/CVA is a common presentation to hospital, with an annual incidence of over 100,000 CVAs in the UK³². Initial management of a TIA is medical, using “best medical therapy” (BMT) consisting of a high dose statin and antiplatelet therapy, with the aim of preventing recurrent event supported by robust evidence³³. Patients presenting with a CVA also ultimately receive BMT, however depending on pattern of disease and mode of

presentation may receive additional therapies to relieve the occlusion, such as systemic thrombolysis or mechanical thrombectomy. These therapies are typically delivered under the care of stroke physicians and are beyond the scope of the present thesis.

Relevant to vascular surgery, 10-15% of patients presenting with TIA/CVA have a culprit stenosis of the internal carotid artery (ICA)³⁴. Should a suitable culprit stenosis be identified, patients can be considered for reconstructive surgery in the form of carotid endarterectomy (CEA), where the atherosclerotic plaque is excised from the arterial wall and a patch reconstruction performed, thereby reducing the risk of future atheroembolisation. Following presentation, patients will typically undergo ultrasonographic interrogation of their carotid arteries. A degree of atherosclerotic carotid stenosis is a common finding, however the majority are not considered suitable for intervention. Following several large scale trials in the 1990s and 2000s, the evidence base suggests criteria for maximal benefit, including stenosis > 70% and a typical pattern of symptoms^{35,36}. Lesions which fit the criteria for being a likely cause of the TIA/CVA are termed “symptomatic”. Identifying patients who will benefit from surgery is key to optimising the risk:benefit ratio of the procedure; the most feared complication of CEA is peri-procedural CVA, with a generally accepted risk of 2-3%³⁷. Notwithstanding, in appropriately selected patients, CEA is beneficial in reducing the risk of further TIA/CVA over a period of 3-5 years^{35,36}. More recently, interventions on asymptomatic (I.e. those identified through screening or incidentally during investigation for an alternative pathology) carotid stenoses, and novel techniques such as carotid stenting have been developed, however these are currently non-standard in UK practice^{38,39}.

1.1.2.4 ISCHAEMIC HEART DISEASE

Ischaemic Heart Disease (IHD) refers to atherosclerotic disease of the coronary circulation. As with CLTI, symptoms are largely dictated by the degree of vessel stenosis or acute occlusion. The range of presentations includes asymptomatic, angina pectoris, or acute myocardial infarction. In the clinical setting, IHD is conventionally managed by cardiologists and cardiothoracic surgeons. In some countries, cardiac and vascular surgical conditions are managed under the umbrella of cardiovascular surgery, however in contemporary UK practice these specialties are discrete entities, and thus cardiac surgery does not come under the remit of vascular surgical specialties. Therefore, exploring IHD as a specific disease entity is beyond the scope of the present thesis, however IHD is

discussed in the context of comorbidity with other conditions. IHD and CVD are responsible for 85% of worldwide deaths attributable to cardiovascular disease³.

1.2 ATHEROSCLEROSIS

1.2.1 DEFINITION

Atherosclerosis refers to the development of lipid-rich obstructive lesions in the arterial component of the circulatory system. These lesions develop slowly over time, typically years or decades, culminating in a range of clinically observed phenotypes of atherosclerotic disease. Atherosclerotic disease is the second most common cause of death in high-income countries, and worldwide is the leading cause of death⁴⁰. Whilst atherosclerotic disease is increasing as a burden on global healthcare systems, it is not exclusively a disease of the modern era. On the contrary, as a disease entity, obstructive arterial disease has been recognised since at least the 18th century⁴¹. Additionally, posthumous examination of mummified individuals from the era of antiquity has revealed evidence of atherosclerotic arterial disease⁴². The term “atherosclerosis” was coined in 1904 by Felix Marchand, derived from the Greek “athero” (gruel, paste) and “sclerosis” (hardening)⁴³. This etymology concisely highlights the classical appearance of atherosclerotic lesions.

1.2.2 PATHOGENESIS

The predominant macroscopic pathological feature of established atherosclerosis is the deposition, within the arterial lumen, of a fibrous atheromatous plaque with a lipid rich core (figure 1.1⁴⁴). The development of such plaques is a gradual process, occurring over decades in the majority of cases. The earliest typical feature is the so-called “fatty streak” visible on the innermost layer of the arterial wall (“intima”). Following the development of an atheromatous plaque, the natural history of these lesions is variable, though classically progresses to calcification and sclerosis⁴⁵. Microscopically, the initial event instigating the development of plaque is thought to be recurrent endothelial injury. The causative event triggering this endothelial injury remains uncertain, though is likely a combination of chemical and mechanical factors, in particular shear stress due to blood flow resulting in desquamation of endothelial cells⁴⁶. There is some evidence that certain arteries are more susceptible to atherosclerosis than others, supporting the potential role the shear stress caused by flow dynamics plays in endothelial injury⁴⁷. Regardless of the instigating event, recurrent injury triggers a local inflammatory cascade mediated by monocytes and T-

cells⁴⁸. Monocyte aggregation is largely mediated by vascular cell adhesion molecule 1 (VCAM-1) which is expressed by the damaged endothelium. Migration of lipid molecules (low density lipoproteins, LDL) into the vessel intima in response to local inflammation occurs, followed by maturation of monocytes into macrophages. These macrophages then incorporate LDL molecules into their structure to become foam cells, which form the fatty lipid-rich core of atherosclerotic plaques. Over time, plaques increase in size as more foam cells are recruited, and subsequent deposition of smooth muscle cells and fibroblasts give the lesions their characteristic fibrous cap. Localised inflammation continues as plaques mature; continued foam cell aggregation results in necrotic transformation of the lipid-rich core, which perpetuates the inflammatory cascade in a positive feedback loop. Necrosis of foam cells releases apoptotic bodies and vesicles, which act as foci for microcalcification⁴⁹. Recurrent episodes of necrosis and microcalcification initiate a relapsing-remitting pattern of localised inflammation, culminating in remodelling and eventual plaque stabilisation through macroscopic plaque calcification⁴⁹.

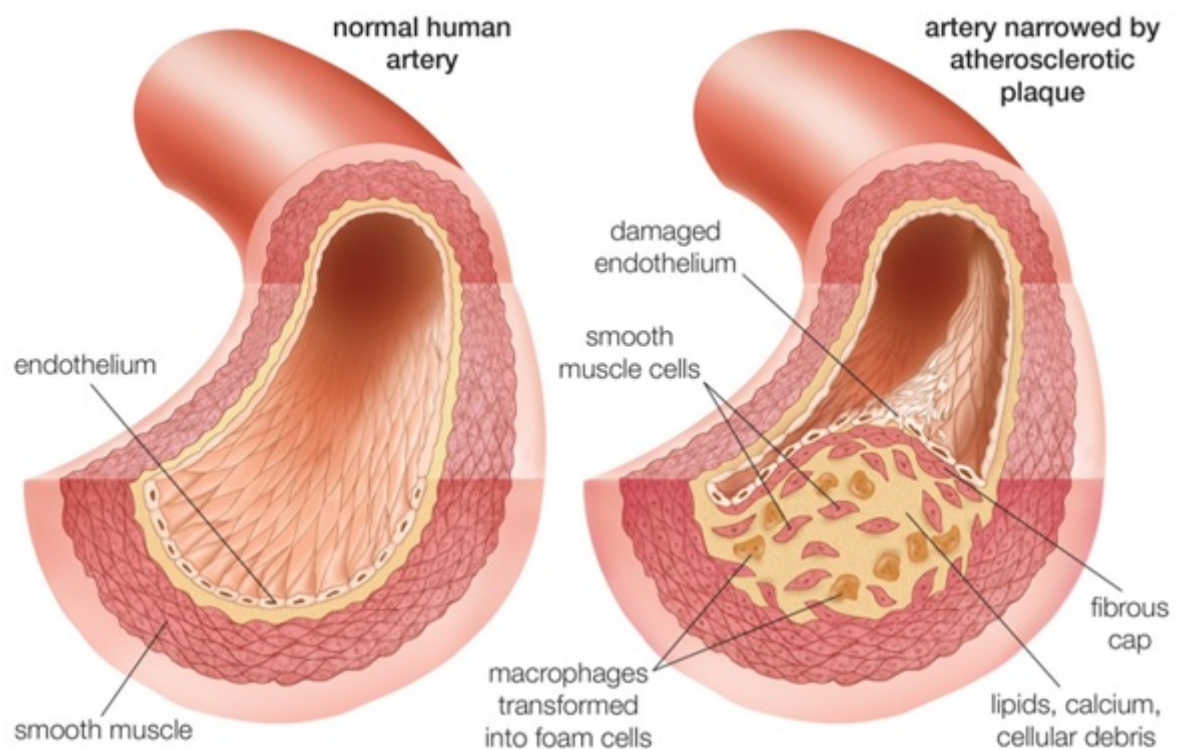


Figure 1.1 Comparison of normal human artery and human artery containing atherosclerotic plaque (adapted from Encyclopaedia Britannica 2023⁵).

1.2.3 RISK FACTORS

Risk factors which predispose an individual to develop atherosclerosis and/or accelerate the rate of plaque progression are well described, and reducing/removing exposure to these risk factors forms a key component of the management of atherosclerosis. Non-modifiable

classical risk factors include increasing age, family history of cardiovascular disease, and male sex. Whilst it is uncommon to develop clinical manifestations of atherosclerosis before the 5th decade of life, microscopic evidence of atherosclerosis can develop in children and young adults. Atherosclerotic disease does not typically present in young women, though from the 7th decade the incidence of myocardial infarction between sexes begins to equalise, highlighting the dominant effect of age⁵⁰. Modifiable classical risk factors include obesity, tobacco smoking, hypertension, diabetes mellitus, sedentary lifestyle, psychological stress, and elevated LDL cholesterol.

Despite a wealth of research into the pathway by which the various risk factors predispose to acceleration of atherosclerosis, there remains uncertainty around the precise molecular mechanisms. Indeed, there is somewhat paradoxical evidence which suggests that there may be an association between extremely high levels of physical activity (endurance athletics) and increased risk of atherosclerotic plaques^{51,52}. Obesity, dyslipidaemia, and diabetes mellitus, which overlap clinically components of the metabolic syndrome, may induce generation of reactive oxygen species (ROS), which are known to precipitate localised inflammation and endothelial injury⁵³. Similarly, the myriad of toxins present in tobacco smoke are thought to induce oxidative stress triggering a cycle of inflammation, thrombosis, remodelling, and calcification⁵⁴. More recently, novel risk factors such as elevated plasma homocysteine have been proposed, though lack validation and have not yet been implemented into guidelines for detection and management of atherosclerotic diseases⁵⁵.

1.2.4 GENERAL PRINCIPLES OF MANAGEMENT

Each atherosclerotic disease phenotype requires specific management, which is discussed in section 1.1.2. However, risk factor modification is an important aspect of management, and is the mainstay of treatment for the majority of patients with atherosclerotic disease, who are asymptomatic and identified either incidentally or via risk assessment in primary care. There is evidence that intervening on lifestyle factors (smoking cessation, dietary modification, reducing stress, and engagement with physical activity) can improve not only symptom burden but also may result in regression of atherosclerotic plaque^{56,57}. Primary prevention strategies refer to risk factor modification in patients at high risk of developing symptomatic atherosclerosis, prior to the onset of symptoms. High risk individuals are typically identified using validated risk assessment scores predicting the risk of major cardiovascular event, with QRISK3 the most widely used in United Kingdom (UK)

practice⁵⁸. Secondary prevention strategies refer to risk factor modification in patients who have developed symptomatic atherosclerotic disease (i.e. have had a cardiovascular “event” such as a stroke or heart attack). Regardless, both strategies include (where required) weight loss, smoking cessation, blood pressure control, optimal glycaemic control, and lipid lowering therapy. The first choice of lipid lowering agent is a statin, a β -hydroxy β -methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. HMG-CoA reductase is necessary for the synthesis of cholesterol; the conventional rationale for the inhibition was that lowering serum cholesterol would result in reduced lipid deposition in the arterial wall. A goal-directed approach to cholesterol management is advised by both North American⁵⁹ and European⁶⁰ guidelines, with higher risk individuals subject to more aggressive cholesterol targets. Whilst this lipid-lowering effect yields benefit in cardiovascular risk reduction, a growing body of evidence that statins suggests that statins have potent anti-inflammatory properties, possibly mediated by upregulation of endothelial cell nitric oxide synthase (eNOS)⁶¹. The JUPITER trial observed that, in patients without dyslipidaemia but with evidence of chronic systemic inflammation (elevated high-sensitivity CRP), statin therapy was associated with reduced rate of cardiovascular events⁶².

Established worldwide practice has been to prescribe an anti-platelet agent, typically aspirin, thought to reduce the platelet-dependent thrombosis associated with ruptured or necrotic plaques. Whilst this remains the case in secondary prevention, in primary prevention strategies recent evidence has challenged this practice due to a higher than previously reported risk of bleeding^{63,64}. Alternative anti-platelet agents such as clopidogrel, ticagrelor, and dipyridamole are less widely used than aspirin, largely due to less favourable side effect profiles, and new evidence combining anti-platelet and anti-thrombotic agents is emerging which may influence future strategies^{65,66}.

1.2.5 CLINICAL MANIFESTATIONS

Clinically, atherosclerosis is most commonly manifest as an incidental finding during investigation performed for an alternative diagnosis, such as coronary artery calcification seen on computed tomography (CT) imaging of the thorax. In symptomatic atherosclerotic disease, disease phenotypes are typically present due to change in arterial morphology, impaired blood flow due to luminal narrowing/occlusion, or abrupt compromise in blood flow due to rupture of plaque and arterial occlusion. Due to the systemic nature of the atherosclerotic process, plaque deposition is seldom confined to one anatomical region,

resulting in a typical clinical phenotype of multiple overlapping diagnoses. Specific conditions relating to atherosclerotic disease are discussed in section 1.1.2.

1.3 SARCOPENIA & BODY COMPOSITION

1.3.1 DEFINITION & MEASUREMENT

The term sarcopenia is derived from the Greek “sarx” (flesh) and “penia” (poverty), and has been identified in modern medicine as a clinical entity for almost 50 years, however its significance in relation to outcomes has only recently become widely acknowledged⁶⁷. The second European Working Group on Sarcopenia in Older People (EWGSOP2) define sarcopenia as “progressive decline in skeletal muscle and function⁶⁸”. Whilst typically associated with aging, sarcopenia can also be observed in younger patients; estimates of prevalence suggest approximately 5-13% of “healthy” individuals aged 60-70 are sarcopenic, which increases to 11-50% in individuals aged 80 and above⁶⁹. A diagnosis of sarcopenia can be made using a variety of clinical and radiological methods; gait speed, bioimpedance analysis, grip strength, dual energy X-ray absorptiometry (DEXA), MRI, or CT, (discussed in 1.2.3)⁶⁷. Of these methods, in recent years CT has emerged as the gold standard measurement technique in the research field. Functional assessments (gait speed, grip strength) are prone to confounding, influenced by patient effort, and are more prone to inter-user variability. DEXA is relatively low cost however is increasingly less available in the clinical setting, and is subject to bias due to the image analysis requirements. Moreover, DEXA is unable to reliably quantify intramuscular fat deposition. MRI provides reproducible accurate measurement of tissue areas, however is costly and time-intensive to acquire, limiting the resource available to dedicate to measurement in the research setting. The major drawback to CT (exposure to ionising radiation) is offset by its reproducibility, short scan acquisition time, a wealth of existing data within the literature, and widespread clinical use and availability. Each of these factors have contributed to it being adopted as the technique of choice to quantify sarcopenia.

1.3.2 AETIOLOGY AND PATHOPHYSIOLOGY

The EWGSOP consider risk factors for sarcopenia as “primary” and “secondary”. Aging is considered the key “primary” risk factor, and sarcopenia in this context is termed “age-associated muscle loss”. “Secondary” risk factors include malnutrition (both under-nutrition and over-nutrition/obesity), disease-specific factors (such as malignancy, degenerative neurological disease, inflammatory disorders) and inactivity (“disuse

atrophy”). The relative contribution of each of these factors is a subject of current research and considerable difference in opinion; inflammation has emerged as the primary aetiological factor in a range of disease states^{70,71}.

The underlying mechanism by which sarcopenia develops in response to risk factor exposure is incompletely understood. Loss of skeletal muscle mass appears to be driven by several potential mechanisms. Development of a catabolic state, through dysregulation of the intrinsic balance in the protein synthesis – proteolysis pathways is likely an early component. Loss of insulin-like growth factor 1 (IGF-1), increased expression of cortisol, interleukin-6, and tumour necrosis factor alpha (TNF- α) all appear to promote a catabolic state and are associated with the sarcopenic phenotype⁷². In addition to the net loss of muscle mass, it appears that the architecture of skeletal muscle is also affected, which may impair strength via degradation in muscle function. Overall there is a conversion of fast type II fibres to slow type I fibres caused by denervation and atrophy of the former, with an associated loss in cross-sectional area of both types of fibre⁷². Additionally, lipid deposition within muscle tissue appears to be associated with sarcopenia⁷³. Adipocytes and myocytes share a common precursor cell, and in patients with sarcopenia there seems to be a propensity towards differentiation into the adipocyte phenotype. Furthermore, mitochondrial loss “mitophagy” and damage to mitochondrial DNA in response to oxidative stress and inflammatory stimulæ results both myocyte apoptosis and a loss of functional muscle units, compromising both muscle mass and function.

In addition to the changes observed in muscle tissue, alteration in body composition can also be observed in adipose tissue. An association between obesity and cardiovascular disease has long been described, however a recent description of the controversial “obesity paradox”, where obese individuals may experience superior prognosis in certain conditions, has challenged conventional dogma^{74–76}. The majority of studies define obesity using traditional body-mass index (BMI) thresholds, which are subject to inherent limitations. Evaluation of adipose tissue using cross sectional imaging allows for a more refined assessment of the distribution of adipose tissue, in particular deposition in the visceral (intra-abdominal) and subcutaneous anatomical regions. Metabolically, visceral and subcutaneous adipose tissue are known to vary in their metabolic activity, inflammatory state, free-fatty acid generation, and risk of poor outcome (with visceral obesity conferring a worse prognosis)⁷⁷. The interactions between distribution of adipose tissue, sarcopenia, and outcomes have been examined, predominantly in patients with

cancer^{78,79}. Regardless, individuals at the extremes of BMI appear to occupy an abnormal nutritional state and therefore are at increased risk of sarcopenia⁶⁸.

1.3.3 BODY COMPOSITION ANALYSIS (MEASUREMENT)

CT-derived body composition analysis (CT-BC) is a technique which allows measurement and quantification of cross-sectional tissue areas. There is considerable variation in reported methodology, however the generally accepted (and most widely reported) method is to measure tissue at the level of the 3rd lumbar vertebra⁸⁰. There are multiple programmes available, using manual, semi-automated, or automated measurement. ImageJ (NIH, Bethesda, Maryland, USA) is a freeware programme widely used to perform manual measurement, whilst Slice-O-Matic (Tomovision, Magog, Canada) and Data Analysis Facilitation Suite (DAFS, Voronoi Health Analytics, Vancouver, British Columbia, Canada) are semi-automated and automated systems respectively^{80–82}. Whilst specific methodology varies depending on the software used, generally similar principles are followed. Additionally, whilst there are small discrepancies between measurement techniques, the values recorded are generally considered comparable⁸⁰. Skeletal muscle, subcutaneous fat, and visceral fat are separately segmented and their areas and densities recorded. This generates skeletal muscle, visceral fat, and subcutaneous fat areas (SMA, VFA, SFA) and skeletal muscle density (SMD). Generally, the muscle and fat areas are normalised to patient's height² to generate indices (SMI, VFI, SFI) whilst SMD is not. Compared with other modalities to diagnose and quantify sarcopenia, CT-BC offers a high degree of accuracy due to direct measurement of muscle area (SMI), which satisfies the muscle mass component of the sarcopenia definition. Regarding the functional element of the EWGSOP2 definition, SMD represents intramuscular fat deposition (myosteatosis)⁸³, and has been proposed as a possible marker of muscle function, however this association remains poorly understood⁸⁰. In order to compare outcomes for patients based on CT-BC parameters, validated thresholds have been proposed by multiple authors, largely based on data derived from patients with cancer (table 1.1)^{78,79,84}. These thresholds have not, as yet, been applied to patients with cardiovascular disease to evaluate their prognostic value in this patient group. Instead, in cardiovascular disease, typical methods of sub-grouping are based on median, tertiles, quartiles, or Receiver Operating Characteristic (ROC) analyses. This use of data-derived thresholds which lack any external validation risks the introduction of bias into any observations drawn from a given dataset, and limits the validity of conclusions. Whilst the thresholds in table 1.1 have been externally validated, to date this has only been performed in cohorts of patients with cancer. Additionally, the

nature of the derivation must be questioned in relation to their generalisability; each of the thresholds in table 1.1 were derived based on the association of each parameter with overall survival in heterogenous cohorts of patients. The thresholds for SMI/SMD were generated based on patients with colorectal cancer, those for SFI were generated based on a range of cancers (including gastrointestinal, respiratory, and metastatic renal cell), and for VFA based on gastrointestinal cancers. Therefore, whilst we discuss similarities between patients with cardiovascular disease and with cancer in later chapters, these are discrete clinical entities with different natural histories and pathophysiological processes, therefore the use of disease-specific thresholds of CT-BC parameters may be warranted.

Table 1.1 Previously reported thresholds associated with mortality of CT-derived body composition parameters derived from patients with cancer^{78,79,84}

SMI (Martin) Males, BMI <25kg/m ² Males, BMI ≥ 25kg/m ² Females, BMI <25kg/m ² Females, BMI ≥ 25kg/m ²	<43 cm ² /m ² <53 cm ² /m ² <41 cm ² /m ² <41 cm ² /m ²
SMD (Martin) BMI <25kg/m ² BMI ≥ 25kg/m ²	<41 HU <33 HU
SFI (Ebadi) Males Females	<50 cm ² /m ² <42 cm ² /m ²
VFA (Doyle) Males Females	163.8 cm ² 80.1 cm ²

1.3.4 BODY COMPOSITION ANALYSIS (CLINICAL UTILITY)

Despite a growing wealth of evidence describing the role of CT-BC in identifying patients at risk of inferior long-term outcome, this has not translated into widespread clinical use. Current clinical application of CT-BC is sporadic and typically limited to the research setting. Moreover, the literature to date is dominated by data derived from patients with cancer, and non-malignant pathologies such as cardiovascular disease are relatively underrepresented. Potential barriers to the clinical utilisation of CT-BC are the learning curve in performing analysis, the time taken to perform analyses (in the context of already over-burdened healthcare systems), the cost of automated measurement systems, and a general lack of awareness of the supporting evidence base. In real-world clinical practice, prognostic factors are seldom used in isolation. On the contrary, a given parameter is typically used as part of a multimodal assessment of a patient, taking into account a range of parameters to provide prognostic information. It is therefore unlikely that CT-BC parameters would be used in an isolated fashion, rather the use of CT-BC may form part of a wider assessment of a patient and their disease.

1.4 SYSTEMIC INFLAMMATORY RESPONSE

1.4.1 BIOLOGICAL BASIS

Inflammation has evolved as an important host response to illness and injury; the systemic inflammatory response (SIR) is a key component of the immune system and potentiates the ability of a host organism to detect and remove pathogens, destroy damaged or infected tissue, and ultimately progress to tissue repair and remodelling⁸⁵. Inflammation can be

classified as “acute” or “chronic” depending on the duration and resolution following removal of stimulus. Acute inflammation is typically characterised by neutrophil chemotaxis mediated by inflammatory cytokine release in response to trauma, or as a result of the innate immune system responding to an exogenous pathogen. The best-described pathways mediating this response are the nuclear factor kappa-B (NF- κ B), mitogen-activated protein kinase (MAPK), and Janus kinase signal transducer and activator of transcription (JAK-STAT) pathways⁸⁶. Chronic inflammation may be initiated by a high magnitude acute response which then perpetuates into a chronic response without resolution or develop secondarily in a host who has experienced a prior sensitizing acute event (“one hit” and “two hit” hypotheses). Chronic activation of the SIR has been associated with various diseases, including cardiovascular disease⁴⁸. In this context, it remains unclear whether the initial instigation of the SIR is driven by an acute infectious or traumatic event, or whether the localised inflammation associated with atherosclerotic plaque deposition leads to activation of the SIR. Regardless, it appears that localised and systemic inflammation perpetuate each other, resulting in a positive feedback loop which drives disease progression and severity. The complex interactions in this disease process remain incompletely understood.

1.4.2 QUANTIFICATION

The SIR can be readily quantified using a wealth of markers, which themselves possess varying clinical application. Typically, cytokine analysis is beyond the scope of clinical practice, and hence (other than in several specific conditions) is largely limited to the research field. Historically the predominant clinical measurement of the SIR has been in the acute setting, to assess response to treatment. However, growing recognition of the role of chronic activation of the SIR in the development of and prognosis of various diseases has resulted in measurement of the SIR outside of an acute insult in an attempt to quantify the magnitude of systemic inflammation. In both acute and chronic settings, the use of routinely available markers such as the differential white cell count (WCC), C-reactive protein (CRP), and albumin can aid clinicians in assessing the degree of activation of the SIR.

1.4.2.1 DIFFERENTIAL WHITE CELL RESPONSE

The differential WCC consists of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and the sum of the differential components. Neutrophils, eosinophils, monocytes and basophils share a common progenitor (myeloblast), whilst lymphocytes are derived

from lymphoblasts. Lymphocytes may differentiate into B-lymphocytes which are involved in the antibody driven immune response, or T-lymphocytes, which are involved in the cell-mediated immune response⁸⁷. Cells derived from a myeloblast lineage are also involved in the cell-mediated response. Each parameter can be abnormal through either elevation or reduction compared to reference values, and the pattern of abnormality may inform likely diagnosis. Elevated neutrophil count is the most common abnormal finding, and is classically associated with bacterial infection, steroid use, mesenteric ischaemia, and sickle cell disease, amongst others⁸⁷. Lymphocytes and monocytes may be deranged in viral illness or in autoimmune disease. Eosinophils and basophils may be deranged in allergic illnesses or in response to medications. Each parameter can also be deranged due to haematological malignancy. Chronic inflammation may result in elevation of certain parameters of the WCC and suppression of others, in particular, elevated neutrophils may suppress circulating levels of other white cells, possibly through activation of myeloid suppressor cells⁸⁸. This forms the rationale for the derivation of the neutrophil:lymphocyte ratio (NLR), defined as the absolute ratio of the neutrophil count to lymphocyte count. The NLR has been extensively investigated as a prognostic factor in patients with cancer, and appears to be associated with long-term outcomes in both early and advanced disease^{89,90}. Thrombocytosis, or elevated platelet count, may also be observed in response to both acute and chronic inflammatory stimuli⁹¹. Similarly to NLR, the platelet:lymphocyte ratio (PLR) is described as a marker of the SIR. PLR is less well reported than NLR; despite this elevated PLR appears to be associated with the presence and severity of cardiovascular disease^{92,93}.

1.4.2.2 ACUTE PHASE RESPONSE

CRP was originally described in 1930 as a finding in the serum of patients with *Pneumococcus* infection⁹⁴. CRP is classed as an acute-phase protein in response to infectious, traumatic, or inflammatory stimuli, with a peak level approximately 48-72 hours following a trigger. CRP plays an important role in the complement-mediated opsonisation of pathogens prior to phagocytosis. Recent evidence has emerged describing a role of CRP as a marker of cardiovascular disease and has contributed to the understanding of the inflammatory nature of cardiovascular disease⁹⁵. Albumin is a protein synthesised by the liver with a range of important roles in maintaining homeostasis. Albumin levels can be abnormal in a range of diseases, through disruption of synthesis or increased excretion. When released in the acute-phase response, TNF and interleukin-1 (IL-1) appear to suppress hepatic albumin synthesis, resulting in decreased serum albumin levels in

response to an inflammatory stimulus^{96,97}. CRP and albumin as markers of inflammation have been combined into the Glasgow Prognostic Score (GPS) and subsequently revised into the modified GPS (mGPS)^{98,99}. mGPS has been extensively investigated, in particular in patients with cancer, and appears to offer prognostic value in early and advanced disease^{100,101}.

1.4.3 INTERACTION WITH BODY COMPOSITION

Inflammation is one of the aetiological factors associated with sarcopenia⁶⁸, and the interactions between these 2 entities are becoming more widely recognised. NLR appears to be associated with low SMI in patients with cancer¹⁰². An association between mGPS and low SMI/SMD has been reported in patients with colorectal cancer¹⁰³. Additionally, NLR and mGPS have been combined into the systemic inflammatory grade (SIG), which offers a more comprehensive overview of the SIR and appears to be associated with both CT-BC and prognosis in patients with curative colorectal cancer^{104,105}. The interactions between body composition and systemic inflammation give biological rationale to their combined investigation. Additionally, several authors note that, in patients with cancer, their prognostic value appears to be independent of each other^{103,105}. However, in patients with cardiovascular disease, there is a paucity of reporting these factors together and investigating their relationships. Whilst conclusions from patients with cancer could be inferred to be valid in patients with cardiovascular disease, formal exploration in this patient cohort is required, particularly due to the potentially confounding effect of variation in systemic inflammation between patients with cancer¹⁰⁶ and patients with cardiovascular disease⁴⁸.

1.5 KEY STUDIES IN THE FIELD

1.5.1 CANTOS

The 2017 “Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease” (CANTOS) study was published in the New England Journal of Medicine¹⁰⁷. In this landmark study, Ridker *et al* performed a randomised double-blind placebo controlled trial of canakinumab (an anti IL-1 β) in over 10,000 patients with recent myocardial infarction and elevated high sensitivity CRP. In the intervention arm, there was an association with the primary composite cardiovascular outcome (HR 0.83, 95% CI 0.73 – 0.95, $p = 0.005$), however there was a greater prevalence of significant infection. These data highlighted the

potential cardiovascular benefit of immunomodulation in patients with atherosclerotic disease, as well as the potential pitfalls of immunomodulation.

1.5.2 BEST-CLI

“Surgery or Endovascular Therapy for Chronic Limb-Threatening Ischemia” (BEST-CLI) was published in the New England Journal of Medicine in 2022¹⁰⁸. This multicentre randomised trial reported outcomes relating to strategy of revascularisation for infrainguinal arterial occlusive disease in 1830 patients with CLTI. A composite outcome including adverse limb event and death was selected as the primary outcome. Patients with suitable autologous great saphenous vein (for use as a bypass conduit) underwent a vein bypass first revascularisation strategy, whilst those who did not have suitable vein underwent endovascular first strategy. In the bypass first cohort the rate of the primary outcome was lower than in the endovascular first cohort (HR 0.68, 0.59 – 0.79, $p < 0.001$). These observations support the continued use of surgical revascularisation in appropriately selected patients, despite marked advance in endovascular therapy in recent years.

1.5.3 UK-COMPASS

Published in the European Journal of Vascular & Endovascular Surgery in 2024, “Comparison of Open Surgery and Endovascular Techniques for Juxtarenal and Complex Neck Aortic Aneurysms: The UK COMPLEX Aneurysm Study” (UK-COMPASS) accessed registry data to report outcomes in a study cohort of patients undergoing repair of aneurysms with juxtarenal, short, or complex neck anatomy¹⁰⁹. Outcomes were compared between patients undergoing endovascular or open intervention. The key finding was that, in patients with a short aneurysm neck, endovascular repair was associated with superior perioperative survival, however in more complex aneurysm necks (>10mm) survival was inferior in the endovascular subgroup.

1.5.4 EVAR-1 / EVAR-2

The EVAR-1 and EVAR-2 studies (both Lancet 2005) were landmark studies performed in the era that EVAR was emerging as a more widespread technique to manage aortic aneurysms^{110,111}. EVAR-1 compared outcomes in 1017 patients who were randomised to either EVAR or open repair. At 4 year follow-up, survival was similar between the two groups, despite superior 30-day survival in the EVAR cohort. EVAR-2 randomised 338 patients who were considered unfit for open repair to either EVAR or no intervention. The

main finding was that there was no difference in all-cause mortality and in aneurysm specific mortality between the two groups at 4 year follow-up. These two trials heavily influenced practice and formed the basis of guidelines in multiple countries.

1.5.5 LINDSTRÖM ET AL, 2020

“Developing sarcopenia predicts long-term mortality after elective endovascular aortic aneurysm repair” was published in the Journal of Vascular Surgery in 2020 by Lindström et al¹¹². CT body composition analysis, measuring psoas muscle area, was performed at baseline (pre-operative) and at follow-up CT. They report a significant decrease in psoas muscle area between timepoints, and a greater change in muscle area was independently associated with inferior survival outcome.

1.6 SUMMARY AND AIMS

Cardiovascular disease encompasses a range of conditions with myriad clinical presentations. In the field of vascular surgery obstructive atherosclerotic disease is the predominant pathology encountered, however a proportion of patients (e.g. AAA) have a condition which is not directly caused by atherosclerosis but shares a common risk factor and comorbidity profile. Vascular surgical intervention is therefore typically performed on patients with multiple comorbidities who are conventionally considered relatively high operative risk. Interventions in vascular surgery either have a well described poor long-term prognosis (rAAA, CLTI) or are prophylactic in nature (elective AAA, CEA). In the former identifying modifiable host factors to improve outcome is an important area for research, whilst in the latter optimal patient selection for intervention is imperative. The evidence describing the potential prognostic role of CT-BC is largely based on patients with cancer, with the prevalence and potential prognostic role of CT-BC parameters in vascular surgical populations generally under-investigated. Similarly, both the prevalence and potential prognostic role of activation of the SIR is relatively under-investigated in vascular surgery, although is better reported in patients with IHD⁴⁸. Immunomodulation in patients with vascular surgical disease has not been as extensively investigated as in patients with either cancer or IHD. Should similar associations be present in patients with vascular surgical disease to those with cancer, both CT-BC parameters and measures of the SIR may prove to be attractive novel therapeutic targets for peri-procedural optimisation, as well as potential novel risk stratification measures to aid patient selection.

The specific aims of the research reported in the present thesis were as follows;

- To critically review the literature describing the prevalence and potential prognostic value of altered body composition in patients with vascular surgical conditions.
- To critically review the literature describing the prevalence and potential prognostic value of activation of the SIR in patients with vascular surgical conditions.
- To provide novel observations on the prevalence and potential prognostic value of altered body composition in patients with vascular surgical conditions using standard methodology derived from patients with cancer.
- To provide novel observations on the prevalence and potential prognostic value of activation of the SIR in patients with vascular surgical conditions derived from patients with cancer.
- To explore the interactions between potentially aetiological host factors, body composition, systemic inflammation, disease state, and outcomes in patients with vascular surgical conditions.
- To use the results obtained to inform and advise the potential future direction of research, in particular with a view to intervention, in patients with vascular surgical conditions.

1.7 METHODOLOGY

Methodology which is common to multiple chapters throughout this thesis is summarised in this section. Specific techniques used on a chapter-by-chapter basis are described in the relevant “Materials & Methods” sections.

1.7.1 SYSTEMATIC REVIEW

For all systematic reviews included in the present thesis, the search strategies were carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All review protocols were registered with the PROSPERO database (registration numbers reported in each chapter), and review protocols are accessible via the PROSPERO database. No patient data were accessed, therefore specific ethical approval was not required.

The MEDLINE database was accessed electronically using the PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD, USA) search engine. Specific search terms are reported in each relevant chapter. Search terms were combined using the operators “AND” and “OR”. Search terms were applied to study title, key words, and Medical Subject Heading (MeSH) terms. Duplicate results were screened by identifying their PubMed Identifier (PMID), an integer value unique to each record. Study abstracts were screened, and studies which did not meet the previously determined inclusion criteria were excluded. Full papers were subsequently screened and again exclusions made. Data were extracted from full text articles, tables, figures, and (where applicable) appendices. Data were recorded using Microsoft Excel.

Risk of bias in the selected studies was assessed by applying the stepwise criteria in the Quality in Prognosis Studies (QUIPS) tool¹¹³. Domains assessed by this tool are Study Participation, Study Attrition, Prognostic Factor Measurement, Outcome Measurement, Study Confounding, and Statistical Analysis and Reporting, with each domain graded as High, Moderate, or Low

1.7.2 PATIENT COHORTS

The data analysed in the present thesis were generated through analysis of several cohorts of patients, the recruitment of which is described here. Specific sub-group analyses used on a chapter-by-chapter basis are described in the relevant “Materials & Methods” sections. West of Scotland Research Ethics Committee approval was obtained for all patient recruitment throughout this thesis (reference 21/WS/0146; approval granted 23/11/2021). Data governance approval was obtained from the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) (reference 2122-0114 Bradley, approval granted 02/03/2022).

For all patient cohorts clinical, demographic, and outcome data were recorded from electronic case records encompassing hospital and community healthcare data. Specific comorbidities were defined as per patients’ community health records and hospital admission data. Age (either <65 / $65 - 75$ / > 75 or ≤ 75 / > 75) and BMI (either <18.5 / $18.5 - 24.9$ / $25.0 - 29.9$ / ≥ 30.0 or < 25.0 / ≥ 25.0) were considered as categorical variables, with precise method of sub-grouping chosen on a chapter-by-chapter basis to avoid low absolute numbers in certain sub-groups. Comorbidity was also summarised using American Society of Anaesthesiologists (ASA) grade derived from preoperative

anaesthetic assessment. Socioeconomic deprivation was assessed using the Scottish Index of Multiple Deprivation (SIMD), a Government-led postcode-based measure of deprivation, with patients classified into deciles and then grouped on the basis of below (“More Deprived”) and above (“Less Deprived”) the median decile. Survival data were obtained from the Community Health Index (CHI) registry, a routinely available registry maintained at a national health board level and populated from both primary and secondary care data. Specific cause of death was not available from this registry.

In each cohort of patients, recruitment occurred during the Covid-19 pandemic. There was therefore a potential confounding effect of Covid-19 on variables of interest. As such, patients with a positive Covid-19 test 30-days before or after admission were excluded. Admission Covid-19 testing was performed during the pandemic as part of routine patient care for both scheduled and unscheduled admissions.

1.7.2.1 AORTIC ANEURYSM

Patients were retrospectively identified from theatre records at three large tertiary referral centres in Scotland, UK, representing cases drawn from three health boards (NHS Grampian, NHS Lanarkshire, NHS Tayside). Theatre records are routinely recorded as part of existing patient care, with each case generating a coded procedure type which can then be accessed retrospectively. This allowed identification of patients undergoing relevant procedures via their unique CHI number, which was then used to access clinical information. Consecutive cases undergoing open or endovascular intervention to treat aortic aneurysmal disease between 01/01/2015 and 10/01/2022 were included. Patients undergoing intervention for isolated iliac aneurysms, aortic dissection, or penetrating aortic ulcer, were excluded. Patients with aneurysms extending into the thoracic aorta are managed at a national level with markedly different interventions and risk profiles, therefore only patients with AAA were included.

1.7.2.2 CHRONIC LIMB THREATENING ISCHAEMIA

This cohort was a retrospective analysis of a pre-existing prospectively maintained audit database from a single health board (NHS Tayside). Consecutive patients presenting as unscheduled admissions with CLTI between 01/01/2020 and 01/06/2021 were prospectively recorded as part of pre-existing institutional audit. CLTI was diagnosed by the on-call vascular surgical team who assessed the patient on admission; institutional practice was to consider CLTI as per the 2019 Global Vascular Guidelines definition²⁶.

Patients who did not undergo CT-imaging for CT-BC, and patients with active malignancy (due to the potentially confounding effect on both CT-BC and systemic inflammation), were excluded.

1.7.2.3 Cerebrovascular Disease

Patients undergoing carotid endarterectomy were retrospectively identified from theatre records at four tertiary referral centres in Scotland, UK, representing cases drawn from four health boards (NHS Grampian, NHS Lanarkshire, NHS Tayside, NHS Lothian). Consecutive cases undergoing carotid endarterectomy for symptomatic carotid lesions between 1st January 2011 and 1st October 2021 were screened for inclusion. Symptomatic lesions were diagnosed collaboratively by both stroke physicians and vascular surgeons at each site to determine suitability for surgery. Specific procedural technique and choice of post-procedure secondary prevention strategy were at the discretion of each institution, though practice was broadly similar between sites throughout the study period. The choice of whether to perform pre-operative CT for surgical planning was at the discretion of each institution (in some cases surgery can be performed based on sonographic evaluation alone). Due to the need for pre-operative CT to perform CT-BC analysis, only patients who underwent CT for surgical planning were included. Patients with active malignancy, active infection (both due to the potential confounding effect on the variables of interest), or corrupted (e.g. due to artefact from dental implants) CT images or relevant pre-operative blood testswere excluded.

1.7.3 CT-Derived Body Composition Analysis

CT-BC analysis was performed by the manual segmentation method using ImageJ v1.53 (NIH, Bethesda, Maryland, USA). Analyses were performed on single slice CTs, at the L3 vertebral level for abdominal CTs. Analysis of non-abdominal CTs is discussed in each relevant chapter. Thresholds of Hounsfield Units (HU) were applied to each CT image to delineate skeletal muscle (-29 to +150 HU) and adipose (-190 to -30 HU) tissue. Tissues were then manually segmented using a polygon region of interest tool (figure 1.2) and values recorded. Parameters recorded and normalisation are discussed in section 1.2.3.

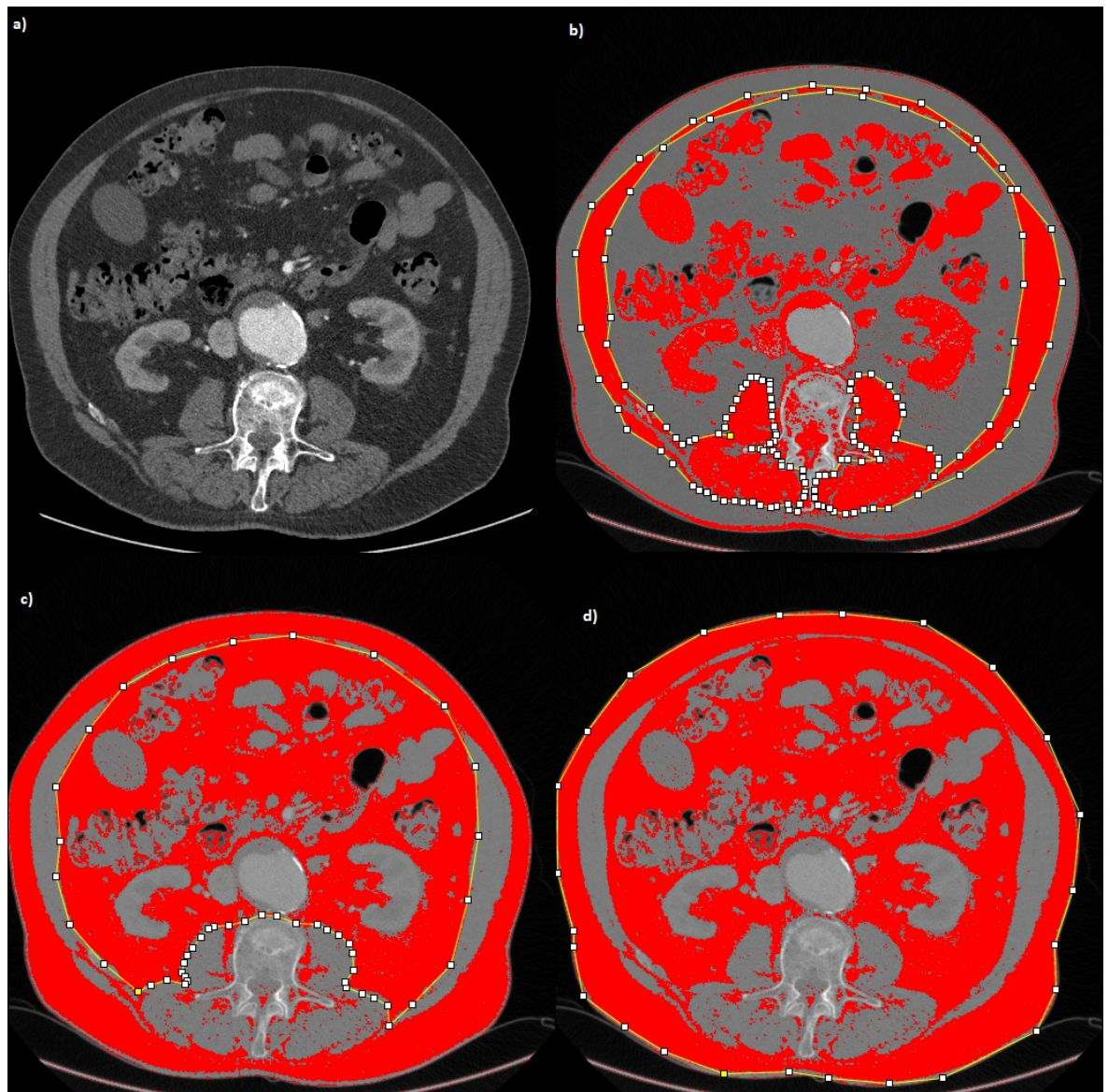


Figure 1.2 Example of CT-BC analysis on a CT cross-section at the L3 vertebral level using ImageJ manual segmentation method. a) unsegmented, b) skeletal muscle segmentation, c) visceral fat segmentation, d) total fat segmentation. Red areas denote region of interest masks applied to each tissue type based on pre-defined ranges of Hounsfield Units, and ensure that measurements are recorded only from the desired tissue group.

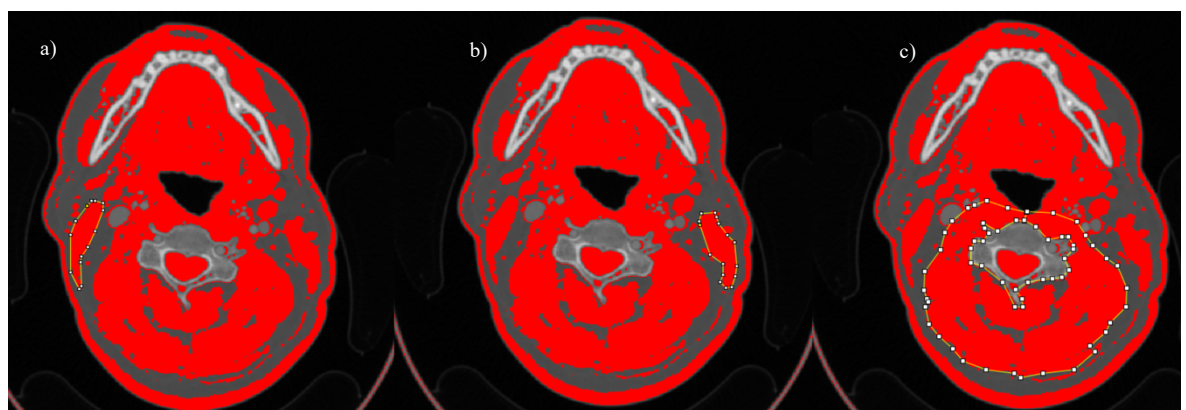


Figure 2.3 Example of CT-BC analysis on a CT cross-section at the C3 vertebral level using ImageJ manual segmentation method. a) unsegmented, b) sternocleidomastoid segmentation, c) paravertebral

muscle segmentation. Red areas denote region of interest masks applied to muscle tissue based on pre-defined ranges of Hounsfield Units, and ensure that measurements are recorded only from the desired tissue group.



Figure 3.4 Example of CT-BC analysis on a CT cross-section at the maximal cross sectional liver area recorded in Carestream PACS Viewer, and demonstration of the Freehand ROI tool used to generate measurements (adapted with permission from McGovern *et al* 2024)

1.7.4 STATISTICAL ANALYSES

General statistical analyses common to all chapters are reported here, specific techniques are also reported on a chapter-by-chapter basis. Data were reported as median (interquartile range, IQR) unless otherwise specified. The effect of factors of interest on outcomes was assessed using receiver operating characteristic (ROC) analyses, with area under the curve (AUC) values and *p* values reported. AUC values of ≥ 0.7 were considered good, $0.5 - 0.7$ considered fair, and < 0.5 considered poor. Differences between medians of independent continuous variables were assessed using the Mann-Whitney-U and Kruskal-Wallis tests. Differences between categorical variables were assessed using the Chi-Squared Test, with

linear-by-linear p values reported. Time-to-event analyses were calculated using the Kaplan-Meier method, with differences between cohorts assessed using the log-rank test. Where time to event survival data did not reach a median survival, the mean (95% CI) values are reported. The association between covariates and overall survival was assessed using a cox proportional hazards model; covariates were initially interrogated in univariate analysis and those with univariate $p < 0.05$ were included in a multivariate model. Both simple multivariate and backwards conditional multivariate modelling were used (specified in relevant chapters). The association between covariates and dichotomous outcomes was assessed using binary logistic regression; covariates were initially interrogated in univariate analysis and those with univariate $p < 0.05$ were included in a multivariate model. All analyses were performed using IBM Statistical Package for Social Sciences (SPSS) 28.0 (IBM, NY, USA) and RStudio 2022.02.01. p values < 0.05 were considered statistically significant.

2 THE RELATIONSHIP BETWEEN PRE-OPERATIVE PSOAS AND SKELETAL MUSCLE PARAMETERS AND SURVIVAL FOLLOWING ENDOVASCULAR ANEURYSM REPAIR: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 INTRODUCTION

In the previous chapter, the aetiology and pathogenesis of both aortic aneurysmal disease (section 1.1.2.1) and sarcopenia (section 1.3) were discussed. In this chapter, the existing literature describing the prognostic associations of CT-derived skeletal muscle measurements in patients undergoing repair of AAA is reviewed. A lack of a standardised definition of radiological sarcopenia in patients with AAA has resulted in a heterogenous evidence base with variable definitions of sarcopenia. Measurement of total skeletal muscle (SMI) is established as the optimal prognostic factor in patients with cancer. Despite this, the majority of studies investigating patients with AAA have reported psoas muscle area/index (PMA/PMI) as the prognostic factor of interest. This likely reflects the technically easier and faster measurement technique required for PMA/PMI analysis. However, not measuring the entire cross sectional skeletal muscle area may limit the validity of any conclusions drawn, and the ability to compare outcomes with the wider literature. In addition, outcomes in relation to SMD remain unreported in patients with AAA.

A previous meta-analysis (Antoniou *et al* 2019) included seven observational studies with a total of 1440 patients undergoing OSR or infrarenal EVAR for AAA in whom preoperative measurements of psoas muscle had been performed¹¹⁴. They reported an overall increased risk of post-operative mortality associated with low PMA/PMI (HR 1.66, 95% CI 1.15 – 2.40; $p = .007$) in their entire (combined OSR and EVAR) study cohort. Subgroup analysis of the EVAR patients showed a trend towards increased mortality in patients with low PMA/PMI, though this was non-significant (HR 1.86, 95% CI 1.00 – 3.43; $p = .05$).

Subsequent observational studies have reported inferior survival outcomes in cohorts consisting of only patients undergoing EVAR, and in patients undergoing F/B-EVAR, though these results have not been reproducible. A recent meta-analysis (Dakis *et al* 2022) described a prognostic role for pre-operative sarcopenia in relation to 5-year mortality,

however only included three studies (604 patients) in quantitative meta-analysis¹¹⁵.

Additionally, Dakis et al did not included patients undergoing F/B-EVAR in their analysis; this patient group is typically less frail than patients undergoing standard EVAR and the incidence and prognostic value of sarcopenia in this setting is uncertain.

The present systematic review & meta-analysis aims to examine the relationship between pre-operative CT-derived psoas and skeletal muscle parameters and clinical outcomes in patients undergoing EVAR and F/B-EVAR for AAA.

2.2 MATERIALS & METHODS

General systematic review methodology is discussed in section 1.7.1. The review protocol was registered with the PROSPERO database (Registration Number: CRD42021273085), and the review protocol can be accessed via the PROSPERO database.

2.2.1 INCLUSION CRITERIA

The following criteria were applied to determine eligibility: retrospective and prospective study design, study population including patients undergoing standard EVAR or complex (F/B-EVAR) endovascular aneurysm repair in the elective and emergency setting, peri-operative CT-imaging used to perform muscle group analysis, studies using CT imaging to calculate PMA/PMI/SMA/SMI with an accepted technique (as reported in previous literature), all-cause mortality reported in relation to PMA/PMI/SMA/SMI using a pre-determined threshold to subgroup patients into “sarcopenic” and “non-sarcopenic” with comparison of survival outcomes (either time to event analyses and log-rank t tests or HR and 95% CI) between the two cohorts, all follow-up duration.

2.2.2 EXCLUSION CRITERIA

The following criteria were applied to determine ineligibility: study population including patients undergoing EVAR or F/B-EVAR for non-aneurysmal disease of the aorta, or isolated iliac artery aneurysms, studies including paediatric patients (age <18).

2.2.3 OUTCOMES

Meta-analysis was performed on primary and secondary outcomes; primary outcome was defined as overall post-operative survival during the follow-up period, and secondary outcome was early (inpatient or <30 day) mortality. Qualitative analysis of included studies was also performed as part of the present review.

2.2.4 SEARCH STRATEGY

General search methodology is discussed in section 1.7.1. For the present review, the search was conducted on the 12th January 2022; any papers published after this date are not included in the present review. Four search terms were used; “sarcopenia” AND “EVAR”, “psoas” AND “EVAR”, “sarcopenia” AND “endovascular”, “psoas” AND “endovascular”.

2.2.5 DATA EXTRACTED FROM STUDIES

The following data were extracted from each study: study design (centres, follow-up, prospective/retrospective) and study information (journal, authors, year), baseline clinical (comorbidities, routine pre-operative blood results) and demographic data of patients, data relating to procedure-specific factors (*n* standard/complex EVAR and emergency/elective), technique of measuring muscle area from pre-operative CT, method used to define sarcopenic patients and *n* of sarcopenic and non-sarcopenic patients (e.g. based on previous literature, data-dependent ROC analysis/tertiles), survival data for overall survival during study & early mortality, length of hospital stay.

2.2.6 RISK OF BIAS ASSESSMENT

Risk of bias assessment is discussed in section 1.7.1.

2.2.7 DATA EXTRACTION

Data extraction was direct where possible; for the primary outcome (overall survival during study follow-up period) this was extraction of Hazard Ratio (HR), *p* value, and 95% CI generated by Cox Proportional Hazards Model comparing sarcopenic vs. non-sarcopenic patients. Where the covariate of interest was reported in both univariate and multivariate analyses, the HR generated by multivariate analysis was chosen. Where studies did not report HR and 95% CI indirect data extraction was performed; time to event Kaplan-Meier plots were digitised using WebPlotDigitizer program¹¹⁶ and survival estimates calculated. HR and 95% CI were calculated from the study-reported numbers at risk and calculated survival estimates using the method described by Tierney et al¹¹⁷. Both directly and indirectly extracted HR and 95% CI were subsequently used to calculate $\ln[\text{HR}]$ and standard error, from which a Forest Plot with each study's effect size was formed using the generic inverse variance method. For the secondary outcome early mortality % of events and non-events (deaths < 30 days post-op) were directly extracted from studies and a dichotomous model used to calculate OR for each study. Where authors reported length of follow-up in years, this was converted to months by the study team.

2.2.8 META-ANALYSIS

The effects observed from meta-analysis will be generalised outside of the included studies. Based on preliminary literature review, heterogeneity between studies was

expected (variation in the number of each type of repair, or different definitions of low PMI between studies) therefore a random effects model was used for meta-analysis. Heterogeneity was quantitatively assessed using I^2 statistic, with values greater than 25%, 50%, and 75% representing low, moderate, and high heterogeneity as per Higgins et al¹¹⁸. Review Manager (RevMan) Version 5.4.1 (Cochrane Collaboration)¹¹⁹ was used to compile and analyse data for meta-analysis.

2.2.9 SUBGROUP ANALYSES

The subgroup "complex EVAR" (patients undergoing F/B-EVAR) were separately analysed to assess the effect of low PMI on survival in this cohort. It was anticipated that each study included should clearly state the numbers of patients undergoing this type of procedure as the risk profile and clinical course are heterogenous compared to standard EVAR.

2.3 RESULTS

2.3.1 STUDY SELECTION

The study selection process is summarised in the PRISMA diagram in figure 2.1. The search terms “sarcopenia” AND “EVAR”, “psoas” AND “EVAR”, “sarcopenia” AND “endovascular”, “psoas” AND “endovascular” returned 14, 28, 39, and 85 records respectively. One additional record was obtained through review of citations from a previous meta-analysis¹¹⁴. This gave an initial total of 167 records.

When duplicate records were removed, 99 records remained, which underwent abstract screening. 81 records were excluded based on abstract screening based on non-eligibility as per inclusion and exclusion criteria. 18 full papers were reviewed for eligibility and eight were subsequently excluded; three performed analysis only on a combined dataset of patients undergoing OSR and EVAR, two reported analysis of factors (change in PMI) other than baseline PMA/PMI/SMA/SMI, two were studies performed on institutional datasets which had subsequently or previously been reported elsewhere which better fit the eligibility criteria (removed to eliminate duplicated patients being included), and one was a published abstract only. This left 10 studies included in the final review process, nine of which were observational retrospective studies, and one of which (Waduud et al) was an observational prospective study^{120–129}.

Of the 10 included studies, to define radiological sarcopenia, nine used measures of psoas muscle (PMA/PMI) and one used measures of total skeletal muscle (SMA). Due to heterogeneity in these methods of assessment, the study measuring SMA (Hale et al¹²⁹) was not included in meta-analysis; qualitative review was instead performed.

2.3.2 STUDY CHARACTERISTICS

A summary of the included studies is shown in Table 2.1. There were a total of 2563 patients included (2062 EVAR, 501 F/B-EVAR), of which 836 (33%) were defined as having radiological sarcopenia (585 EVAR (28% of total), 251 F/B-EVAR (50% of total)). One study (Oliveira et al¹²¹) excluded female patients, whilst the remaining studies included both males and females. Inclusion and exclusion criteria were otherwise similar in all studies; all authors excluded patients undergoing procedures for non-aneurysmal disease. There were no emergency cases included. The mean follow-up period ranged from 25.2 to 100.8 months in 8 studies, and was not specifically reported in two studies. Eight

studies were single centre, one was multicentre, and in one the dataset was based on interrogation of national registry data.

2.3.3 RISK OF BIAS IN INCLUDED STUDIES

The risk of bias assessment using the QUIPS tool is shown in table 2.2. 5 of 60 (8%) domains were classified as high risk of bias, 31 of 60 (52%) domains were classified as moderate risk of bias, and 24 of 60 (40%) domains were classified as low risk of bias. There were no studies where all domains were graded as low risk of bias. Visual inspection of domains shows that study attrition, and statistical analysis & reporting were generally low risk of bias, however prognostic factor measurement, outcome measurement, and study confounding were generally moderate-high risk of bias.

2.3.4 META-ANALYSIS OF PRIMARY OUTCOME

Nine studies reported psoas muscle parameters in 2363 patients which were extracted for meta-analysis of primary outcome; seven of these were direct extraction of hazard ratios in sarcopenic vs. non-sarcopenic patients, and two were indirect extraction from time-to-event curves. A Forest Plot for overall survival is shown in figure 2.2. The combined HR for all-cause mortality in sarcopenic versus non-sarcopenic patients was 2.61 (1.67 – 4.08), $p < .00001$. Heterogeneity between studies was high ($I^2 = 81\%$).

2.3.5 META-ANALYSIS OF SECONDARY OUTCOME

Three studies reported early mortality in 853 patients and were included in meta-analysis. Of the remaining studies, two did not report early mortality, two reported overall cohort early mortality without specifying the difference based on muscle area analysis, and one did not report any early deaths. A Forest Plot for early mortality is shown in figure 2.3. The combined HR for early mortality in sarcopenic versus non-sarcopenic patients was 1.95 (0.35 – 10.94), $p = .45$. Heterogeneity between studies was low ($I^2 = 46\%$).

2.3.6 META-ANALYSIS OF SUBGROUPS

There were two studies which reported primary outcome in F/B-EVAR patients (table 2.1). A Forest Plot for overall survival is shown in figure 2.4. The combined HR for all-cause mortality in sarcopenic versus non-sarcopenic patients was 3.08 (1.66 – 5.71), $p = .004$. Heterogeneity between studies was low ($I^2 = 0\%$).

2.3.7 SKELETAL MUSCLE AREA MEASUREMENT

One study reported SMA as the variable of interest; Hale et al retrospectively analysed a prospectively recruited cohort of 200 patients undergoing elective standard EVAR¹²⁹. Analysis was defined on absolute values of SMA; SMA < 114.0cm² (men) / <89.8cm² (women), based on values derived from patients undergoing liver transplantation and subsequently validated in patients with critical limb ischaemia^{130,131}. Median follow-up was 100.8 months. Patients in the low SMA cohort (n = 25, 13%) were older and more likely to be female, with other baseline variables similar between the group. Overall mortality during the follow-up period was higher in the low SMA cohort (76% vs. 48%, *p* = .016). Low SMA status was associated with increased odds of mortality on multivariate analysis (OR 3.17, 95% CI 1.20 – 9.54), however this was not independent of age at the time of procedure.

2.3.8 TIMING OF CT (TABLE 2.1)

Timing of CT from which images were extracted for subsequent analysis was heterogenous across the included studies. Five studies did not specify timing of CT in relation to the procedure. Two studies included only pre-operative CTs, from <12 and <1 months prior to the procedure. Three studies included both pre- and post-operative CTs, ranging from <12 months pre-operatively to <1 month post-operatively.

2.3.9 SOFTWARE USED FOR ANALYSIS (TABLE 2.1)

There was heterogeneity in the choice of software used to analyse muscle areas. Four studies used semi-automated techniques (Osirix, Synapse Vincent, Centricity). The remaining six studies used manual techniques, with each of these studies using different software (Aquarius, Carestream, QReads, Coral Ris, Impax, AGFA PACS).

2.3.10 THRESHOLDS FOR SKELETAL MUSCLE (TABLE 2.1)

Of the 10 included studies only one (Oliveira et al¹²¹) specified the thresholds of HU used to define muscle tissue for body composition analysis; the widely accepted thresholds -29 - +150 HU were used by these authors.

2.3.11 NORMALISATION (TABLE 2.1)

Five of the 10 included studies normalised PMA measurements to patient height² to produce PMI, five studies reported data without normalisation in the form of PMA (4 studies) and SMA (one study).

2.3.12 THRESHOLDS USED TO STRATIFY PATIENTS (TABLE 2.1)

Two studies used absolute values of muscle area to stratify patients for survival analysis; Thurston et al used PMI $< 500 \text{ mm}^2/\text{m}^2$, and Hale et al used SMA $< 114.0 \text{ cm}^2$ (male patients) / $< 89.8 \text{ cm}^2$ (female patients)^{122,129}. Eight studies used thresholds derived from their own population data; tertiles/quartiles were used in four studies, whilst four used ROC analysis to determine optimal threshold based on sensitivity.

2.4 DISCUSSION

The present systematic review and meta-analysis shows that, in patients undergoing elective standard and complex EVAR to treat AAA, radiological sarcopenia, as defined by low PMA/PMI/SMA, was associated with significantly poorer survival outcome with a trend towards increased risk of early mortality. However, the number of studies/patients identified was small, there was considerable heterogeneity in the meta-analysis, poorly described methodology and study quality with considerable risk of bias. For example, approximately half of the studies identified did not describe their methodology in detail and/ or normalise their results to patient height², which compromised comparison between studies. Therefore, further studies of the potential prognostic value of skeletal mass and quality in patients undergoing EVAR to treat AAA are warranted.

This relationship between CT-derived low PMI and outcomes in patients with AAA undergoing OSR has previously been described by Antoniou *et al* in a 2019 meta-analysis¹¹⁴. Subgroup analysis performed by these authors demonstrated a trend towards inferior survival in the EVAR-only cohort. Dakis *et al* recently reported a similar review of studies to the present study¹¹⁵. However, they excluded 73% of the studies in their review from meta-analysis, due to significant heterogeneity in outcome measures included studies. We note that despite their study selection, heterogeneity in meta-analysis remained high ($I^2 = 95.05\%$). Dakis *et al* performed meta-analysis on 5-year survival, resulting in the exclusion of the majority of studies. Given that patients undergoing endovascular repair may have been selected to not undergo open surgical repair due to fitness and comorbidity, reporting outcomes at less than 5-year follow-up is clinically relevant and therefore the results observed in the present study support and complement those observed by Dakis *et al*.

The studies included in the previous and the present meta-analyses were limited by the lack of a consensus definition of body composition parameters to define radiological sarcopenia in patients with AAA. Moreover, there was significant heterogeneity in the muscle group analysed, lack of normalisation of muscle areas, limited information on the timing of CT from which measurements are taken, thresholds used to determine the “sarcopenic” cohort and software used to perform muscle area analysis. The greatest disparity in hazard ratios was observed between two groups of studies; Huber *et al* and Waduud *et al* vs. Cheng *et al* and Ito *et al*^{123,125,127,128}. The former studies use manual software to measure muscle areas, report non-normalised (to height) values of muscle parameters, and use percentile-based

(quartile, tertile) thresholds to define sarcopenia. The latter studies use semi-automated techniques, report normalised values of psoas muscle parameters, and use thresholds based on sensitivity and specificity (ROC) of their own data. The use of ROC analysis to define the sarcopenic cohort may introduce bias through maximising chance of observing a difference, which may account for the higher hazard ratios observed. In patients with cancer there are several proposed thresholds for different body composition parameters^{78,79,84,132}, which have been subsequently applied to different patient groups. To date these thresholds have not been applied to patients with AAA, and their validity in this patient group is lacking. Further work to either derive novel thresholds or apply existing thresholds to patients with AAA is required.

Variation in body composition analysis between different software packages has been described, with several authors reporting that manual segmentation yields higher values of cross sectional area¹³³. The advantages and disadvantages of each software are based on a variety of factors, such as speed of measurement, cost, and learning curve required. Furthermore, eight studies used thresholds derived from their own datasets to define sarcopenia and only one study¹³⁴ used a threshold derived from another cohort. This may have limited the conclusions derived from the present meta-analysis. There are several widely used thresholds used in cancer patients derived from large cohort studies however to date such data are not available in patients with AAA^{84,132,135}.

The choice of muscle group analysed was psoas muscle (PMA/PMI) in nine of the included studies, with only one study performing analysis of total skeletal muscle area (SMA). There may be significant variation in the utility of PMI or SMI as a prognostic marker. For example, SMI has been shown to better predict outcomes in non-AAA populations^{80,136}. To date PMA/PMI has been more widely utilised in AAA populations, perhaps due to less anatomical complexity and the less time-consuming measurement process¹³⁷. Radiological assessment of abdominal muscle groups may be limited in the case of ruptured AAA, with retro- or intra-peritoneal haematoma precluding accurate delineation of muscle borders. Therefore, variations in the above factors may have limited the inter-study comparison performed in the present review.

The present study included both patients undergoing EVAR and F/B-EVAR. Whilst there may be heterogeneity between technical procedural differences and aneurysm morphology, we would not expect there to be significant difference in the underlying pathophysiology of the aneurysmal disease. Indeed, risk factors between patients with infra- and juxta-/para-

renal AAA are likely to be similar. Whilst periprocedural complications are known to be different between the 2 interventions¹³⁸, these may not extend to alterations in long-term mortality as observed by the present review. We hypothesise that the hazard of mortality in patients with AAA is reflective of the underlying cardiovascular morbidity in this patient group. Whilst AAA is not a primary atherosclerotic pathology, the risk factors for atherosclerotic disease are common to those for AAA, and a large proportion of patients with AAA may have systemic manifestations of atherosclerosis¹⁴. Sarcopenia in this setting may be reflective of more severe underlying generalised cardiovascular disease and this may explain the prognostic implications. Whilst patients undergoing F/B-EVAR typically have more complex aneurysms, it remains unclear whether aneurysmal extent itself is a prognostic factor in long-term mortality.

The contemporary definition of sarcopenia (EWGSOP2) includes not only loss in skeletal muscle volume but also reduced skeletal muscle function⁶⁸. The use of CT-BC to quantify muscle function has been proposed via the reporting of SMD, however the association between SMD and muscle function is poorly understood¹³⁹. The potential prognostic value of SMD in patients with AAA is unreported, and requires further investigation in order to determine its clinical utility.

NICE guidance recommends offering open surgical repair (OSR) unless there is a contra-indication: including co-pathology; anaesthetic risk; and/or medical pathology²². Those patients who do not meet the fitness criteria to undergo OSR may be offered an endovascular procedure if aneurysm morphology is suitable. Therefore, it may be anticipated that the prevalence of low PMI would be higher in patients undergoing EVAR compared with those undergoing OSR. However, Waduud et al report a higher PMA in patients undergoing EVAR, whilst Drudi et al report a higher proportion of patients in their low PMI tertile undergoing EVAR^{128,140}.

Subgroup analysis in the present study demonstrated inferior survival in sarcopenic patients undergoing F/B-EVAR, in keeping with the findings in standard EVAR. The increased risk of morbidity following F/B-EVAR compared to EVAR is well established^{138,141}. Only 501 (19.5%) of patients in the present study underwent F/B-EVAR, with meta-analysis weighted heavily (72.7%) towards a single study. The lack of reporting on such patients limits the ability to draw meaningful conclusions from meta-analysis, however we believe it concisely highlights the paucity of evidence.

The results of the present study did not support increased early mortality in patients with sarcopenia. The maximal physiological compromise following surgery is expected to occur in the immediate post-operative period, where the level of inflammatory cytokines responding to the surgical insult peak and then gradually decline^{142,143}. Stent-graft implantation provokes an inflammatory reaction, with variable cytokine response depending on graft material used¹⁴⁴. This is manifest as the clinical “Post-Implantation Syndrome” (PIS), which has been reported to be associated with increased early mortality, though there is a paucity of long-term follow-up data. There is a well-described pro-inflammatory component of sarcopenia¹⁴⁵, as is the relationship between chronic inflammation and increased cardiovascular mortality and morbidity^{146,147}. There appears to be a complex relationship between chronic inflammation in patients with sarcopenia though this remains poorly defined in patients with AAA. Further characterisation of the inflammatory pathways in this patient group, including the effect of stent-graft deployment, is required.

The implication of these findings on the decision to proceed to repair in patients with sarcopenia may yield clinical benefit. Rate of aneurysm rupture in AAA 5.5 - 6.0 cm which are untreated has recently been reported as 2.2 - 3.5%, lower than previously thought^{148,149}. Whilst the results of the present study are insufficient to directly apply body composition analysis to the clinical setting, we demonstrate that the derivation and validation of thresholds for muscle area to define patients as sarcopenic is required, as well as standardisation of measurement and reporting techniques. Both the National Institute for Health and Care Excellence (NICE)²² and the European Society for Vascular Surgery (ESVS)¹⁵⁰ highlight the challenges in pre-operative assessment in their most recent guidelines which emphasise selective use of pre-operative testing at the discretion of clinicians. The use of body composition may complement existing methods of pre-operative risk assessment in this patient group.

2.5 TABLES

Table 2.1: Studies included in the final review of the potential prognostic effect of radiological sarcopenia in patients undergoing EVAR and F/B-EVAR.

Table 2.2: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review.

Table 2.1: Studies included in the final review of the prognostic effect of radiological sarcopenia in patients undergoing EVAR and F/B-EVAR

Study	n	Definition of “Sarcopenic” Cohort	n (%) sarcopenic	Normalisation?	Follow-up (mean)	Data Extraction	Centres	Technique of Muscle Analysis (Software, Thresholds, Level)	Timing of CT
Ikeda et al (2022) ¹²⁰	324 elective EVAR	PMA, ROC analysis	166 (51%)	No	56.7 months	Direct (HR)	Single	Aquarius (manual) NR L4	NR
Oliveira et al (2021) ¹²¹	105 elective EVAR**	PMA; Lowest tertile	35 (33%)	No	27.6 months	Direct (HR)	Single	Osirix (semi-automated) -29 - +150 L3	NR
Thurston et al (2018) ¹²²	191 elective EVAR	PMI <500mm ² /m ²	30 (16%)	Height ²	NR	Direct (HR)	Multi	Osirix (semi-automated) NR L3	NR
Huber et al (2019) ¹²³	407 elective EVAR	PMA; Lowest quartile	102 (25%)	No	39.0 months	Direct (HR)	Single	Carestream (manual) NR L4	NR
Kärkkäinen et al (2020) ¹²⁴	244 elective F/B-EVAR	PMI; adjusted hazard model defined threshold	165 (68%)	Height ²	25.2 months	Indirect	Single	QReads (manual) NR L3	NR
Ito et al (2020) ¹²⁵	310 elective EVAR	PMI; 30 th Percentile, ROC defined threshold	93 (30%)	Height ²	35.3 months	Direct (HR)	Single	Synapse Vincent (semi-automated) NR L3	<1 month pre-operatively
Alenezi et al (2021) ¹²⁶	257 elective F/B-EVAR	PMA; Lowest tertile	86 (33%)	No	32.7 months	Direct (HR)	Single	Coral Ris (manual) NR L3	<12 months pre-operatively - <1 week post-operatively

Table 2.2: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Ikedo et al (2022) ¹²⁰	Moderate	Low	Moderate	Moderate	Moderate	Low
Oliveira et al (2021) ¹²¹	High	High	Moderate	Moderate	Moderate	Low
Thurston et al (2018) ¹²²	Moderate	Low	Low	Moderate	Moderate	Low
Huber et al (2019) ¹²³	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Kärkkäinen et al (2020) ¹²⁴	Moderate	Low	Moderate	Low	Moderate	Low
Ito et al (2020) ¹²⁵	Low	Low	Moderate	High	Moderate	Low
Alenezi et al (2021) ¹²⁶	Moderate	Low	High	Moderate	Moderate	Low
Cheng et al (2019) ¹²⁷	Moderate	Low	Moderate	Low	Moderate	Low
Waduud et al (2019) ¹²⁸	Low	Moderate	Moderate	Low	Moderate	Low
Hale et al (2016) ¹²⁹	Moderate	High	Low	Low	Moderate	Low

2.6 FIGURES

Figure 2.1: PRISMA diagram showing study inclusion.

Figure 2.2: Forest Plot of the risk of post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing EVAR and F/B-EVAR for each of the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients.

Figure 2.3: Forest Plot of the risk of 30 day post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing EVAR and F/B-EVAR in the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients.

Figure 2.4: Forest Plot of the risk of post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing F/B-EVAR for the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients.

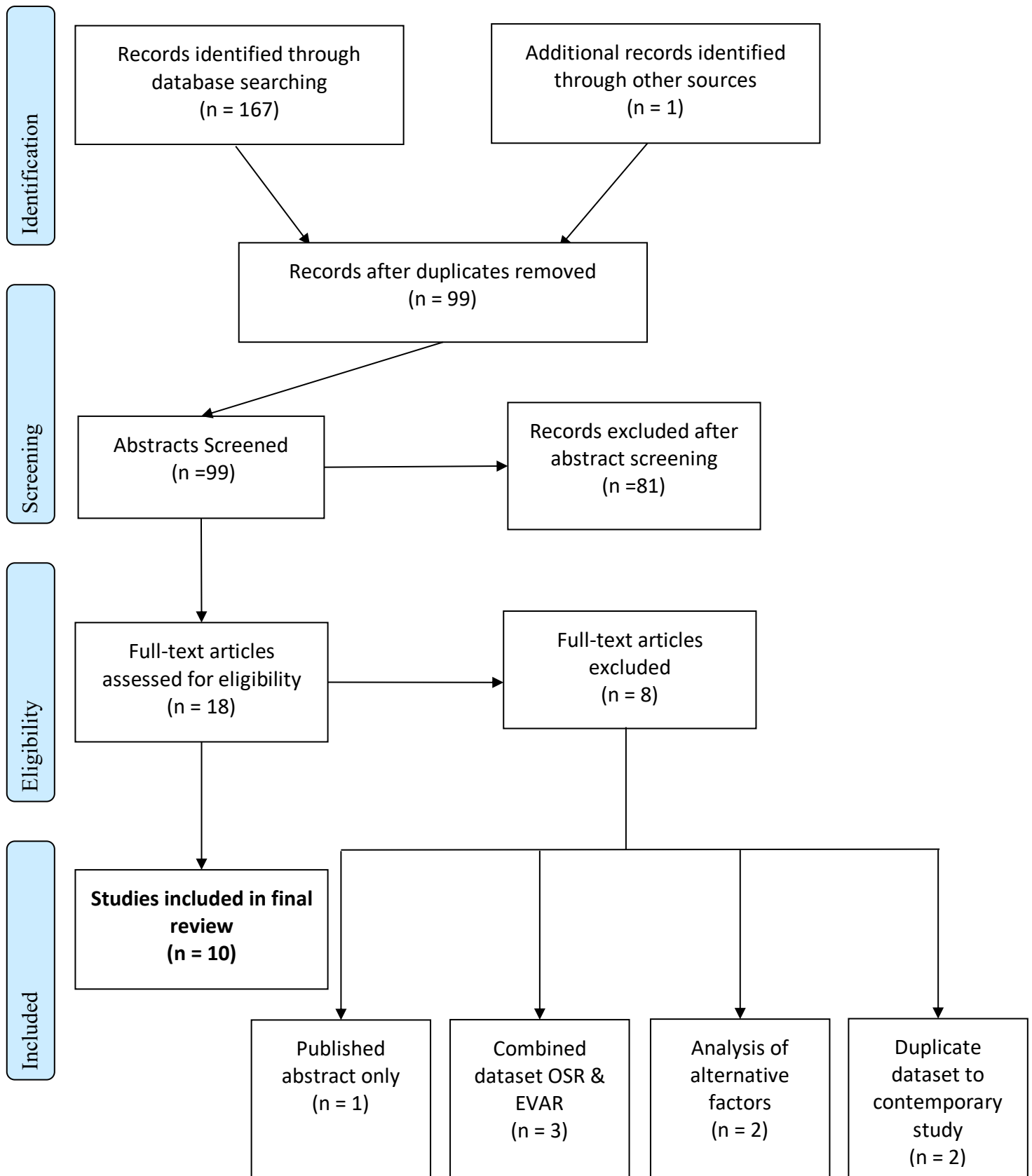


Figure 2.1 PRISMA diagram showing study inclusion

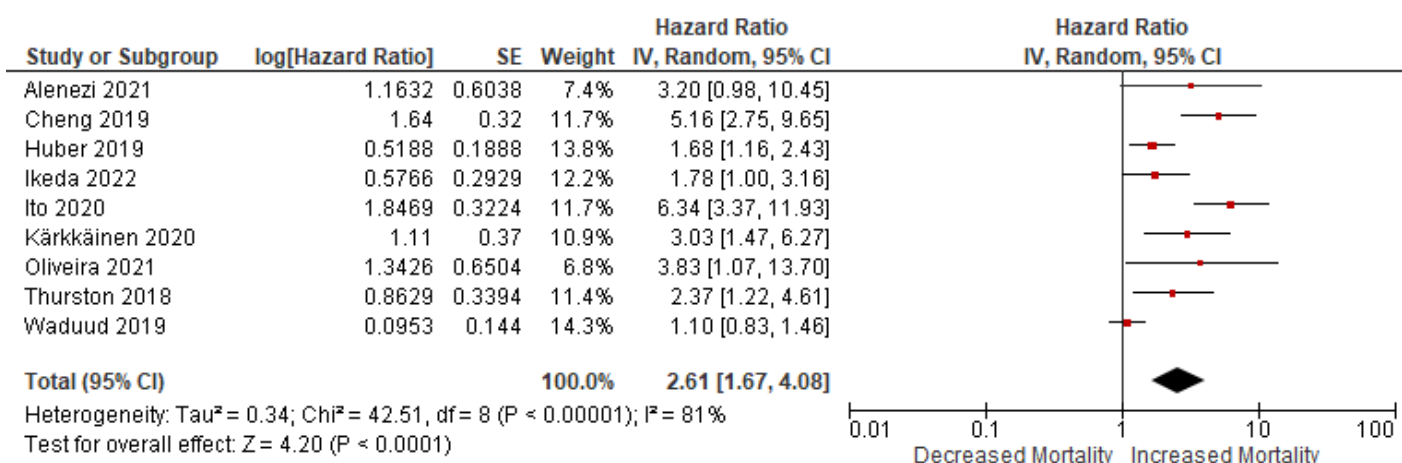


Figure 2.2 Forest Plot of the risk of post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing EVAR and F/B-EVAR for each of the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients

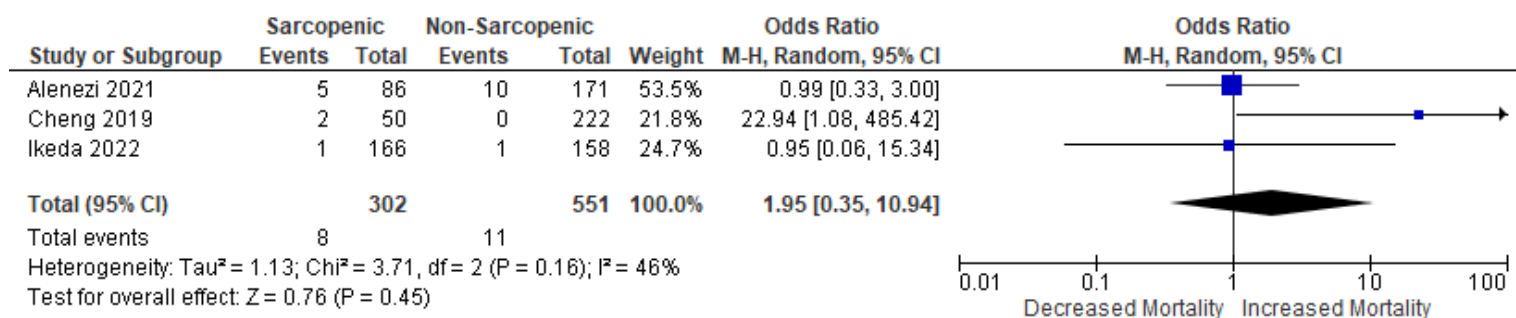


Figure 2.3 Forest Plot of the risk of 30 day post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing EVAR and F/B-EVAR in the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients

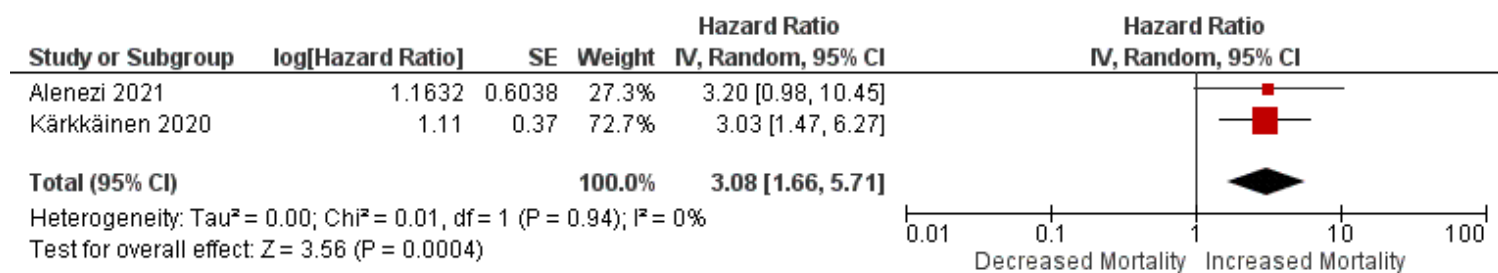


Figure 2.4 Forest Plot of the risk of post-operative mortality in sarcopenic vs. non-sarcopenic patients undergoing F/B-EVAR for the included studies. Plots to the right of the X-axis represent an increased risk of mortality in sarcopenic patients

3 EVALUATION OF THE POTENTIAL PROGNOSTIC VALUE OF CT-DERIVED BODY COMPOSITION IN PATIENTS UNDERGOING ENDOVASCULAR ANEURYSM REPAIR

3.1 INTRODUCTION

In chapter 2, the existing literature describing the prognostic association between CT-derived muscle analysis and survival following EVAR was reviewed. On meta-analysis there was an association between low muscle mass and inferior post-operative survival, however the limitations of the evidence base were highlighted. Chiefly among these were heterogeneity in measurement technique, lack of standardised thresholds, and choice of body composition parameter measured.

As discussed in section 1.3.3, CT-BC methodology in patients with cancer is largely (though not formally) standardised both in terms of measurement technique and choice of parameter. Moreover, thresholds to sub-group individuals based on each parameter have been reported and validated, typically in the setting of colorectal cancer (table 1.1). The use of such thresholds provides the opportunity for comparison between cohorts or studies, and reduces the potential impact of bias introduced through the use of thresholds based on certain centiles (e.g. tertiles, median) from a given dataset. Indeed, the use of externally validated thresholds is a component of the QUIPS assessment tool for assessing risk of bias¹¹³. At the time of writing, there are no validated thresholds for CT-BC parameters derived from cohorts of patients with AAA. The use of existing thresholds derived from patients with cancer in patients with cardiovascular disease is also unreported, however is a potential source of bias.

In the present chapter, the CT-BC methodology widely employed in patients with cancer is used to derive CT-BC parameters in a cohort of patients undergoing EVAR for AAA. Thereafter, novel disease-specific thresholds are derived, and their potential prognostic value following aneurysm repair is assessed.

3.2 MATERIALS & METHODS

3.2.1 PATIENT SELECTION

Patients were retrospectively identified as per the methodology described in section 1.7.2.1. The majority of patients in the AAA cohort underwent EVAR rather than OSR, and due to potential heterogeneity between patients undergoing these procedures, the decision was made to include only those undergoing EVAR. Patients were sub-grouped based on age (<65, 65 – 75, > 75), and procedure priority (asymptomatic AAA, symptomatic AAA, ruptured AAA). Haemoglobin and creatinine were recorded as pre-operative factors which may influence the outcome following surgery. Low haemoglobin was defined as < 130 g/L (male patients) and < 120 g/L (female patients), high creatinine was defined as > 106 μ mol/L (male patients) and > 80 μ mol/L (female patients), both based on local laboratory values. The primary outcome of interest was overall survival during the follow-up period.

3.2.2 CT-BC ANALYSIS

Body composition analysis was performed using the established manual segmentation technique previously described by Dolan et al¹³³ and summarised in section 1.7.3. All measurements were performed systematically by one researcher (Nicholas A Bradley). A random 15% sample of images were then analysed independently by a second researcher who has previous peer reviewed publication with this methodology (Ross Dolan)¹³³. An intraclass correlation coefficient between the two researchers' results was calculated as 0.992, indicating an excellent correlation.

Image compromise was defined as L3 CT slices where measurement of certain body composition parameters was not possible. This was assessed on a case-by-case and parameter-by-parameter basis, for example, in cases of ruptured AAA, where the extent of haematoma precluded accurate measurement of skeletal muscle area, yet it remained feasible to measure subcutaneous fat area. Where there was dubiety around the accuracy of body composition analysis, images were selectively excluded based on the compromised parameter.

ROC analysis was performed to assess the predictive value of each body composition parameter on both overall and 2-year survival, which was chosen as a clinically relevant endpoint. To determine optimal thresholds for dichotomisation of body composition

parameters into “High” and “Low”, the “surv_cutpoint” function of the “survminer” R package was used, using the maximally selected rank statistic technique. Sex-specific thresholds were derived to account for the established variation in body composition. For each body composition parameter, ROC curves were then visually inspected and thresholds derived by maximising sensitivity + specificity. These thresholds were compared to those generated by “surv_cutpoint” and were each within a 5% difference, therefore the “surv_cutpoint” values were used for subgroup analysis.

3.2.3 STATISTICAL ANALYSES

General statistical analyses are described in section 1.7.4. Linear regression was used to assess the relationship between continuous covariates. The effect of body composition on one and 5-year mortality was assessed using binary logistic regression. The relationship between covariates and survival was assessed using a Cox Proportional Hazards Model; covariates were initially interrogated in univariate analysis and those with univariate $p < 0.05$ were included in a multivariate backwards conditional model with the threshold for removal set at $p < 0.10$. Fat and muscle body composition parameters were modelled separately with significant baseline clinical characteristics. Analyses were performed using R version 4.2.0 and IBM SPSS 28.0.

3.3 RESULTS

674 patients (541 EVAR, 133 F/B-EVAR) were eligible for inclusion into the study; 58 (8.6%) patients were female, and the mean (SD) age was 74.4 (6.8) years. Median (IQR) time from CT to surgery was 80 (103) days. All patients completed a minimum of 18 months follow-up. When compromised images were excluded on a parameter-by-parameter basis, there were 605 cases (SFI), 641 cases (VFI), 666 cases (PMI), 647 cases (SMI), and 654 cases (SMD). Median (IQR) follow-up was 60.0 (27.0) months, and there were 191 deaths during the follow-up period (158 asymptomatic AAA, 7 symptomatic AAA, 26 ruptured AAA). Mean (95% CI) survival in the entire study population was 73.8 (71.1 – 76.6) months.

ROC curves describing the association of body composition parameters with 2-year survival are shown in Figure 3.1. SFI (AUC 0.605, fair), SMI (AUC 0.592, fair), and SMD (AUC 0.572, fair) provided association with 2-year survival ($p < 0.05$); PMI and VFI did not provide significant association ($p > 0.05$).

Thresholds of body composition parameters to define the “Low” subgroups in male patients were: SFI 40.32 cm²/m², VFI 58.61 cm²/m², PMI 5.85 cm²/m², SMI 49.69 cm²/m², SMD 40.32 HU. Thresholds of body composition parameters to define the “Low” subgroups in female patients were: SFI 44.89 cm²/m², VFI 59.36 cm²/m², PMI 3.82 cm²/m², SMI 37.73 cm²/m², SMD 31.01 HU. When these thresholds were applied to the patient cohort, there were 81 patients (13.4%) with low SFI, 162 patients (25.3%) with low VFI, 167 patients (25.1%) with low PMI, 296 patients (45.7%) with low SMI, and 443 patients (67.7%) with low SMD.

Figure 3.2A displays a scatter plot of SFI (cm²/m²) vs VFI (cm²/m²) with the interpolation line of best fit. Linear regression analysis produced an R² value of 0.139. A scatter plot of SMI (cm²/m²) vs PMI (cm²/m²) with the interpolation line of best fit is displayed in Figure 3.2B. Linear regression analysis produced an R² value of 0.497.

Mean (95% CI) survival in the Low SFI vs. High SFI subgroups was 56.4 (48.2 – 64.7) vs. 77.1 (74.2 – 80.1) months ($p < 0.001$, figure 3.3A). Mean (95% CI) survival in the Low VFI vs. High VFI subgroups was 64.3 (58.8 – 69.8) vs. 77.4 (74.3 – 80.5) months ($p < 0.001$, figure 3.3B). Mean (95% CI) survival in the Low PMI vs. High PMI subgroups was 63.7 (57.7 – 69.7) vs. 77.3 (74.3 – 80.4) months ($p < 0.001$, figure 3.4A). Mean (95%

CI) survival in the Low SMI vs. High SMI subgroups was 62.6 (58.5 – 66.7) vs. 82.0 (78.7 – 85.3) months ($p < 0.001$, figure 3.4B). Mean (95% CI) survival in the Low SMD vs. High SMD subgroups was 71.1 (67.7 – 74.6) vs. 80.0 (75.7 – 84.3) months ($p < 0.001$).

Table 3.1 displays the univariate cox proportional hazards model describing the association between baseline clinical characteristics & body composition parameters, and overall survival. Ruptured AAA (HR 1.78, 95% CI 1.45 – 2.18, $p < 0.001$), increasing age (HR 1.98, 95% CI 1.52 – 2.58, $p < 0.001$), current tobacco smoking (HR 1.48, 95% CI 1.09 – 2.01, $p < 0.05$), low haemoglobin (HR 2.01, 95% CI 1.50 – 2.69, $p < 0.001$), high creatinine (HR 1.48, 95% CI 1.09 – 2.01, $p < 0.05$), Low SFI (HR 2.35, 95% CI 1.63 – 3.37, $p < 0.001$), Low VFI (HR 1.78, 95% CI 1.31 – 2.42, $p < 0.001$), Low PMI (HR 1.94, 95% CI 1.44 – 2.61, $p < 0.001$), Low SMI (HR 2.55, 95% CI 1.88 – 3.46, $p < 0.001$) and Low SMD (HR 1.82, 95% CI 1.28 – 2.59, $p < 0.001$) were associated with inferior survival. High BMI (HR 0.77, 95% CI 0.64 – 0.93, $p < 0.01$) was associated with superior survival.

Table 3.2 displays the multivariate backwards conditional cox proportional hazards model describing the association between baseline clinical characteristics & body composition parameters, and overall survival. Regarding body composition parameters, SMI and SFI were chosen for inclusion in the multivariate model based on their superior association on ROC and univariate analyses. Following stepwise removal of covariates; ruptured AAA (HR 1.46, 95% CI 1.10 – 1.93, $p < 0.01$), increasing age (HR 1.56, 95% CI 1.16 – 2.09, $p < 0.01$), current tobacco smoking (HR 1.42, 95% CI 1.00 – 2.00, $p < 0.05$), low haemoglobin (HR 1.42, 95% CI 1.01 – 2.00, $p < 0.05$), Low SFI (HR 1.90, 95% CI 1.30 – 2.76, $p < 0.001$), and low SMI (HR 1.88, 95% CI 1.34 – 2.63, $p < 0.001$) were associated with inferior survival.

Subgroup analysis was performed on the asymptomatic AAA ($n = 604$) cohort alone, in which there were 158 deaths during the follow-up period. Table 3.3 displays the univariate cox proportional hazards model describing the association between baseline clinical characteristics & body composition parameters, and overall survival in patients with asymptomatic AAA. Increasing age (HR 2.07, 95% CI 1.54 – 2.77, $p < 0.001$), current tobacco smoking (HR 1.61, 95% CI 1.15 – 2.25, $p < 0.01$), low haemoglobin (HR 2.00, 95% CI 1.44 – 2.80, $p < 0.001$), high creatinine (HR 1.46, 95% CI 1.04 – 2.06, $p < 0.05$), Low SFI (HR 1.98, 95% CI 1.32 – 2.97, $p < 0.001$), Low VFI (HR 1.76, 95% CI 1.27 – 2.45, $p < 0.001$), Low PMI (HR 1.73, 95% CI 1.24 – 2.40, $p < 0.01$), Low SMI (HR 2.30, 95% CI 1.66 – 3.18, $p < 0.001$) and Low SMD (HR 1.85, 95% CI 1.26 – 2.72, $p < 0.01$)

were associated with inferior survival. High BMI (HR 0.72, 95% CI 0.59 – 0.88, $p < 0.01$) was associated with superior survival.

Table 3.4 displays the multivariate backwards conditional cox proportional hazards model describing the association between baseline clinical characteristics & body composition parameters (SFI, SMI), and overall survival in patients with asymptomatic AAA.

Following stepwise removal of covariates; increasing age (HR 1.74, 95% CI 1.26 – 2.40, $p < 0.001$), current tobacco smoking (HR 1.60, 95% CI 1.11 – 2.31, $p < 0.05$), low haemoglobin (HR 1.59, 95% CI 1.11 – 2.28, $p < 0.05$), Low SFI (HR 1.54, 95% CI 1.01 – 2.35, $p < 0.05$), and low SMI (HR 1.71, 95% CI 1.20 – 2.42, $p < 0.01$) were associated with inferior survival.

The potential prognostic value of previously reported body composition thresholds was assessed by applying the thresholds for SMI and SMD proposed by Martin *et al*¹⁵¹ to the AAA cohort in the present study. The prevalence of patients with low SMI and low SMD was 54.4% and 38.1% respectively. On univariate models, both SMI (HR 1.67, 95% CI 1.22 – 2.70, $p < 0.01$) and SMD (1.87, 95% CI 1.39 – 2.52, $p < 0.001$) were associated with inferior survival.

One-year mortality in the low SMI vs. high SMI subgroups was 10% vs. 3% ($p < 0.001$). Low SMI was associated with increased odds of one-year mortality (OR 3.19, 95% CI 1.60 – 6.34, $p < 0.001$). Five-year mortality in the low SMI vs. high SMI subgroups was 55% vs. 28% ($p < 0.001$). Low SMI was associated with increased odds of five-year mortality (OR 1.54, 95% CI 1.11 – 2.14, $p < 0.01$).

3.4 DISCUSSION

The present study demonstrates the potential prognostic value of pre-operative CT-derived body composition analysis in patients undergoing EVAR and F/B-EVAR for AAA. Body composition analysis as a method of predicting mortality has been predominantly performed in patients with cancer, where there is a generally agreed consensus regarding measurement techniques and thresholds to define the pathological state. In contrast to this, body composition analysis in patients with AAA is in its relative infancy. Most authors reporting outcomes in patients with AAA have reported patients with asymptomatic AAA only, with emergency cases and F/B-EVAR underrepresented. Body composition analysis is more technically challenging in the setting of ruptured AAA, which is the likely justification for including asymptomatic cases only. The results in our unselected consecutive cohort represent a real-world application of the use of body composition analysis and highlight the importance of further evaluation of this technique to develop a clinical tool for prognostication. Furthermore, the association observed by the present study was preserved in our subgroup analysis of asymptomatic AAA alone, strengthening the potential clinical application of body composition analysis.

SMD is a marker of myosteatorsis and is postulated to reflect muscle function; there appears to be an association with clinically assessed muscle strength¹⁵². However, this association is incompletely described and requires further assessment. The underlying rationale for myosteatorsis as a marker of muscle function is that with increasing intramuscular fat deposition, there is a synchronous loss of muscle fibre volume (i.e. the adipose tissue replaces muscle tissue within a given muscle group)¹⁵³. There is a paucity of evidence correlating CT-derived SMD and intramuscular fat deposition measured on muscle biopsy; this is an important area for further research which may increase the understanding of this phenomenon. The present study is the first to report SMD in patients undergoing EVAR, and the results are in keeping with findings from studies including patients with cancer¹⁵¹.

We also describe an association between SFI & VFI and prognosis in patients undergoing EVAR and F/B-EVAR, with SFI appearing to offer superior association. Interestingly, our data describe only a weak correlation between SFI & VFI. To date, these parameters have not been reported with regards to prognosis in patients undergoing intervention for AAA. Charette et al report that low VFI & SFI appear to confer inferior prognosis in patients with metastatic chemorefractory colorectal cancer¹⁵⁴. The mechanism by which fat indices

confer prognosis is unclear and requires further validation in both external AAA and non-AAA cohorts to accurately define this association. The so called “obesity paradox” describes a controversial hypothesis that high BMI may be protective in a variety of conditions^{155,156}, however may reflect reverse causality and inherent statistical bias. In patients with AAA, high BMI has not been identified as a clear risk factor for inferior prognosis¹⁵⁷, however in the present study higher BMI category predicted superior survival outcomes. Further interrogation of the complex interaction between BMI, body composition parameters, and postoperative prognosis is required.

As discussed in chapter 2, there is general consensus that the superior prognostic marker in patients with cancer is SMI¹³⁶, with very few authors reporting PMI in isolation. The present study is the first to directly compare PMI and SMI in this patient cohort. The results observed suggest that SMI offers superior association in both ROC and proportional hazards analyses. Despite the significant *p* values achieved on ROC analyses, the AUC values were, across all parameters, at best only fair. This is somewhat surprising given the encouraging results on survival analyses, however may be explained by the methodology chosen. ROC analyses were performed on each CT-BC parameter as a continuous variable, as analyses were not possible on binary categorical data. However, categorical data are more useful in a clinical setting, hence the decision to use them to perform the remaining survival analyses. Whilst the AUC values are below what may have been expected, the significant association confirms the underlying hypothesis. These data may also be influenced by the relatively modest sample size in the present study. The linear association between SMI and PMI revealed only a fair association ($R^2 = 0.468$), suggesting that despite the systemic nature of sarcopenia and cachexia, certain muscle groups may experience preferential muscle loss. This may relate to physical function and the use of psoas muscle as an aid to ambulation and maintaining posture. The data presented in this chapter suggest that SMI may be superior to other muscle parameters however this requires external validation. Future studies investigating CT-derived muscle mass in patients with AAA, in particular reporting SMI as the factor of interest, are warranted.

The thresholds derived for muscle analyses (SMI, SMD) in the present study were similar to those described by Martin et al¹⁵¹, although the present study did not stratify thresholds based on BMI categories. Furthermore, when the thresholds proposed by Martin et al were applied to the AAA cohort a high prevalence of sarcopenia, and association with outcome were observed, though this was inferior to our newly-derived thresholds. The prevalence of sarcopenia in patients with cancer appears to be similar irrespective of primary tumour

origin and stage¹⁵⁸. The present study is the first to apply thresholds derived from patients with cancer to a non-cancer population, with the novel observation that these thresholds may offer potential prognostic value irrespective of the nature of the underlying disease. It therefore appears that sarcopenia is prevalent across a range of chronic illnesses irrespective of the method used to define it, suggesting that there may be common host factors responsible for the development of sarcopenia, though there may be some disease-specific variation. Increased recognition of host, and not just disease-specific, factors contributing to the development of sarcopenia across a range of pathologies is required. Direct comparison of body composition between patients with cancer and patients with cardiovascular disease may allow for a greater understanding of the heterogeneity in sarcopenia between these patient groups.

The mechanism by which sarcopenia confers inferior prognosis remains poorly understood; reduced function and frailty are known to confer inferior prognosis in a range of conditions, and describing the relationship between body composition, function, and outcomes is an important area for further research.

3.5 TABLES

Table 3.1: The relationship between baseline clinical characteristics and pre-operative CT-derived body composition parameters and overall survival in patients undergoing EVAR and F/B-EVAR (univariate model, n = 674).

Table 3.2: The relationship between baseline clinical characteristics, pre-operative CT-derived SFI & SMI, and overall survival in patients undergoing EVAR and F/B-EVAR (significant residual covariates from backwards conditional multivariate model, n = 674).

Table 3.3: The relationship between baseline clinical characteristics and pre-operative CT-derived body composition parameters and overall survival in patients undergoing EVAR and F/B-EVAR for asymptomatic AAA (univariate model, n = 604).

Table 3.4: The relationship between baseline clinical characteristics, pre-operative CT-derived SFI & SMI, and overall survival in patients undergoing EVAR and F/B-EVAR for asymptomatic AAA (significant residual covariates from backwards conditional multivariate model, n = 604).

Table 3.1: The relationship between baseline clinical characteristics and pre-operative CT-derived body composition parameters and overall survival in patients undergoing EVAR and F/B-EVAR (univariate model, n = 674)

Covariate	N (%)	HR	95% CI	p
Ruptured AAA	44 (6.5%)	1.78	1.45 – 2.18	<0.001
Age (< 65 / 65 – 75 / >75)	38 (5.6%) / 338 (50.1%) / 298 (44.2%)	1.98	1.52 – 2.58	<0.001
Female Sex	58 (8.6%)	1.45	0.92 – 2.28	0.11
F/B-EVAR	133 (19.7%)	0.83	0.57 – 1.21	0.33
Diabetes Mellitus	112 (16.6%)	1.13	0.78 – 1.63	0.52
IHD	235 (35.0%)	1.17	0.87 – 1.57	0.30
Hypertension	452 (67.1%)	1.15	0.84 – 1.56	0.39
Prior CVA	85 (12.6%)	1.02	0.67 – 1.54	0.95
COPD	160 (23.7%)	1.20	0.87 – 1.65	0.28
Current Tobacco Smoker	162 (24.0%)	1.48	1.09 – 2.01	<0.05
Statin Use	511 (76.0%)	0.74	0.54 – 1.02	0.67
BMI (<18.5 / 18.5 – 24.9 / 25.0 – 29.9 / ≥ 30.0 kg/m²)	6 (0.9%) / 129 (19.3%) / 288 (42.7%) / 245 (36.4%)	0.77	(0.64 – 0.93)	<0.01
Low Haemoglobin	167 (24.8%)	2.01	1.50 – 2.69	<0.001
High Creatinine	174 (25.8%)	1.48	1.09 – 2.01	<0.05
Low SFI	81 (13.4%)	2.35	1.63 – 3.37	<0.001
Low VFI	162 (25.3%)	1.78	1.31 – 2.42	<0.001
Low PMI	167 (25.1%)	1.94	1.44 – 2.61	<0.001
Low SMI	296 (43.9%)	2.55	1.88 – 3.46	<0.001
Low SMD	443 (65.7%)	1.82	1.28 – 2.59	<0.001

Table 3.2: The relationship between baseline clinical characteristics, pre-operative CT-derived SFI & SMI, and overall survival in patients undergoing EVAR and F/B-EVAR (significant residual covariates from backwards conditional multivariate model, n = 674)

Covariate	HR	95% CI	<i>p</i>
Ruptured AAA	1.46	1.10 – 1.93	<0.01
Age (< 65 / 65 – 75 / >75)	1.56	1.16 – 2.09	<0.01
Current Tobacco Smoker	1.42	1.00 – 2.00	<0.05
Low Haemoglobin	1.42	1.01 – 2.00	<0.05
Low SFI	1.90	1.30 – 2.76	<0.001
Low SMI	1.88	1.34 – 2.63	<0.001

Table 3.3: The relationship between baseline clinical characteristics and pre-operative CT-derived body composition parameters and overall survival in patients undergoing EVAR and F/B-EVAR for asymptomatic AAA (univariate model, n = 604)

Covariate	N (%)	HR	95% CI	p
Age (< 65 / 65 – 75 / >75)	31 (5.1%) / 311 (51.5%) / 262 (43.4%)	2.07	1.54 – 2.77	<0.001
Female Sex	48 (7.9%)	1.20	0.69 – 2.07	0.52
F/B-EVAR	129 (21.4%)	0.85	0.57 – 1.27	0.44
Diabetes Mellitus	107 (17.7%)	1.13	0.77 – 1.68	0.53
IHD	217 (36.0%)	1.17	0.85 – 1.61	0.34
Hypertension	407 (67.4%)	0.94	0.67 – 1.30	0.69
Prior CVA	78 (13.0%)	0.95	0.60 – 1.50	0.81
COPD	145 (24.0%)	1.28	0.90 – 1.81	0.16
Current Tobacco Smoker	144 (24.0%)	1.61	1.15 – 2.25	<0.01
Statin Use	473 (78.3%)	0.75	0.52 – 1.07	0.12
BMI (<18.5 / 18.5 – 24.9 / 25.0 – 29.9 / ≥ 30.0 kg/m²)	6 (1.0%) / 116 (19.3%) / 254 (42.2%) / 226 (37.5%)	0.72	0.59 – 0.88	<0.01
Low Haemoglobin	130 (21.7%)	2.00	1.44 – 2.80	<0.001
High Creatinine	144 (24.0%)	1.46	1.04 – 2.06	<0.05
Low SFI	70 (12.5%)	1.98	1.32 – 2.97	<0.001
Low VFI	146 (24.5%)	1.76	1.27 – 2.45	<0.001
Low PMI	146 (24.3%)	1.73	1.24 – 2.40	<0.01
Low SMI	259 (44.3%)	2.30	1.66 – 3.18	<0.001
Low SMD	395 (66.8%)	1.85	1.26 – 2.72	<0.01

Table 3.4: The relationship between baseline clinical characteristics, pre-operative CT-derived SFI & SMI, and overall survival in patients undergoing EVAR and F/B-EVAR for asymptomatic AAA (significant residual covariates from backwards conditional multivariate model, n = 604)

Covariate	HR	95% CI	<i>p</i>
Age (< 65 / 65 – 75 / >75)	1.74	1.26 – 2.40	<0.001
Current Tobacco Smoker	1.60	1.11 – 2.31	<0.05
Low Haemoglobin	1.59	1.11 – 2.28	<0.05
Low SFI	1.54	1.01 – 2.35	<0.05
Low SMI	1.71	1.20 – 2.42	<0.01

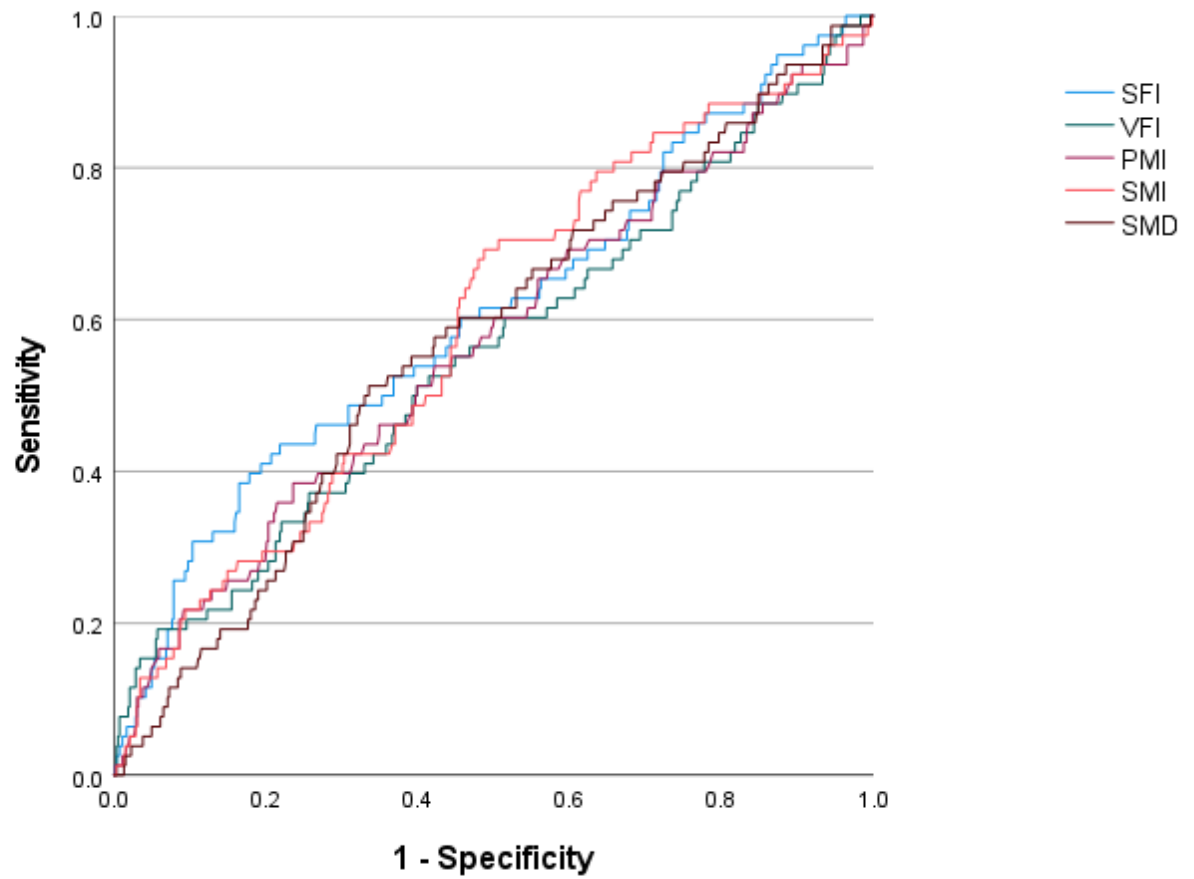
3.6 FIGURES

Figure 3.1: ROC curve and AUC values for the predictive value of body composition parameters on 2-year survival in patients undergoing EVAR and F/B-EVAR.

Figure 3.2: Scatter plots of a) SFI (cm²/m²) vs. VFI (cm²/m²) and b) SMI (cm²/m²) vs. PMI (cm²/m²) in patients undergoing EVAR and F/B-EVAR with a linear interpolation line.

Figure 3.3: Overall survival in patients undergoing EVAR and F/B-EVAR when subgrouped into a) Low and High SFI, $p < 0.001$ and b) Low and High VFI, $p < 0.001$.

Figure 3.4: Overall survival in patients undergoing EVAR and F/B-EVAR when subgrouped into A). Low and High PMI, $p < 0.001$ and B). Low and High SMI, $p < 0.001$.



	AUC	95% CI	<i>p</i>
SFI	0.605	0.533 – 0.677	<0.01
VFI	0.555	0.481 - 0.628	0.12
PMI	0.568	0.496 - 0.641	0.05
SMI	0.592	0.524 - 0.660	<0.01
SMD	0.572	0.504 - 0.640	<0.05

Figure 3.1 ROC curve and AUC values for the predictive value of body composition parameters on 2-year survival in patients undergoing EVAR and F/B-EVAR

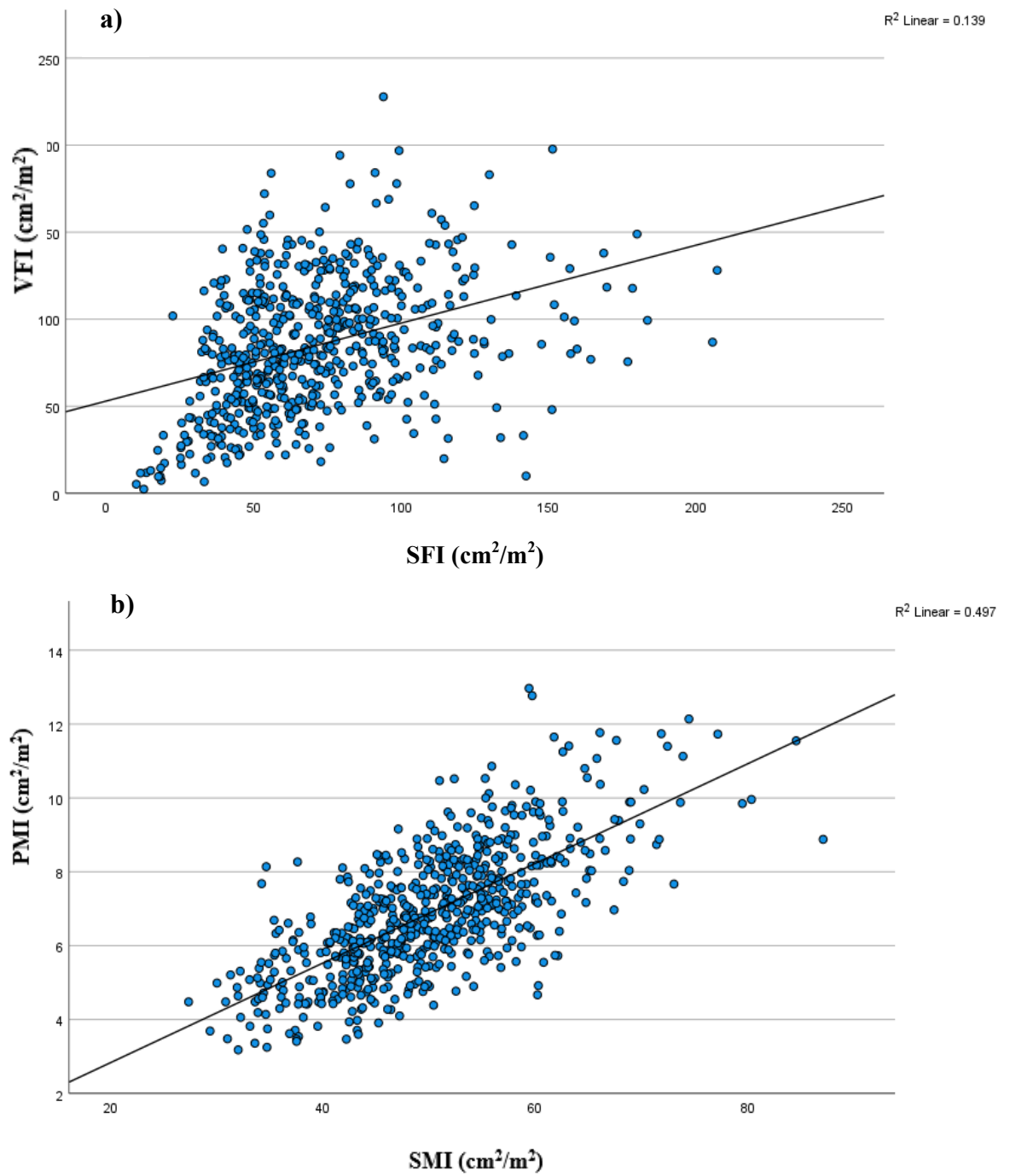


Figure 3.2 Scatter plots of a) SFI (cm^2/m^2) vs. VFI (cm^2/m^2) and b) SMI (cm^2/m^2) vs. PMI (cm^2/m^2) in patients undergoing EVAR and F/B-EVAR with a linear interpolation line

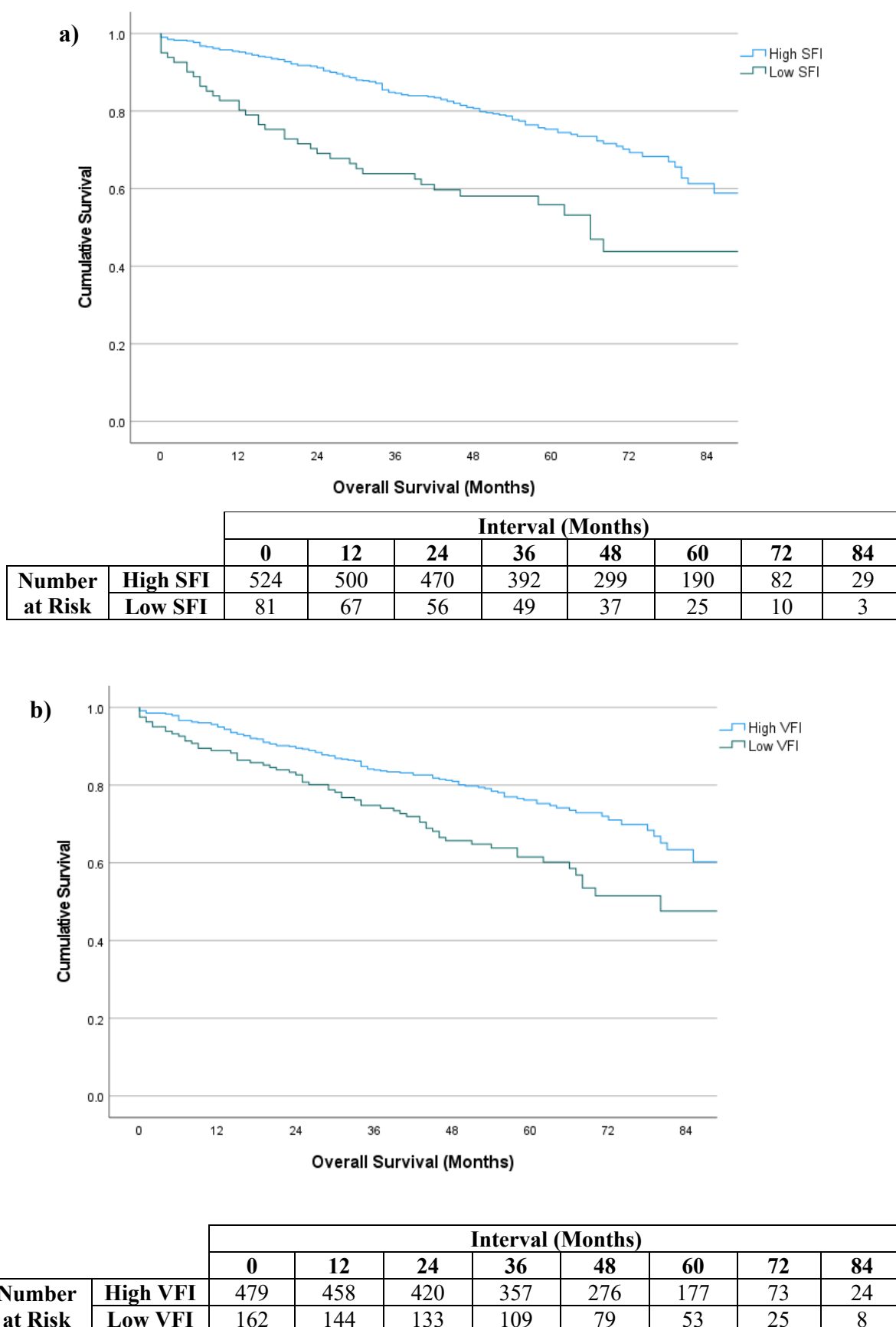


Figure 3.3 Overall survival in patients undergoing EVAR and F/B-EVAR when sub-grouped into a) Low and High SFI, $p < 0.001$ and b) Low and High VFI, $p < 0.001$

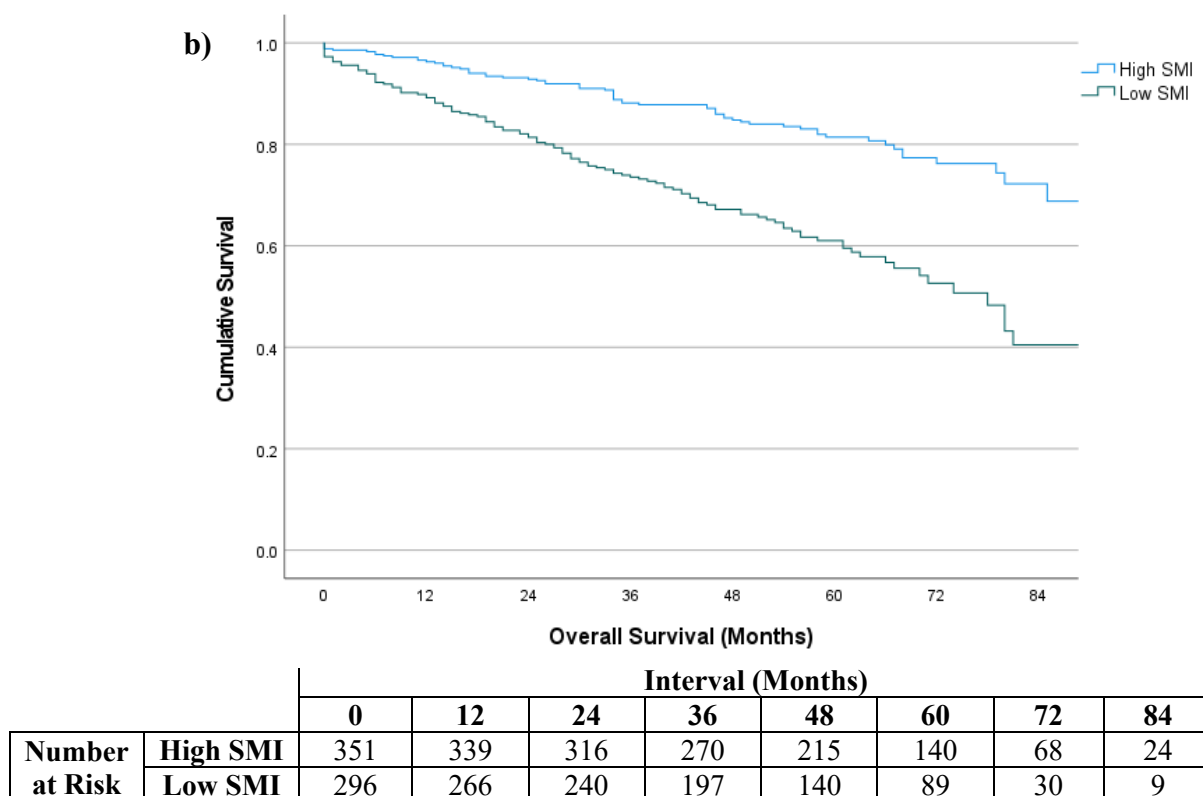
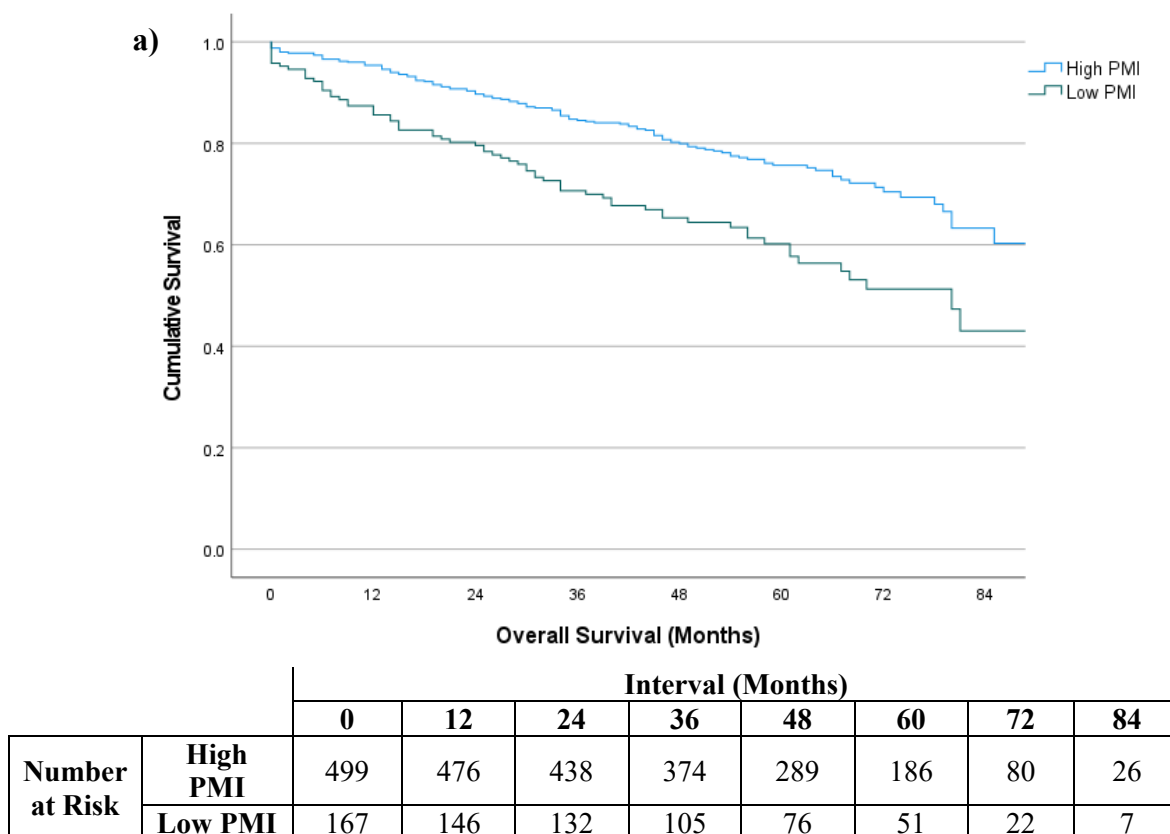


Figure 3.4 Overall survival in patients undergoing EVAR and F/B-EVAR when sub-grouped into A). Low and High PMI, $p < 0.001$ and B). Low and High SMI, $p < 0.001$

4 A SYSTEMATIC REVIEW OF THE ROLE OF SYSTEMIC INFLAMMATION-BASED PROGNOSTIC SCORES IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

4.1 INTRODUCTION

The principles of management of AAA are discussed in section 1.1.2.1, and activation of the SIR as a potential aetiological and prognostic factor in cardiovascular disease is discussed in section 1.4.

The most widely described inflammation-based prognostic scoring systems, the NLR, PLR, and mGPS are discussed in section 1.4.2. An additional, less well reported prognostic score is the systemic immune-inflammatory index (SII). Originally described in patients with hepatocellular carcinoma, it is based on the differential white cell count, and is calculated by: $\text{platelet count} \times (\text{neutrophil count} / \text{lymphocyte count})^{159}$. A diagnostic threshold of 330 has been proposed by the original authors though this lacks external validation.

This review aims to summarise the contemporary evidence base describing the association between systemic inflammation-based prognostic scoring systems in predicting mortality in patients undergoing intervention for AAA

4.2 MATERIALS & METHODS

The general methodology described in this review is described in section 1.7.1. Following preliminary literature search, there was a clear lack of prospective data available, therefore both prospective and retrospective studies were included. Furthermore, there was a clear lack of evidence reporting outcomes relating to mGPS in the eligible patient group. This lead to NLR, PLR, and SII being chosen as the scoring systems of interest. The review protocol was registered with the PROSPERO database (Registration Number: CRD42022363765).

4.2.1 OUTCOMES

The primary outcome of interest was the overall survival following intervention for AAA (either endovascular or open surgical repair, elective or emergency) in patients subgrouped by periprocedural NLR, PLR, or SII reported as categorical or continuous variables. The secondary outcome was how each study defined “high” and “low/normal” NLR PLR, or SII .

4.2.2 SEARCH STRATEGY

The MEDLINE database was accessed electronically using the PubMed (National Centre for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD, USA) search engine. The search was conducted on the 14th February 2024; any papers published after this date are not included in this review. Though NLR was first described in 1967¹⁶⁰ the first widespread clinically relevant studies reporting NLR, PLR, and SII were published in 2001, 2010, and 2014 respectively^{159,161,162}, therefore studies published before 2001 were excluded. Review articles, case reports, editorials/comments, animal studies, and studies unavailable in English as a full text version were excluded. The following search string was used:

“((NLR) OR (PLR) OR (SII)) AND ((EVAR) OR (AAA) OR (aneurysm))”

This search term was applied to study title, key words, and MeSH terms. Duplicate results were screened by identifying their PMID. Relevant review articles underwent bibliography screening to identify additional relevant papers. Abstract screening was performed on the initial results to generate a list of studies to undergo full paper screening for final inclusion.

4.2.3 DATA EXTRACTION

Data extracted from study documents included:

Study design (centres, follow-up, prospective/retrospective) and study information (journal, authors, year).

Baseline clinical and demographic data of patients.

Classification of "high" vs. "low/normal" i.e. cut-off of NLR/PLR/SII (whether using data derived cut-offs or absolute values), or whether analysed as a continuous variable.

Survival data for overall survival, where hazard ratio and 95% confidence intervals are reported these were extracted. Where univariate and multivariate results are reported, relevant multivariate values were preferred for inclusion in this review.

Preliminary literature review showed that significant heterogeneity between outcome measures reported and patient selection across all studies precluded meaningful meta-analysis. Therefore, studies were grouped based on their reporting of NLR, PLR, and/or SII in relation to outcomes in patients undergoing OSR and/or EVAR. Qualitative review of each of these subgroups was performed.

4.3 RESULTS

The study selection process is summarised in the PRISMA diagram in figure 4.1. There were 8 studies included in the final review reporting outcomes on a total of 4065 patients^{163–170}; 1256 (31%) patients underwent OSR, and 2809 (69%) patients underwent EVAR. 3850 (95%) patients underwent a procedure for uAAA, 215 (5%) patients underwent an emergency procedure for rAAA.

The variable of interest was NLR in 5 studies, PLR in 1 study, both NLR & PLR in 2 studies, with 1 study reporting SII. The characteristics of each study and main outcomes are summarised in table 4.1. Values of NLR or PLR were derived from pre-operative blood results in 7 studies, and from post-operative blood results in 1 study. The study reporting SII reported values based on pre-operative blood results. All studies were retrospective, and 7 were single centre whilst 1 (Bath *et al* 2019¹⁶⁸) was based on registry data from multiple centres. Table 4.2 summarises the results of each study's primary outcome.

4.3.1 OUTCOMES RELATING TO NLR IN PATIENTS UNDERGOING OSR

5 studies reported outcomes by NLR on cohorts of patients undergoing OSR, with one of these (Bath *et al* 2019¹⁶⁸) reporting on a combined OSR and EVAR cohort. 3 studies reported increased mortality associated with elevated NLR with follow-up ranging from 30 days to 1 year, whilst 2 studies did not observe a significant association.

Ko *et al* (2021)¹⁶³ report 1-year mortality on a cohort of 334 patients with rAAA (n = 98) and uAAA (n = 236) undergoing OSR. NLR was analysed from preoperative blood sampling though the specific timing of this sample is not reported, and it was analysed as a continuous variable. In all patients, high NLR was associated with increased 1-year mortality on multivariate analysis (OR 1.09, 95% CI 1.02 – 1.16, $p < 0.05$). In the rAAA subgroup, elevated NLR was associated with increased 1-year mortality on multivariate analysis (OR 1.14, 95% CI 1.03 – 1.27, $p < 0.05$). NLR was not associated with survival in the uAAA subgroup.

Kordzadeh *et al* (2015)¹⁶⁹ included 80 consecutive patients undergoing OSR for rAAA, with NLR calculated from pre-operative blood samples, without specific report of timing of sampling. NLR > 5.0 was used to subgroup patients based on ROC analysis, with 25 patients in the “low NLR” subgroup and 55 patients in the “high NLR” subgroup. The 30-

day mortality in low vs. high subgroups was 8.0% vs. 16.4% ($p = 0.488$). Regression analyses were not performed due to low absolute number of events.

Appleton *et al* (2014)¹⁷⁰ recruited 350 consecutive patients undergoing elective OSR for uAAA. All patients were followed-up for a minimum of 12 months though median follow-up is not reported. NLR ≥ 5.0 was considered elevated, which the authors base on previous literature from patients with colorectal cancer¹⁷¹. 30-day mortality in the patients with high NLR was 23.0% vs. 6.7% in the low NLR group ($p < 0.01$). Each of the 30-day deaths in patients with high NLR were due to myocardial infarction. Overall mortality during the follow-up period was 50.0% vs. 34.2% in the high vs. low NLR groups ($p < 0.05$).

Bath *et al* (2019)¹⁶⁸ performed retrospective registry interrogation of patients undergoing elective OSR ($n = 379$) and EVAR ($n = 1529$) for AAA. Due to the limitations of their methodology, only inpatient mortality is reported. NLR was recorded from post-operative results, with NLR ≥ 4.0 (based on an ROC curve) considered elevated. Results are presented as a combined cohort of both procedure types. On multivariate analysis, OSR was associated with increased inpatient mortality (OR 11.8, 95% CI 5.26 – 26.60, $p < 0.05$), but high NLR was not ($p > 0.05$).

4.3.2 OUTCOMES RELATING TO NLR IN PATIENTS UNDERGOING EVAR

4 studies reported outcomes by NLR in cohorts of patients undergoing EVAR, with one of these (Bath *et al* 2019¹⁶⁸) reporting on a combined OSR and EVAR cohort (reported previously). 3 studies reported increased mortality in patients with elevated NLR, whilst 1 study did not observe a significant association.

Octeau *et al* (2021)¹⁶⁴ included 777 patients undergoing procedures over a 16-year period, who were followed up for a median of 4 years. NLR values were taken from pre-operative blood sampling within 6 months of surgery. A multivariate model including age, cardiac comorbidity, aneurysm diameter, intraoperative complications, diabetes as covariates found that NLR (High) (HR 1.59, 95% CI 1.22 – 2.06, $p = 0.001$) and NLR (continuous) (HR 1.05, 95% CI 1.02 – 1.08, $p = 0.003$) were predictive of mortality. This cohort of patients included 12 patients undergoing EVAR for rAAA; we note that emergency procedure was not included as a covariate in this multivariate model.

Lecumberri *et al* (2021)¹⁶⁵ report on 284 patients undergoing elective EVAR with follow-up for 5 years in all patients. Their survival analysis included the development of a

predictive regression model using significant covariates (haemoglobin, statin use, atrial fibrillation, heart failure, coronary artery disease) and assessing response of goodness of fit parameters when NLR or PLR were added to the model. NLR had significant univariate predictive value on 2- and 5-year survival (HR 1.07 and 1.07 respectively, $p < 0.05$ and $p < 0.01$). When added to the predictive model NLR increased the continuous net reclassification index ($p < 0.05$) however did not significantly increase model C-statistic. Subsequent analysis based on dichotomous NLR values revealed that $\text{NLR} \geq 3.0$ was independently associated with inferior 2-year (HR 1.98, 95% CI 1.07 – 3.66, $p < 0.05$) and 5-year (HR 1.84, 95% CI 1.22 – 2.78, $p < 0.05$) survival.

King *et al* (2020)¹⁶⁶ report on a cohort of 108 patients undergoing elective EVAR, with NLR values taken within 30 days prior to surgery. Median follow-up was 36.4 months. On multivariate analysis, High NLR was associated with mortality (HR 1.19, 95% CI 1.12 – 1.27, $p < 0.001$).

4.3.3 OUTCOMES RELATING TO PLR IN PATIENTS UNDERGOING OSR

2 studies reported outcomes by PLR in cohorts of patients undergoing OSR, with one of these studies (Lareyre *et al* 2019)¹⁶⁷ reporting on a combined OSR and EVAR cohort. 1 study observed reduced mortality associated with elevated PLR, and 1 study did not observe a significant association.

Ko *et al* (2021, described in the previous section)¹⁶³ also reported outcomes on pre-operative PLR. In all patients, PLR was not significantly associated with survival, nor was it associated in the uAAA subgroup. In the rAAA subgroup, elevated PLR was associated with reduced 1-year mortality on multivariate analysis (OR 0.99, 95% CI 0.98 – 0.99, $p < 0.05$).

Lareyre *et al* (2019)¹⁶⁷ investigated the effect of pre-operative PLR on 30-day mortality in a combined cohort of patients with rAAA and uAAA undergoing either OSR or EVAR. Outcomes in open and endovascular procedures were not reported separately. PLR was analysed according to subgroups of quartiles, with the authors reporting a non-significant trend towards increased 30-day mortality in the quartiles 1 and 4 vs. quartiles 2 and 3 (7.1% and 8.9% vs. 0.0% and 3.6%, $p > 0.05$).

4.3.4 OUTCOMES RELATING TO PLR IN PATIENTS UNDERGOING EVAR

2 studies reported outcomes in patients undergoing EVAR in relation to PLR, of which one study (Lareyre *et al* 2019, described in the previous section)¹⁶⁷ reported on a combined OSR and EVAR cohort. 1 study observed increased mortality associated with elevated PLR, and 1 study did not observe a significant association.

The methodology used by Lecumberri *et al* (2021)¹⁶⁵ is described in a previous section in relation to NLR. The same analysis was performed using PLR as the variable of interest. PLR had significant univariate predictive value on 2- and 5-year survival (HR 1.002 and 1.002 respectively, $p < 0.05$). However, when added to the predictive model PLR did not significantly improve model fit.

4.3.5 OUTCOMES RELATING TO SII

Lecumberri *et al* (2021, methodology described in a previous section)¹⁶⁵ repeated their analyses in patients undergoing EVAR for uAAA using SII as the variable of interest. Whilst they report that SII was significantly associated with 2- and 5-year survival, they report HR of 1.000 and 1.000 and p values of 0.066 and 0.043 respectively. The addition of SII to their predictive model did not improve model fit.

4.3.6 METHODS USED TO SUBGROUP PATIENTS

Subgrouping of patients is summarised in table 4.3. NLR was subgrouped by tertiles in 1 study (Ko *et al* 2021¹⁶³), by ROC analysis in 4 studies (Lecumberri *et al* 2021¹⁶⁵, King *et al* 2020¹⁶⁶, Bath *et al* 2019¹⁶⁸, Kordzadeh *et al* 2015¹⁶⁹), by absolute values based on previous literature¹⁷¹ in 1 study (Appleton *et al* 2014¹⁷⁰), and by the maximally selected log rank statistic technique in 1 study (Octeau *et al* 2021¹⁶⁴).

PLR was subgrouped by quartiles in 1 study (Lareyre *et al* 2019¹⁶⁷), and analysed as a continuous variable in 2 studies (Ko *et al* 2021¹⁶³, Lecumberri *et al* 2021¹⁶⁵). SII was analysed as a continuous variable by Lecumberri *et al*¹⁶⁵.

4.3.7 RISK OF BIAS ASSESSMENT

The summary assessment outcomes of the risk of bias assessment using the QUIPS tool in the included studies is shown in table 4.4. High risk of bias was judged in 5 of 48 (10%) domains, moderate risk in 28 of 48 (59%) domains, and low risk in 15 of 48 (31%) domains. Visual inspection of domains shows that study participation and statistical

analysis & reporting were generally low risk of bias, however prognostic factor measurement, outcome measurement, and study confounding were generally moderate-high risk of bias.

4.4 DISCUSSION

The present review summarises the evidence base describing the potential prognostic value of NLR, PLR, and SIR in patients undergoing intervention for AAA. The majority of studies investigating NLR described an association between elevated NLR and increased mortality, at a range of follow-up points, in patients undergoing both OSR and EVAR. This is in keeping with observations from other authors in non-cancer populations. Regarding PLR, the association with outcomes is less well defined, with fewer studies reporting an association with survival. SIR did not appear to offer prognostic value in this patient group, though there is a relative lack of evidence. The mechanism by which activation of the SIR produces inferior survival in patients with AAA is not well defined, however is likely reflective of increased risk of cardiovascular event in a patient group already prone to cardiovascular morbidity¹⁴. Whilst the association between inflammation and atherosclerosis to date has largely been in the research setting, an association between the clinically measurable NLR and both generalised atherosclerosis and impaired outcome in cerebrovascular and coronary artery disease is described¹⁷². Endothelial microinjury triggers a localised inflammatory response, and subsequent lipid deposition accelerates the progression to atherosclerotic plaque. Moreover, the formation of a necrotic plaque core is itself an inflammatory event, which allows micro- and macro- calcification of plaque to occur.

In an attempt to improve cardiovascular morbidity and mortality, modulation of the SIR in patients with cardiovascular disease is beginning to emerge as a promising strategy, though one which is currently in its infancy. The CANTOS trial showed a benefit to IL-1 β blockade in patients with ischaemic heart disease both in a reduction in cardiovascular events¹⁷³ and reduced rate of incident lung cancer¹⁷⁴. However, this immunomodulation resulted in an increased rate of infection in the treatment group. Eagerly awaited follow-up studies targeting alternative cytokines may pave the way to clinical implementation of immunomodulation in this setting. Translating this strategy to other “high risk” patient groups, for example those with other manifestations of arterial disease, is of particular interest. In patients with AAA, perioperative methylprednisolone has been investigated with results suggesting mitigation of the post-operative inflammatory response and improved recovery^{175,176}, though the effects on long-term outcomes are unreported.

In patients undergoing EVAR, early activation of the SIR may manifest clinically as the PIS, which appears to confer inferior mid-term outcomes¹⁴⁴. PIS is influenced by a variety

of factors, including inflammatory response to graft material, mechanical disruption of thrombus, and endothelial disruption. In patients undergoing OSR, the massive inflammatory response provoked by extensive dissection makes the subtleties of the inflammatory environment more challenging to characterise. The effect of PIS on systemic inflammation-based scoring systems is not described, however may confound outcomes and is an area for future research.

The majority of the studies included in the present review reported outcomes on patients undergoing intervention for infrarenal AAA; patients undergoing intervention for juxta- or para-renal AAA are underrepresented. Both open and endovascular repairs of these aneurysms are more complex procedures than for infrarenal AAA, carrying a different risk profile. Open repair of complex aneurysms is typically a longer operation with a greater degree of dissection, and may produce a greater peak in the well-described post-operative inflammatory cytokine response¹⁴². F/B-EVAR are typically longer procedures than EVAR, with increased contrast and radiation doses. Contrast is known to induce an inflammatory response¹⁷⁷, and a cytokine response following high doses of radiation is described¹⁷⁸. The acute inflammatory insult following these procedures may be potentiated by underlying chronic activation of the SIR, and this relationship warrants further investigation.

There is no validated cutoff of NLR, PLR, or SII to indicate pathological state. Regarding NLR, typical cutoff values are 3.0 and 5.0, which have been extensively studied in patients with cancer⁸⁹. Only 2 of the studies included in this review used 5.0 as a cutoff based on previous results, although 2 studies used 3.0 and 5.0 respectively based on ROC analysis. A potential benefit to mGPS is that it provides a categorical method of subgrouping patients therefore can be readily compared in clinical and research settings. Evaluating the role of mGPS in this setting is a clear area for further investigation. Determining optimal values is a key component to allow the translation of these scoring systems from the research sector to clinically useful parameters.

A limitation of the present review is that there were 3 studies^{179–181} which the authors were unable to obtain in full in the English language, which introduces evidence selection bias into the findings of this review. Additionally, 2 studies had relevant patient populations however included only pooled outcomes on patients with AAA and non-AAA pathologies, and so were discounted. Furthermore, the studies included in the review are subject to

significant bias due to the inherent limitations in their study design. Finally, inter-study heterogeneity precluded meaningful quantitative analysis.

In conclusion, NLR provides potential prognostic value in patients undergoing intervention for AAA. PLR and SII currently have insufficient evidence to support their role. mGPS is unreported and is a potentially valuable tool in prognostication. Each of these parameters require further prospective evaluation and standardisation to optimise their potential clinical utility.

4.5 TABLES

Table 4.1: Study design of the included studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA.

Table 4.2: Main findings of included studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA.

Table 4.3: Methods to subgroup patients in studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA.

Table 4.4: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Table 4.1: Study design of the included studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA

Authors	Country	Design	Centres	Parameter	Pre/Post-Op	Procedure	Priority
Ko et al (2021) ¹⁶³	S. Korea	Retrospective	Single	NLR, PLR	Pre-op	334 OSR	236 uAAA, 98 rAAA
Octeau et al (2021) ¹⁶⁴	USA	Retrospective	Single	NLR	Pre-op	777 EVAR	765 uAAA, 12 rAAA
Lecumberri et al (2021) ¹⁶⁵	Spain	Retrospective	Single	NLR, PLR, SII	Pre-op	284 EVAR	284 uAAA
King et al (2020) ¹⁶⁶	USA	Retrospective	Single	NLR	Pre-op	108 EVAR	108 uAAA
Bath et al (2019) ¹⁶⁸	USA	Retrospective	Multicentre Registry Data	NLR	Post-op	1529 EVAR, 379 OSR	1908 uAAA
Lareyre et al (2019) ¹⁶⁷	France	Retrospective	Single	PLR	Pre-op	113 OSR, 111 EVAR	199 uAAA, 25 rAAA
Kordzadeh et al (2015) ¹⁶⁹	UK	Retrospective	Single	NLR	Pre-op	80 OSR	80 r AAA
Appleton et al (2014) ¹⁷⁰	UK	Retrospective	Single	NLR	Pre-op	350 OSR	350 uAAA
						1256 OSR, 2809 EVAR	3850 uAAA, 215 rAAA
						Total n = 4065	

Table 4.2: Main findings of included studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA

Authors	Follow-Up	Primary Outcome	Summary of Results of Primary Outcome
Ko et al (2021) ¹⁶³	12.0 months (final)	12.0-month mortality	<u>All patients</u> : NLR (Continuous); OR 1.09, (95% CI 1.02 – 1.16), $p < 0.05$. PLR (Continuous); NS. <u>rAAA</u> : NLR (Continuous); OR 1.14, (95% CI 1.03 – 1.27), $p < 0.05$. PLR (Continuous); OR 0.99, (95% CI 0.98 – 0.99), $p < 0.05$. <u>uAAA</u> : NLR & PLR (Continuous); NS.
Octeau et al (2021) ¹⁶⁴	48.0 months (median)	Mortality during follow-up	<u>All patients</u> : NLR (≥ 3.6); HR 1.59, (95% CI 1.22 – 2.06), $p = 0.001$. NLR (Continuous); HR 1.05, (1.02 – 1.08), $p < 0.01$.
Lecumberri et al (2021) ¹⁶⁵	60.0 months (final)	2-year and 5-year survival	<u>All patients, 2-year survival</u> : NLR (≥ 3.0); HR 1.98, (95% CI 1.07 – 3.66), $p < 0.05$. PLR (Continuous); HR 1.002, $p < 0.05$. SII (Continuous); HR 1.000, $p = 0.066$. <u>All patients, 5-year survival</u> : NLR (≥ 3.0); HR 1.98, (95% CI 1.07 – 3.66), $p < 0.05$. PLR (Continuous); HR 1.002, $p < 0.05$. SII (Continuous); HR 1.000, $p < 0.05$.
King et al (2020) ¹⁶⁶	36.4 months (median)	Mortality during follow-up	<u>All patients</u> : NLR (≥ 4.0); HR 1.19, (95% CI 1.12 – 1.27), $p < 0.001$
Bath et al (2019) ¹⁶⁸	Inpatient (<30 days) (final)	Inpatient (<30 days) mortality	<u>All patients</u> : NLR; NS.
Lareyre et al (2019) ¹⁶⁷	Inpatient (<30 days) (final)	Inpatient (<30 days) mortality	<u>All patients</u> : PLR; NS.

Kordzadeh et al (2015) ¹⁶⁹	Inpatient (<30 days) (final)	Inpatient (<30 days) mortality	<u>All patients:</u> NLR; NS.
Appleton et al (2014) ¹⁷⁰	NR (minimum 12 months)	Mortality during follow-up, 30-day mortality	<u>Overall Mortality:</u> NLR (≥ 5.0) 50.0% mortality vs. NLR (< 5.0) 34.2% mortality, $p < 0.05$. <u>30-day Mortality:</u> NLR (≥ 5.0) 23.0% mortality vs. NLR (< 5.0) 6.7% mortality, $p < 0.05$.
NS; not significant ($p > 0.05$).			

Table 4.3: Methods to subgroup patients in studies investigating the effect of the SIR on mortality following OSR/EVAR for AAA			
Authors	Subgrouping of NLR	Subgrouping of PLR	Subgrouping of SII
Ko et al (2021) ¹⁶³	Tertiles ($T1 \leq 2.41$, $2.41 \leq T2 \leq 6.07$, $T3 > 6.07$) & Continuous	Continuous	-
Octeau et al (2021) ¹⁶⁴	NLR ≥ 3.6 (Maximally selected log rank statistic)	-	-
Lecumberri et al (2021) ¹⁶⁵	NLR ≥ 3.0 (ROC curve)	Continuous	Continuous
King et al (2020) ¹⁶⁶	NLR ≥ 4.0 (ROC curve)	-	-
Bath et al (2019) ¹⁶⁸	Post-operative NLR ≥ 4.0 (ROC curve)	-	-
Lareyre et al (2019) ¹⁶⁷	-	Quartiles ($Q1 < 91.5$, $91.5 < Q2 < 120.8$, $120.8 < Q3 < 163.3$, $Q4 > 163.3$)	-
Kordzadeh et al (2015) ¹⁶⁹	NLR ≥ 5.0 (ROC curve)	-	-
Appleton et al (2014) ¹⁷⁰	NLR ≥ 5.0 (Previous literature ¹⁷¹)	-	-

Table 4.4: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Ko et al (2021) ¹⁶³	Green	Green	Yellow	Yellow	Yellow	Green
Octeau et al (2021) ¹⁶⁴	Yellow	Red	Yellow	Yellow	Yellow	Green
Lecumberri et al (2021) ¹⁶⁵	Green	Yellow	Yellow	Yellow	Yellow	Green
King et al (2020) ¹⁶⁶	Yellow	Yellow	Yellow	Yellow	Red	Yellow
Bath et al (2019) ¹⁶⁸	Green	Yellow	Red	Red	Yellow	Green
Lareyre et al (2019) ¹⁶⁷	Green	Green	Yellow	Yellow	Yellow	Yellow
Kordzadeh et al (2015) ¹⁶⁹	Green	Green	Yellow	Yellow	Yellow	Green
Appleton et al (2014) ¹⁷⁰	Green	Green	Yellow	Yellow	Red	Yellow

Green – low risk of bias. Amber – moderate risk of bias. Red – high risk of bias

4.6 FIGURES

Figure 4.1: PRISMA diagram showing study inclusion.

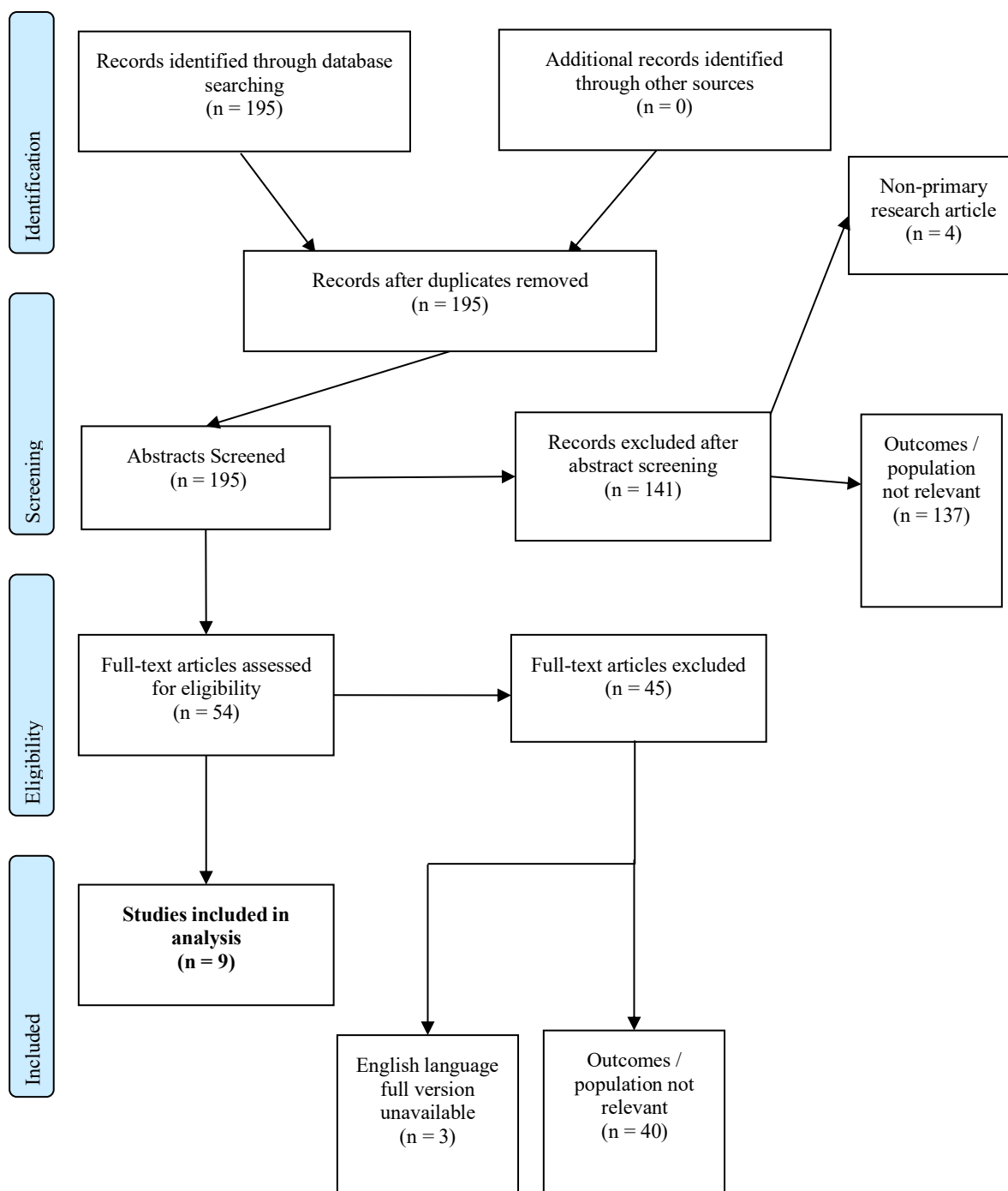


Figure 4.1: PRISMA diagram showing study inclusion

5 THE PROGNOSTIC VALUE OF PRE-OPERATIVE SYSTEMIC INFLAMMATION-BASED SCORING IN PATIENTS UNDERGOING ENDOVASCULAR REPAIR OF AAA

5.1 INTRODUCTION

The literature describing the prognostic associations between elevated magnitude of the pre-operative SIR, as measured by the readily available NLR, PLR, and SII, and survival following intervention for AAA was reviewed in chapter 4. Whilst similar prognostic associations to those described in other disease states were observed, there is a relative paucity of evidence; several studies fail to observe a significant association. Prognostic scoring systems measuring the acute phase response are not represented in the current literature. Moreover, heterogenous methodology was also present, mirroring the limitations of the evidence base investigating the potential prognostic role of CT-BC parameters in this patient group (described in chapter 2).

The GPS/mGPS has been extensively reported as an inflammation-based prognostic scoring system in patients with cancer¹⁸². Calculated using albumin and CRP, mGPS is therefore based on the acute phase inflammatory response. To date, there are no studies reporting outcomes following AAA repair in relation to mGPS. In addition to mGPS alone, the combination of mGPS and NLR into the Systemic Inflammatory Grade (SIG) has recently been proposed by Golder et al¹⁰⁴. This composite measure recognises the differing contributions to overall systemic inflammatory response from acute phase proteins (using mGPS) and differential white cell response (using NLR). The association between both of these measures and outcomes, including survival, have been extensively reported separately in cohorts of patients with a range of conditions, with the majority of studies reporting on patients with cancer. The benefit to this approach is therefore the extensive validation and reproduction of both scoring systems, however a potential drawback is a less comprehensive assessment of the overall SIR. NLR and mGPS describe the activation of different components of the SIR. Indeed, the inflammatory response is a complex phenomenon with myriad components, and using a single measure to entirely represent it is fraught with difficulty. However, the use of SIG has the potential to provide a more holistic assessment of the SIR, and therefore examining the association between increased magnitude of SIG and survival in patients with cardiovascular disease may identify a potentially superior tool for prognostication.

Indeed, SIG offered superior prognostic value compared to NLR or mGPS alone in patients with colorectal cancer managed by curative intent¹⁰⁴. This more holistic assessment of the SIR and the superior prognostic value make SIG a potentially attractive factor of interest in patients with cardiovascular disease.

The aim of the present study was therefore to examine the relationship between SIG and long-term survival in patients undergoing elective EVAR for AAA.

5.2 MATERIALS & METHODS

5.2.1 PATIENT SELECTION

The description of the recruitment of the AAA cohort is in section 1.7.2.1. To avoid the potential risk of bias introduced due to a heterogeneous patient cohort, only patients undergoing EVAR (rather than OSR) were included. Comorbidity was assessed using ASA, which was recorded from operative records and sub-grouped (≤ 2 / > 2) in keeping with previous literature¹⁸³. Patients were sub-grouped based on age (<65 , $65 - 75$, > 75). High creatinine was defined as > 1.20 mg/dL (male patients) and > 0.90 mg/dL (female patients), based on local laboratory values.

5.2.2 PRIMARY OUTCOME

The primary outcome was all-cause mortality during the follow-up period.

5.2.3 INFLAMMATORY PROFILING

NLR (from absolute neutrophil and lymphocyte counts) and mGPS (from CRP and albumin) were calculated based on pre-operative blood investigations using previously described methodology^{89,99}. Institutional policy during the study period was to admit patients to hospital on the evening prior to surgery, where pre-operative blood work was routinely performed as part of existing patient care. NLR and mGPS were then combined into SIG as per Golder et al¹⁰⁴. The calculation of these inflammation-based prognostic scores is summarised in table 5.1. Outcomes were compared between groups based on absolute values of SIG.

5.2.4 STATISTICAL ANALYSES

General statistical analyses are described in section 1.7.4. ROC analysis was performed to determine the predictive value of SIG on 1-year mortality with AUC values evaluated. To examine the relative contributions of NLR and mGPS to SIG, 1-year survival rates and % SE were compared between subgroups. The association between covariates and overall survival was assessed using a Cox Proportional Hazards Model; covariates were initially interrogated in univariate analysis and those with univariate $p < 0.05$ were included in a multivariate model. The association between baseline variables and increasing SIG were assessed with multinomial logistic regression, with SIG 0 used as the reference category.

5.3 RESULTS

674 patients were screened for inclusion into the study. 168 patients were excluded: 60 patients who underwent emergency or urgent repair for ruptured or symptomatic AAA, 3 patients due to haematological malignancy, 1 patient due to mycotic aneurysm, 3 due to no pre-operative results available, and 101 patients due to missing pre-operative CRP or albumin (figure 5.1). This resulted in 506 elective patients with a pre-operative SIG who were eligible for inclusion into the final study cohort. There were 108 (21%) F/B-EVAR cases, 461 (91%) males, and a median (IQR) age of 74.0 (11.0) years. Median (IQR) follow-up was 68.0 (27.3) months, and there were 163 (32%) deaths during the follow-up period.

Mean (95% CI) survival in the entire study population was 78.1 (74.8 – 81.5) months. Mean (95% CI) survival in the SIG 0 vs. SIG 1 vs. SIG 2 vs. SIG 3 vs. SIG 4 subgroups was 80.7 (76.5 – 85.0) vs. 78.7 (72.7 – 84.7) vs. 61.0 (51.1 – 70.8) vs. 65.1 (45.0 – 85.2) vs. 54.9 (34.4 – 75.3) months ($p < 0.05$, figure 5.2).

Table 5.2 shows the association of baseline covariates with all-cause mortality in the study cohort. On univariate analysis, increasing age ($p < 0.001$), high creatinine ($p < 0.05$), and increasing SIG ($p < 0.05$) were associated with increased mortality, whilst high BMI ($p < 0.05$) was associated with decreased mortality. On multivariate analysis increasing age (HR 1.72, 95% CI 1.29 – 2.31, $p < 0.001$), and increasing SIG (HR 1.20, 95% CI 1.02 – 1.40, $p < 0.05$) were associated with increased mortality.

1-year survival and %SE stratified by NLR and mGPS subgroups is shown in table 5.3. In the NLR < 3 there was a significant trend towards inferior survival with increasing mGPS ($p < 0.05$), whilst in other subgroups these trends were non-significant.

ROC analysis to determine the predictive value of SIG on 1-year mortality in the entire study cohort is shown in figure 5.3; SIG significantly predicted 1-year mortality however with only a fair AUC value; AUC 0.68 (95% CI 0.58 – 0.78, $p < 0.01$).

In order to account for patients with missing pre-operative SIG resulting in selection bias, patients with a missing SIG were compared with the final study cohort (table 5.4). There was a lower rate of statin use amongst the patients with missing SIG (70% vs. 80%, $p < 0.05$), but other characteristics were similar between groups. Survival analysis was

performed on this subgroup and compared with the final study cohort; mean (SD) survival in the “missing SIG subgroup” was 72.9 (67.1 – 78.8) months, comparable to the final study cohort.

The association between each of pre-operative diabetes, ischaemic heart disease, hypertension, prior stroke, chronic obstructive pulmonary disease, tobacco smoking, statin use, and juxta-/para-renal aneurysm and increased SIG was examined using multinomial logistic regression. For each covariate of interest, there was no significant association with any magnitude of SIG ($p > 0.05$ for each).

5.4 DISCUSSION

The results of the present study suggest that combined markers of the systemic inflammatory response may offer potential prognostic value in patients undergoing elective EVAR and F/B-EVAR for AAA. These results indicate that activation of the systemic inflammatory response may provide useful routinely available clinical information on long-term outcomes in this patient group. In the present study, the systemic inflammation-based prognostic score of interest was SIG, which incorporates both NLR and mGPS. Prognostication is of paramount importance in the elective sub-group, where procedures are by their very nature, prophylactic. Therefore, identifying a sub-group of patients in whom long-term cardiovascular outcomes are inferior may allow for direction of patients towards a conservative management strategy, and effective allocation of resource. The need for an optimal prognostication tool is highlighted by the preliminary results of the UK-COMPASS trial¹⁸⁴; where an overall mortality of 21.6% was observed during a median follow-up period of 3 years. This mortality rate is broadly in keeping with the 32% mortality rate over a median follow-up of 5.5 years observed by the present study.

It was of interest that, from visual inspection of the survival plots, SIG identifies subgroups who diverge in their survival within the first 3 years of follow-up. If this were to be the case then SIG may be useful in identifying those patients who will benefit from intervention, rather than conservative management. However, low absolute numbers in certain subgroups during later follow-up intervals may limit the generalizability of these conclusions. The present results, using routine clinical measure of systemic inflammation, may be readily validated in large external cohorts of patients.

As discussed in chapter 4, prior studies investigating NLR and AAA have not universally demonstrated an association with survival. The literature investigating this association is heterogeneous, with inter-study variation in measurement timing, outcome measures, and definition of threshold for “abnormal” NLR. The present study used previously reported values to subgroup based on NLR, however these were originally described in patients with cancer⁸⁹. Furthermore, few studies reliably report which component of the NLR leads to the reported value, i.e. whether neutrophilia or lymphopenia predominate. The “normal” mean value of NLR recently reported in a cohort of over 400,000 disease-free controls in the UK Biobank was 2.35¹⁸⁵, broadly in keeping with the lower threshold used in the present study. A benefit to the implementation of the mGPS to assess the SIR is the pre-defined subgroups removing inter-study heterogeneity. Whilst these are derived from

continuous variables, the cutoff values for CRP and albumin (10 mg/L and 35 g/L respectively) are typical “normal” values already used in routine clinical practice. Evaluating both NLR and mGPS allows for a comprehensive assessment of the multiple systems contributing to activation of the SIR, including both the differential white cell and acute phase responses^{94,186}.

The mechanism by which chronic systemic inflammation confers increased long-term mortality in patients undergoing intervention for AAA is poorly described. Given that the survival advantage is demonstrated over long-term follow-up, and that the nature of endovascular repair does not inherently remove the aneurysm from the circulation (in contrast to resection for cancer), it does not seem likely that the aneurysm itself is the source of both the inflammatory stimulus or the survival effect. Furthermore, chronic inflammation is an established risk factor for long-term cardiovascular mortality^{187–190}. We hypothesise that the chronic inflammation reported in the present study is a symptom of the underlying chronic disease (largely atherosclerotic) and comorbidity burden; however we acknowledge that there is also likely to be an element of a “chicken and egg” phenomenon, where chronic inflammation may be either the instigating event or a consequence of the chronic atherosclerotic burden. Indeed, patients with AAA typically show other systemic features of cardiovascular morbidity and atherosclerotic disease¹⁴; in the present study cohort 35.0% and 12.6% of patients had prior diagnoses of IHD and CVA respectively, and the burden of cardiovascular disease in patients with AAA is well recognised¹⁹¹. The underlying role of chronic inflammation in predisposing patients with AAA to increased risk of mortality may be associated with this heightened cardiovascular risk.

The effect of immunomodulation in patients with cardiovascular disease has been investigated; Ridker et al demonstrated that interleukin-1 β blockade with Canakinumab in patients with IHD resulted in a decreased incidence of cardiovascular events (CANTOS)¹⁷³. Subsequent analyses have shown additional benefits, for example a lower incidence of lung cancer¹⁷⁴. Canakinumab has been investigated in patients with peripheral arterial disease¹⁹², however long-term clinically relevant results are not yet reported. An additional promising target for immunomodulation, IL-6, is incompletely investigated and requires further prospective evaluation¹⁹³. The cross-sectional results of the present study cannot differentiate between cause and effect. Specifically, it is not clear whether comorbid factors or aneurysm specific factors drive the systemic inflammatory response, or whether the systemic inflammatory response drives the progression of aneurysmal disease.

However, the results of CANTOS¹⁷³ would suggest that there may be an inflammatory basis to cardiovascular disease. If this would prove to be the case, then such studies in AAA cohorts may be warranted.

The present study did not identify an association between female sex and prognosis; this is an incompletely understood phenomenon with some contemporary literature reporting comparable mid- and long-term survival between males and females^{194,195}. In our patient cohort, there was no significant difference in SIG between males and females ($p = 0.81$). Small absolute numbers preclude meaningful sub-group analyses of the female patients in the present study. Whilst we cannot fully assert whether systemic inflammation is responsible for a potential difference in prognosis, this warrants further investigation.

The role of inflammation in the pathogenesis of “conventional” (i.e. non-inflammatory/mycotic) AAA has been described, though is incompletely understood^{196–200}. Potential novel biomarkers and therapeutic targets may allow for modulation of AAA development and progression. An additional factor influencing post-operative systemic inflammation in patients undergoing EVAR and F/B-EVAR is the pro-inflammatory effect of stent-graft deployment¹⁴⁴, which may contribute to the effect of the inflammatory environment on outcomes.

The natural progression of chronic systemic inflammation in this patient cohort has not been completely defined. Despite this, there is a wealth of evidence observed in patients with cancer (another chronic disease) regarding the potential prognostic value of activation of the systemic inflammatory response, including multiple systematic reviews and meta-analyses. Given that these studies have been carried out in operable and inoperable cancer (for example, Dolan and colleagues^{201,202}) it is likely that the systemic inflammatory response observed is chronic in nature. Therefore, it is of interest that, in cardiovascular disease, although the potential prognostic value is less well established, there appears to be an association between atherosclerotic disease burden and magnitude of the systemic inflammatory response in patients with peripheral arterial disease^{203,204}. Further study of the association between the magnitude of the systemic inflammatory response and atherosclerotic morbidity/ mortality is warranted. Additionally, the magnitude of the post-operative inflammatory response, and its relationship with pre-operative chronic systemic inflammation is of interest and requires further investigation.

The present study was limited by its retrospective design and missing data for some patients who were otherwise eligible for inclusion, however steps were taken to assess whether missing pre-operative SIG introduced selection bias. There were heterogeneous subgroup sizes based on SIG (with low absolute numbers in some sub-groups), however the patient group was representative of real-world practice with a clinically relevant follow-up interval. The specific cause of death was not available and therefore limits what can be concluded from the present study. Nevertheless, since the majority of patients would die due to cardiovascular morbidity this is unlikely to be a major confounding factor in the present analysis in patients with AAA¹⁹¹. The present study did not include the use of immunosuppressive or anti-inflammatory medications as a covariate in analyses, which is a potential source of bias. However, it may be expected that patients taking such medications may have a reduction in systemic inflammatory response and may result in an underestimation of the prognostic value of the systemic inflammatory response in the present study.

SIG is readily calculable from routine pre-operative blood investigations and may offer prognostic value in patients undergoing endovascular repair of AAA. though these observations require further validation. Further work including serial peri-operative inflammatory profiling, and characterisation of inflammatory pathways and therapeutic targets is required to accurately define this relationship and to aid perioperative risk prediction.

5.5 TABLES

Table 5.1: The calculation of inflammation-based prognostic scores using pre-operative blood results.

Table 5.2: The effect of clinicopathological characteristics and systemic inflammatory grade on all-cause mortality in patients undergoing elective EVAR and F/B-EVAR for asymptomatic AAA (n = 506).

Table 5.3: % 1-year survival in patients undergoing EVAR and F/B-EVAR for AAA (n = 566) stratified by NLR (<3, 3 – 5, >5) and mGPS (0 / 1 / 2) categories.

Table 5.4: Baseline clinical and demographic characteristics of the “missing SIG” patients and the final study cohort in patients undergoing elective EVAR and F/B-EVAR for AAA.

Table 5.1 The calculation of inflammation-based prognostic scores using pre-operative blood results

Neutrophil:Lymphocyte Ratio (NLR)	Absolute Neutrophil Count / Absolute Lymphocyte Count	
Modified Glasgow Prognostic Score (mGPS)	mGPS 0	CRP ≤ 10mg/L
	mGPS 1	CRP > 10mg/L and Albumin > 35 g/L
	mGPS 2	CRP > 10mg/L and Albumin < 35 g/L
Systemic Inflammatory Grade (SIG)	SIG 0	mGPS 0 and NLR < 3
	SIG 1	mGPS 0 and NLR 3 – 5 or mGPS 1 and NLR < 3
	SIG 2	mGPS 0 and NLR > 5 or mGPS 2 and NLR < 3 or mGPS 1 and NLR 3 - 5
	SIG 3	mGPS 1 and NLR > 5 or mGPS 2 and NLR 3 - 5
	SIG 4	mGPS 2 and NLR > 5

Table 5.4 Baseline clinical and demographic characteristics of the “missing SIG” patients and the final study cohort in patients undergoing elective EVAR and F/B-EVAR for AAA

	Final Study Cohort (n = 506)	“Missing SIG” subgroup (n = 101)	<i>p</i>
Age			
< 65	26 (5%)	5 (5%)	0.22
65 - 75	254 (50%)	57 (58%)	
> 75	226 (45%)	36 (37%)	
Sex			
Male	461 (91%)	95 (96%)	0.06
Female	45 (9%)	6 (4%)	
Diabetes Mellitus			
Yes	96 (19%)	11 (11%)	0.07
No	410 (81%)	87 (89%)	
Ischaemic Heart Disease			
Yes	181 (36%)	36 (37%)	0.87
No	324 (64%)	62 (63%)	
Hypertension			
Yes	345 (68%)	62 (63%)	0.34
No	161 (32%)	36 (37%)	
Prior Stroke			
Yes	64 (13%)	14 (14%)	0.67
No	440 (87%)	84 (86%)	
Chronic Obstructive Pulmonary Disease			
Yes	123 (24%)	22 (22%)	0.69
No	382 (76%)	76 (78%)	

Current Tobacco Smoking			
Yes	114 (23%)	30 (31%)	
No	389 (77%)	68 (69%)	0.09
Current Statin Use			
Yes	404 (80%)	69 (70%)	
No	102 (20%)	29 (30%)	<0.05
F/B-EVAR			
Yes	108 (21%)	21 (21%)	
No	398 (79%)	77 (79%)	0.99
BMI			
< 25 kg/m ²	100 (20%)	21 (21%)	
≥ 25 kg/m ²	404 (80%)	77 (79%)	0.72
ASA			
≤ 2	282 (56%)	65 (66%)	
> 2	222 (44%)	33 (34%)	0.06
One-Year Survival			
Yes	476 (94%)	95 (97%)	
No	30 (6%)	3 (3%)	0.25

5.6 FIGURES

Figure 5.1: Patient selection into the study.

Figure 5.2: Kaplan-Meier survival curves and life table for SIG (0 / 1 / 2 / 3 / 4) subgroups in patients undergoing elective EVAR and F/B-EVAR for AAA. $p < 0.05$ (log-rank method).

Figure 5.3: ROC curve of the predictive value of SIG on 1-year mortality in patients undergoing elective EVAR and F/B-EVAR for AAA (n=506), AUC = 0.68 (95%CI 0.58 – 0.78, $p < 0.001$).

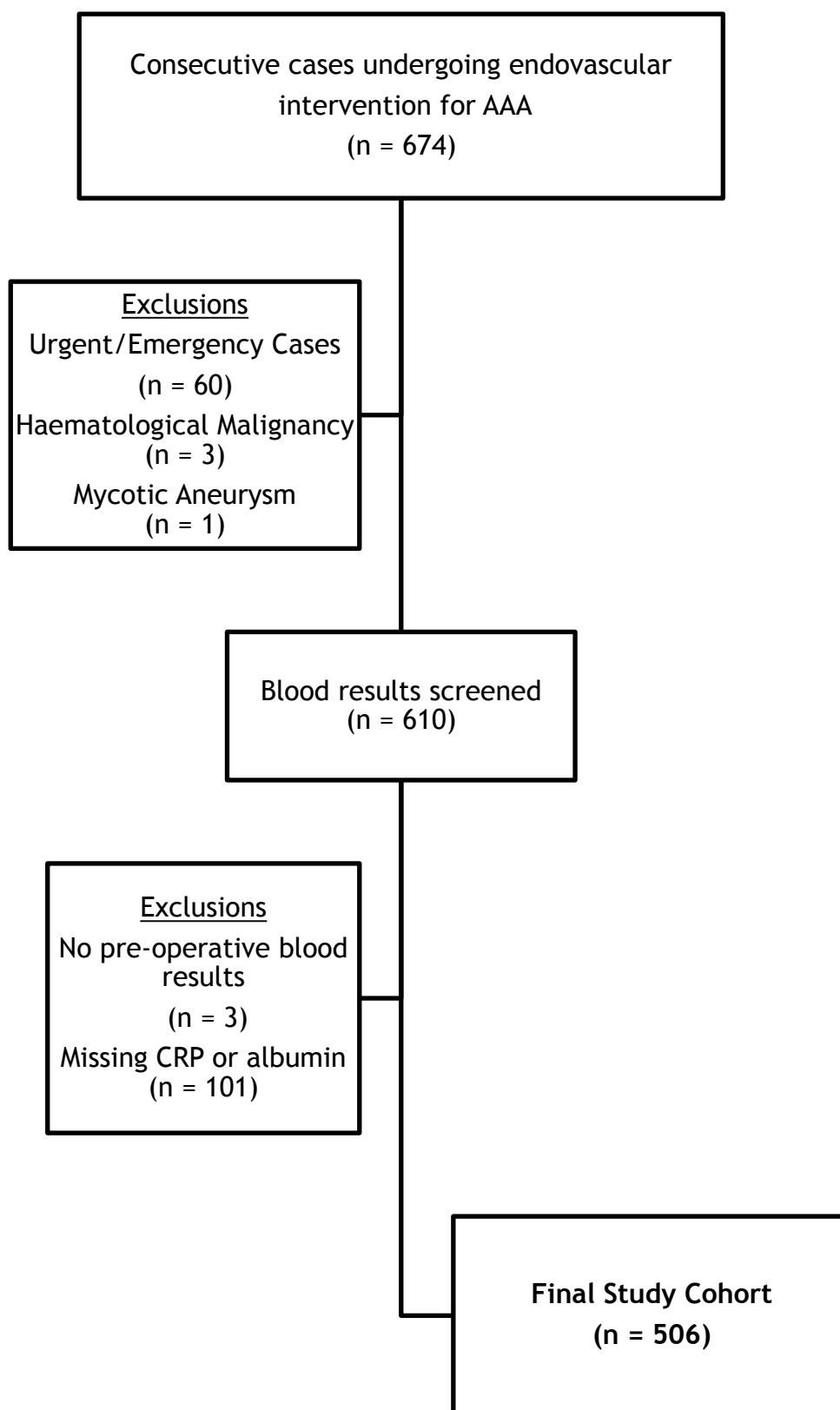
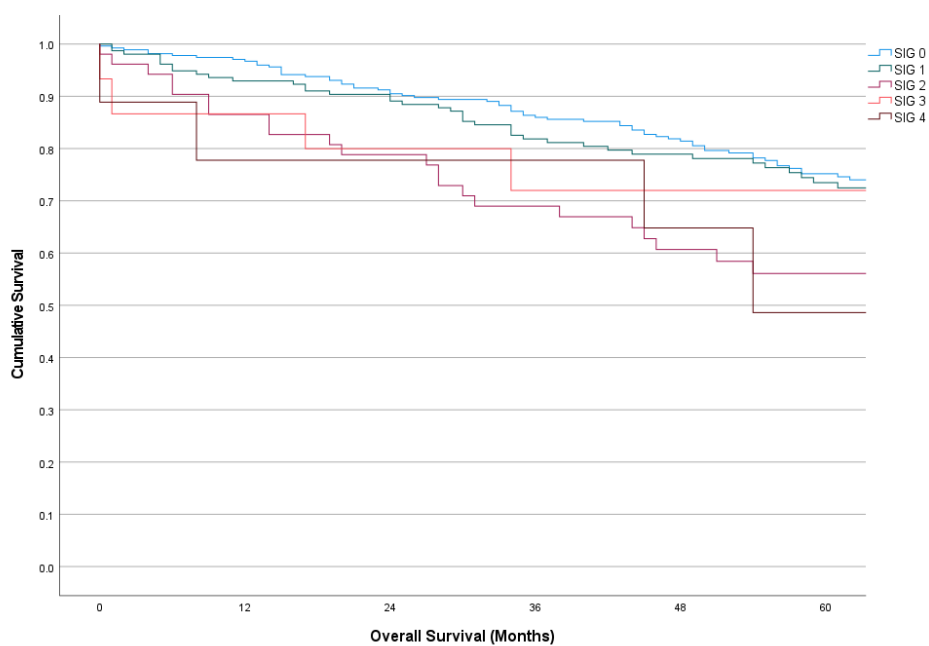


Figure 5.1 patient selection into the study



	Number at Risk					
Months	0	12	24	36	48	60
SIG 0	274	266	250	226	186	135
SIG 1	156	145	141	120	96	76
SIG 2	52	45	41	34	29	21
SIG 3	15	13	12	9	8	6
SIG 4	9	7	6	5	4	3

Figure 5.2 Kaplan-Meier survival curves and life table for SIG (0 / 1 / 2 / 3 / 4) subgroups in patients undergoing elective EVAR and F/B-EVAR for AAA. $p < 0.05$ (log-rank method)

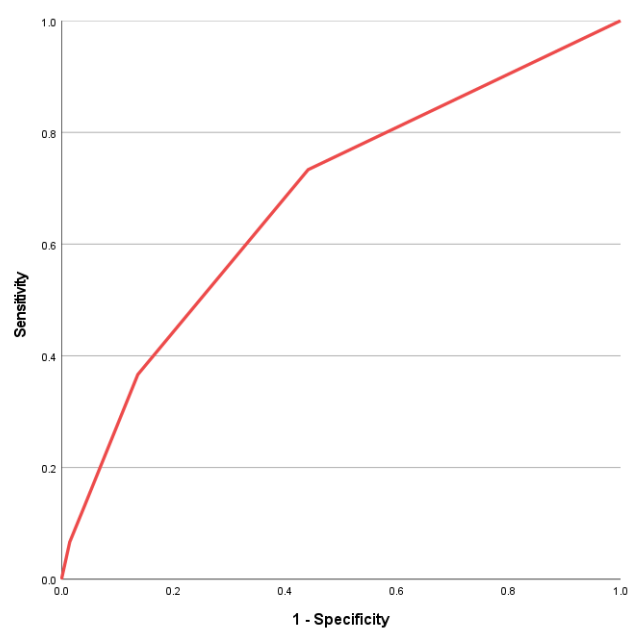


Figure 5.3 ROC curve of the predictive value of SIG on 1-year mortality in patients undergoing elective EVAR and F/B-EVAR for AAA (n=506), AUC = 0.68 (95%CI 0.58 – 0.78, $p < 0.001$)

6 THE RELATIONSHIP BETWEEN CT-DERIVED BODY COMPOSITION, SYSTEMIC INFLAMMATION, AND SURVIVAL IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

6.1 INTRODUCTION

In previous chapters the possible prognostic value of CT-BC parameters (chapter 3) and the SIR (chapter 5) were described in a cohort of patients undergoing intervention for AAA.

Regarding CT-BC parameters, SMI and SMD were examined as discrete prognostic entities, which is in keeping with prior literature. However, the contemporary EWGSOP2 definition of sarcopenia includes loss of both skeletal muscle mass and skeletal muscle function. Sarcopenia and cachexia are terms which are often incorrectly used synonymously, however there is overlap between them in real-world clinical practice. In terms of CT-BC, SMI represents muscle mass and SMD may be associated with muscle function, although the nature of SMD is less well understood than that of SMI.

SMI has been extensively reported in multiple disease states, and considered the gold standard for quantification of muscle mass in the research setting. In contrast, SMD is less well examined. In particular, in patients with cardiovascular disease, the present thesis is the first to extensively examine SMD. The relationship between aetiological factors of sarcopenia and SMD is poorly understood. Moreover, the relationship between SMI and SMD, and the potential association with survival, is also poorly understood. As discussed in chapter 3, SMD is considered to represent myosteatosis (intramuscular fat deposition), and may be related to muscle function. Therefore, examination of SMI and SMD in combination rather than separately is of particular interest, as a single measure may potentially fulfil both components of the EWGSOP2 definition of sarcopenia, and enhance the clinical utility of CT-BC through a more accessible, readily calculable measure. McGovern *et al* proposed the novel CT-Sarcopenia Score (CT-SS), a composite score calculated using SMI and SMD, and describe an association between elevated CT-SS and inferior survival outcomes²⁰⁵. The potential prognostic role of both SMD and CT-SS are poorly described in patients with cardiovascular disease.

Activation of the SIR is accepted as an aetiological factor in the development of sarcopenia⁶⁷, however the underlying mechanism is incompletely understood. Moreover, sarcopenia is a multifactorial condition and therefore not every patient who develops sarcopenia has activation of the SIR, and vice versa. The relationships between clinically measured markers of sarcopenia and the SIR (e.g. using CT-BC and inflammation-based prognostic scores) are unreported in patients with cardiovascular disease. However, CT-SS appears to be associated with the SIR, measured by both mGPS and NLR, in patients with cancer²⁰⁵.

We hypothesise that patients with both abnormal CT-BC and activation of the SIR are at particular risk of inferior survival outcome. The present study therefore aimed to examine the associations and combined potential prognostic value of CT-BC parameters and systemic inflammation, measured by SIG, in patients undergoing elective intervention for AAA.

6.2 MATERIALS & METHODS

6.2.1 PATIENT SELECTION

Patient recruitment to the AAA cohort is summarised in section 1.7.2.1. In the present study, both patients undergoing EVAR and OSR were included. Patients without CT-SS (e.g. due to corrupted CT imaging, missing height for normalisation) or without SIG (e.g. due to incomplete pre-operative blood work) were excluded. Clinical, demographic, and comorbidity data were recorded from electronic case records and patients' community health records. Comorbidity was summarised using ASA, which was extracted from anaesthetic charts (recorded by vascular anaesthetists) and sub-grouped (≤ 2 / > 2) in keeping with previous literature¹⁸³. Age (<65 , $65 - 75$, > 75) and BMI ($<25\text{kg/m}^2$, $\geq 25\text{kg/m}^2$) were considered as categorical variables.

6.2.2 OUTCOMES OF INTEREST

The primary outcome was overall mortality during the follow-up period. The secondary outcomes were 5-year mortality and sac regression at planned 12-month follow-up, defined as reduction in sac size on surveillance imaging of $\geq 5\text{mm}$ from baseline.

6.2.3 CT-BC ANALYSIS

Body composition analysis was performed using methodology described in section 1.7.3 to generate continuous CT-BC parameters. The thresholds derived in chapter 3 were applied to each parameter to dichotomise into categorical variables (High/Low). CT-SS was then calculated based on SMI/SMD as per McGovern et al²⁰⁵, with each parameter assigned an integer value of 0 (High SMI/SMD) or 1 (Low SMI/SMD) and the combined score (range 0 -2) calculated, with analyses between sub-groups of CT-SS performed.

6.2.4 INFLAMMATORY PROFILING

SIG was chosen as the inflammatory parameter of interest, calculated as described in chapter 5. Outcomes were compared between groups of SIG 0 (considered “non-inflamed”) vs. SIG 1 (considered “mildly inflamed”) vs. SIG ≥ 2 (considered “inflamed”). Patients were grouped in this way to reduce the number of sub-groups with low absolute numbers, with the rationale that SIG ≥ 2 may pertain to marked elevation of one of mGPS and NLR, or moderate elevation of both.

6.2.5 STATISTICAL ANALYSES

General statistical analyses are discussed in section 1.7.4. In the present study, the relationship between CT-BC and systemic inflammation, as well as the baseline demographic or pathological factors associated with each, was felt to represent a potential source of bias through confounding. In order to account for this, the decision was made to perform propensity matching. Multivariable logistic regression was performed to generate propensity scores for each possibly confounding covariates. Two separate propensity matched analyses were performed; based on both CT-SS (to evaluate the difference in SIG between matched cohorts sub-grouped by CT-SS magnitude), and on SIG (to evaluate the difference in CT-SS between matched cohorts sub-grouped by SIG magnitude). CT-SS (0/1 vs. 2) was matched 1:1 based on Age, Sex, BMI, and SIG. SIG (0/1 vs. ≥ 2) was matched 1:1 based on Age, Sex, BMI, and CT-SS. The match tolerance was 0 for both matching algorithms based on propensity score of sub-group membership generated through multivariable logistic regression. Satisfactory matching was confirmed based on visual inspection of propensity score histograms (confirmed by primary author NAB and supervisor DCM), and pairwise comparisons of factors of interest was performed. To account for potential selection bias, excluded patients were compared with the final study cohort. The association between factors of interest and sac regression ≥ 5 mm was examined by binary logistic regression.

6.3 RESULTS

829 patients were screened for inclusion into the study. 218 patients were excluded: 66 patients who underwent emergency or urgent repair for ruptured or symptomatic AAA, 3 patients due to haematological malignancy, 1 patient due to mycotic aneurysm, 20 due to missing CT-SS, and 128 due to missing SIG (Figure 6.1). This resulted in 611 elective patients who were eligible for inclusion into the final study cohort. There were 122 (20%) OSR cases, 558 (91%) males, and a median (IQR) age of 73.0 (11.0) years. Median (IQR) follow-up was 67.0 (32) months, and there were 194 (32%) deaths during the follow-up period. Mean (95% CI) survival in the entire study population was 87.1 (81.4 – 92.9) months.

The characteristics of the study cohort when sub-grouped by CT-SS are shown in table 6.1. There were 138 patients (23%) with CT-SS 0, 283 patients (46%) with CT-SS 1, and 190 (31%) with CT-SS 2. Patients with elevated CT-SS were older ($p < 0.001$), with a lower proportion of females ($p < 0.001$), were more likely to undergo EVAR ($p < 0.01$), and had a lower BMI ($p < 0.01$). SIG was similar between subgroups of CT-SS. 5-year survival was lower in patients with elevated CT-SS; CT-SS 0 (86%) vs. CT-SS 1 (72%) vs. CT-SS 2 (63%) ($p < 0.001$).

The association between baseline covariates, CT-SS, SIG, and mortality is shown in table 6.2. On univariate analysis age ($p < 0.001$), elevated CT-SS ($p < 0.001$) and elevated SIG ($p < 0.01$) were associated with increased hazard of mortality. On multivariate analysis, age (HR 1.66, 95% CI 1.28 – 2.14, $p < 0.001$), elevated CT-SS (HR 1.58, 95% CI 1.28 – 1.94, $p < 0.001$), and elevated SIG (HR 1.29, 95% CI 1.07 – 1.55, $p < 0.01$) were independently associated with increased hazard of mortality. A sensitivity analysis on patients aged < 80 years with pre-operative AAA diameter ≤ 6.0 cm ($n = 261$, 65 deaths) was performed; CT-SS (HR 1.63, 95% CI 1.14 – 2.33, $p < 0.01$) remained associated with mortality but age (HR 1.19, 95% CI 0.74 – 1.90, $p = 0.47$) and SIG (HR 1.23, 95% CI 0.89 – 1.70, $p = 0.22$) were not.

5-year survival in patients stratified by CT-SS and SIG is shown in table 6.3. Patients with CT-SS 0 & SIG 0 had 90% (SE 4%) 5-year survival, compared with 34% (SE 9%) in patients with CT-SS 2 & SIG ≥ 2 ($p < 0.001$). In the CT-SS 2 sub-group, there was a trend towards inferior survival with increasing SIG ($p < 0.05$), and in the SIG 0 and ≥ 2 sub-groups, there were trends towards inferior survival with increasing CT-SS ($p < 0.05$).

Figures 6.2, 6.3, and 6.4 display Kaplan-Meier survival plots for sub-groups of CT-SS (figure 6.2), SIG (figure 6.3), and age (figure 6.4). Regarding CT-SS, mean (95% CI) survival in the CT-SS 0 vs. CT-SS 1 vs. CT-SS 2 subgroups was 98.1 (88.5 – 107.7) vs. 87.3 (82.0 – 92.7) vs. 72.4 (64.7 – 80.0) months ($p < 0.001$). Regarding SIG, mean (95% CI) survival in the SIG 0 vs. SIG 1 vs. SIG ≥ 2 subgroups was 89.9 (82.6 – 97.1) vs. 85.5 (77.9 – 93.1) vs. 71.5 (62.4 – 80.6) months ($p < 0.05$). Regarding age, mean (95% CI) survival in the age < 65 vs. age 65 – 75 vs. age > 75 subgroups was 97.8 (87.1 – 108.4) vs. 94.3 (86.8 – 101.8) vs. 72.7 (66.3 – 79.1) months ($p < 0.001$). Mean (95% CI) survival in the CT-SS 0 & SIG 0 sub-group was 92.6 (84.8 – 100.4) months, compared with 44.9 (30.6 – 59.2) months in the CT-SS 2 & SIG ≥ 2 sub-group ($p < 0.001$, figure 6.5).

Patients with CT-SS 0 & SIG 0 were younger than those with CT-SS 2 & SIG ≥ 2 (median age 68 vs. 79 years, $p < 0.001$). To account for this a sensitivity analysis on patients aged 65 – 75 years in the CT-SS 0 & SIG 0 and CT-SS 2 & SIG ≥ 2 sub-groups was performed ($n = 53$). On both univariate cox proportional hazards model ($p < 0.001$) and time-to-event ($p < 0.001$) analyses patients with CT-SS 2 & SIG ≥ 2 had inferior survival outcomes.

Baseline variables in propensity matched cohorts are shown in table 6.4, and histograms of propensity score distributions are shown in figure 6.6. The matched CT-SS 0/1 ($n = 183$) vs. CT-SS 2 ($n = 190$) cohorts were well matched for all variables other than a higher proportion of patients with CT-SS 2 undergoing OSR ($p < 0.01$). In these matched cohorts, CT-SS 2 was associated with inferior survival on univariate analysis (HR 1.60, 95% CI 1.14 – 2.23, $p < 0.01$), and mean (95% CI) survival in the CT-SS 0/1 vs. CT-SS 2 cohorts was 79.5 (74.0 – 84.9) vs. 72.4 (64.7 – 80.0) months ($p < 0.01$). The matched SIG 0/1 ($n = 89$) vs. SIG ≥ 2 ($n = 90$) cohorts were well matched for all variables other than a higher proportion of patients with SIG ≥ 2 undergoing OSR ($p < 0.01$) and having a higher ASA ($p < 0.001$). In these matched cohorts, SIG ≥ 2 was not associated with inferior survival on univariate analysis (HR 1.36, 95% CI 0.86 – 2.15, $p = 0.19$), and mean (95% CI) survival in the SIG 0/1 vs. SIG ≥ 2 cohorts was 72.6 (66.3 – 78.9) vs. 71.4 (62.3 – 80.6) months ($p = 0.19$).

In patients who underwent EVAR, 431 (88%) had data available on sac size at planned 12-month follow-up. 202 of these (47%) were noted to have ≥ 5 mm sac regression. Neither CT-SS (OR 0.98, 95% CI 0.75 – 1.26, $p = 0.84$) nor SIG (OR 0.84, 95% CI 0.65 – 1.10, $p = 0.20$) were associated with sac regression.

In order to account for selection bias due to patients with missing pre-operative CT-SS or SIG, patients who were excluded on this basis were compared with the final study cohort (table 6.5). Compared with patients who were excluded, the final study cohort had a higher proportion of females (9% vs. 2%, $p < 0.01$) and a higher proportion of patients with ASA > 2 (47% vs. 36%, $p < 0.05$), whilst other characteristics were similar. Survival analysis was performed on this sub-group and compared with the final study cohort; mean (SD) survival in the excluded sub-group was 98.2 (85.7 – 110.7) months, comparable to the final study cohort ($p = 0.74$).

6.4 DISCUSSION

The results of the present study highlight the combined association with survival of body composition and systemic inflammation in patients undergoing elective intervention for AAA. This is the first study to demonstrate the combined potential prognostic value in this patient group. Furthermore, we add the novel observation of association with survival of the composite measure of sarcopenia, CT-SS, in patients with AAA.

Optimal prognostication in patients undergoing elective intervention for AAA is a clinically relevant and important area for service improvement. The landmark EVAR-2 trial failed to demonstrate a survival advantage in performing EVAR versus no treatment in patients unfit for OSR²⁰⁶, although these findings have recently been challenged by a contemporary series²⁰⁷. Moreover, the recent preliminary observations from the UK-COMPASS study (where poor mid-term survival was observed in the endovascular subgroup)¹⁸⁴ emphasise the need for validated prognostic factors to identify those patients who are likely to benefit from prophylactic aneurysm repair, thereby optimising patient selection and resource allocation. Prognostic tools in this patient cohort have been previously explored, though there remains heterogeneous uptake and a lack of implementation into guidelines²⁰⁸. Whilst rapid calculation and routinely available parameters make SIG an attractive candidate for clinical risk prediction, CT-BC analysis is more time intensive. Feasibility studies of the implementation of CT-BC analysis into pre-operative AAA pathways are lacking, and may help to resolve the concerns around resource use. A benefit of CT-SS is in its simple scoring system allowing for easy stratification. Direct comparisons between CT-SS, SIG, and other risk prediction tools or frailty assessment scores may allow the optimal strategy to be defined.

It is important to differentiate between the related but different entities of sarcopenia and cachexia. In contrast to the EWGSOP2 definition of sarcopenia, cachexia has been defined as “*cachexia is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass*”²⁰⁹. However, the authors (Evans *et al* 2008) then go on to highlight the key importance of weight loss in diagnosing cachexia, which does not feature in definitions of sarcopenia. When appraising the literature it is apparent that the two terms are often used synonymously. Similarly to sarcopenia, cachexia (widely described as “cancer cachexia”) appears to be considered as a cancer-specific phenomenon. Weight loss is an almost ubiquitous feature of how cachexia is defined. We suggest that, whilst both may co-exist, sarcopenia represents a specific

syndrome affecting muscle tissue, often only defined by formal investigation of muscle mass and function, whilst cachexia is more readily clinically diagnosed and is characterised by weight loss. Sarcopenia may be an element of the cachexia syndrome but does not define it.

Sub-group analyses showed a significantly inferior prognosis in patients with both elevated CT-SS and elevated SIG. The observation of a mean survival of 44.9 months in this sub-group draws into question the merit of elective intervention in such patients, particularly those with aneurysms only modestly above threshold, given recent data suggesting a lower than expected rate of rupture in 55-60mm aneurysms¹⁴⁸. Absolute numbers in these sub-groups may limit the validity of conclusions drawn, however we describe a potentially “high-risk” patient cohort who may be exposed to substantial long-term cardiovascular morbidity. Whilst this “high-risk” cohort was older than the “low-risk” patients, steps were taken to adjust for this and similar trends observed. Further validation of these findings is required, however the potential clinical utility of CT-SS and SIG, in combination with existing risk predication measures, is highlighted by these results.

The mechanism by which low skeletal muscle mass and density confer inferior prognosis is incompletely described. Of particular interest, on visual inspection of CT-SS survival plots, the divergence between sub-groups initially occurs between 18 and 24 months and is sustained throughout later follow-up intervals. This suggests that the predominant survival advantage occurs later in the post-operative period. Repeated follow-up of the present patient cohort with a longer follow-up interval may clarify the nature of the potential prognostic value of CT-SS in patients with AAA. To better define the benefit of AAA repair in these cohorts, a comparative study investigating CT-SS and SIG in patients who did not undergo repair would be of interest, however this was outwith the scope of the present study.

Similarly, the mechanism underlying inferior prognosis in relation to chronic activation of the SIR in this patient group is incompletely understood. Inferior short-term survival has been reported in patients who experience a significant inflammatory response following EVAR¹⁴⁴. Chronic inflammation appears to predispose patients to cardiovascular events, and cytokine blockade (IL-1 β) has been shown to reduce cardiovascular morbidity in a large trial of patients with coronary artery disease¹⁷³. Patients with AAA typically have a high prevalence of synchronous atherosclerotic disease, indicating a potential susceptibility to cardiovascular events, which may explain the increased mortality conferred by chronic

activation of the SIR in this patient group. Furthermore, an association between clinical frailty and inflammation has been described²¹⁰. The presence of both abnormal skeletal muscle and chronic inflammation may have a composite effect on physical function and performance status, impairing physiological reserve and predisposing to inferior outcomes.

The present study did not observe an association between elevated CT-SS and magnitude of SIG. This is in contrast to studies from patients with cancer, which observed association between activation of the SIR and both SMI and SMD^{211–213}. There appears to be an association between presence of a tumour and elevated magnitude of systemic inflammation^{90,214}. Chronic activation of the systemic inflammatory response may result in a proteolytic catabolic state, mediated by cytokines such as TNF, IL-6, and IL-1 β ^{215,216}, which may be responsible for altered skeletal muscle volume and density. It may be that this relationship is less marked in patients with AAA due to the lower magnitude of systemic inflammation as compared with patients with CRC. This complex mechanistic pathway requires further prospective characterisation, with interventional studies performing longitudinal CT-BC analysis a potential route to more comprehensive understanding. Upcoming studies²¹⁷ investigating the effect of immunomodulation in patients with coronary artery disease are eagerly awaited, and may be reproducible in other cardiovascular patient groups, particularly those with AAA.

The present study did not observe an association between elevated CT-SS or SIG and sac regression at 12-months. Whilst prior series have demonstrated an association between early post-operative inflammation and sac dynamics¹⁴⁴, these observations are not widely reported and this potential relationship requires further prospective evaluation.

The present study is limited by retrospective study design, and the use of data-derived thresholds for CT-BC analysis, which are a potential source of bias and require external validation. There were a considerable number (19%) of potentially eligible patients who were excluded due to missing data, however steps were taken to mitigate the potential risk of bias through comparative analyses of excluded patients. Low absolute numbers in some sub-groups of CT-SS and SIG limits the conclusions drawn. The observations may have been strengthened though reporting of peri-operative / 30-day mortality, however the low rate (0.8%) precluded meaningful comparisons between sub-groups. Ideally, a “disease-free” control group for comparison would strengthen the present study by allowing us to investigate whether the survival differences seen are present independent of disease state. However, this is not feasible given the need to obtain CT-imaging, and the inherent risks

associated with exposure to contrast medium and ionising radiation. Moreover, the results of the present study contribute to the growing body of evidence describing inferior prognosis in sarcopenic, inflamed patients across a range of disease states. Whilst we infer that the major cause of mortality is cardiovascular, given that specific cause of death is not available, this is a potential source of bias. The lack of in-hospital complication data may limit the clinical utility of the present study and requires further investigation.

The results in the present study describe a potential novel prognostic role for CT-BC and SIG in patients with AAA undergoing elective intervention. The use of these measures to identify patients at a high risk of poor outcome may allow for the development of targeted therapies, or expectant management of certain high-risk groups. Further prospective analysis of AAA cohorts is required, including to externally validate the thresholds used by the present study.

6.5 TABLES

Table 6.1: The relationship between baseline clinical characteristics, pre-operative CT-derived body composition parameters, systemic inflammation, and 5-year survival in patients undergoing elective intervention for AAA (n = 611).

Table 6.2: The association between baseline clinical characteristics, pre-operative CT-derived body composition parameters, systemic inflammation, and mortality in patients undergoing elective intervention for AAA (n = 611).

Table 6.3: % 5-year survival in patients undergoing elective intervention for AAA stratified by CT-SS and SIG subgroups (n = 611).

Table 6.4: The comparison between clinical parameters, CT-BC parameters, and systemic inflammation in sub-groups propensity matched for CT-SS and SIG.

Table 6.5: The comparison between the final study cohort and patients excluded from the study on the basis of missing CT-SS or SIG.

Table 6.1 The relationship between baseline clinical characteristics, pre-operative CT-derived body composition parameters, systemic inflammation, and 5-year survival in patients undergoing elective intervention for AAA (n = 611)

	CT-SS 0 (n = 138)	CT-SS 1 (n = 283)	CT-SS 2 (n = 190)	<i>p</i>
Age				
< 65	21 (15%)	17 (6%)	7 (4%)	<0.001
65 - 75	81 (59%)	161 (57%)	75 (39%)	
> 75	36 (26%)	105 (37%)	108 (57%)	
Sex				
Male	108 (78%)	268 (95%)	182 (95%)	<0.001
Female	30 (22%)	15 (5%)	8 (4%)	
Repair Type				
Open	34 (25%)	63 (22%)	25 (13%)	<0.01
EVAR	104 (75%)	220 (78%)	165 (87%)	
BMI				
< 25 kg/m ²	23 (17%)	51 (18%)	53 (28%)	<0.01
≥ 25 kg/m ²	115 (83%)	232 (82%)	137 (72%)	
ASA				
≤ 2	74 (54%)	150 (53%)	100 (53%)	0.76
> 2	62 (46%)	132 (47%)	90 (47%)	
High SFI				
Yes	109 (86%)	244 (90%)	161 (87%)	0.98
No	18 (14%)	28 (10%)	25 (13%)	
High VFI				
Yes	91 (66%)	217 (77%)	136 (72%)	0.37
No	47 (34%)	66 (23%)	54 (28%)	
SIG				
0	75 (54%)	149 (53%)	96 (51%)	0.51
1	42 (30%)	96 (34%)	63 (33%)	
≥ 2	21 (16%)	38 (13%)	31 (16%)	
5-year Survival				
Yes	119 (86%)	204 (72%)	120 (63%)	<0.001
No	19 (14%)	79 (28%)	70 (37%)	

Table 6.4 The comparison between clinical parameters, CT-BC parameters, and systemic inflammation in sub-groups propensity matched for CT-SS and SIG

	CT-SS 0/1 (n = 183)	CT-SS 2 (n = 190)	<i>p</i>	SIG 0/1 (n = 89)	SIG ≥ 2 (n = 90)	<i>p</i>
Age						
< 65	7 (4%)	7 (4%)		4 (4%)	4 (5%)	
65 - 75	75 (41%)	75 (40%)		39 (44%)	40 (44%)	
> 75	101 (55%)	108 (56%)	0.76	46 (52%)	46 (51%)	0.95
Sex						
Male	175 (96%)	182 (96%)		81 (91%)	81 (90%)	
Female	8 (4%)	8 (4%)	0.94	8 (9%)	9 (10%)	0.82
Repair Type						
Open	8 (4%)	25 (13%)		1 (1%)	16 (18%)	
EVAR	175 (96%)	165 (87%)	<0.01	88 (99%)	74 (82%)	<0.001
BMI						
< 25 kg/m ²	46 (25%)	53 (28%)		23 (26%)	24 (27%)	
≥ 25 kg/m ²	137 (75%)	137 (72%)	0.55	66 (74%)	66 (73%)	0.90
ASA						
≤ 2	107 (59%)	100 (53%)		60 (68%)	37 (42%)	
> 2	75 (41%)	90 (47%)	0.23	28 (32%)	52 (58%)	<0.001
High SFI						
Yes	153 (85%)	161 (87%)		75 (86%)	73 (86%)	
No	27 (15%)	25 (13%)	0.67	12 (14%)	12 (14%)	0.95
High VFI						
Yes	126 (69%)	136 (72%)		61 (68%)	58 (64%)	
No	57 (31%)	54 (28%)	0.57	28 (32%)	32 (36%)	0.56
CT-SS						
0	-	-		21 (24%)	21 (23%)	
1	-	-		37 (42%)	38 (42%)	
2	-	-	-	31 (34%)	31 (35%)	0.99
SIG						
0	93 (51%)	96 (51%)		-	-	
1	61 (33%)	63 (33%)		-	-	
≥ 2	29 (16%)	31 (16%)	0.92	-	-	-

Table 6.5 The comparison between the final study cohort and patients excluded from the study on the basis of missing CT-SS or SIG

	Excluded Patients (n = 148)	Final Study Cohort (n = 611)	<i>p</i>
Age			
< 65	8 (5%)	45 (7%)	0.21
65 - 75	90 (61%)	317 (52%)	
> 75	50 (34%)	249 (41%)	
Sex			
Male	145 (98%)	558 (91%)	<0.01
Female	3 (2%)	53 (9%)	
Repair Type			
Open	33 (22%)	122 (20%)	0.53
EVAR	115 (78%)	489 (80%)	
BMI			
< 25 kg/m ²	31 (22%)	127 (21%)	0.81
≥ 25 kg/m ²	112 (78%)	484 (79%)	
ASA			
≤ 2	94 (64%)	324 (53%)	<0.05
> 2	53 (36%)	284 (47%)	
High SFI			
Yes	101 (84%)	514 (88%)	0.19
No	20 (16%)	71 (12%)	
High VFI			
Yes	101 (73%)	444 (73%)	0.90
No	37 (27%)	167 (27%)	
CT-SS*			
0	27 (22%)	138 (23%)	0.68
1	64 (51%)	283 (46%)	
2	34 (27%)	190 (31%)	
SIG*			
0	11 (55%)	320 (52%)	0.89
1	6 (30%)	201 (33%)	
≥ 2	3 (15%)	90 (15%)	
5-year Survival			
Yes	110 (74%)	440 (72%)	0.84
No	38 (26%)	171 (28%)	
* - some missing data in excluded sub-group.			

6.6 FIGURES

Figure 6.1: Patient selection into the study.

Figure 6.2: Kaplan-Meier survival plots and life table for CT-SS (0 / 1 / 2) subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method).

Figure 6.3: Kaplan-Meier survival plots and life table for SIG (0 / 1 / ≥ 2) subgroups in patients undergoing elective intervention for AAA. $p < 0.05$ (log-rank method).

Figure 6.4: Kaplan-Meier survival plots and life table for age (< 65 / $65 - 75$ / > 75) subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method).

Figure 6.5: Kaplan-Meier survival plots and life table for CT-SS 0 & SIG 0 vs. CT-SS 2 & $\text{SIG} \geq 2$ subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method).

Figure 6.6: Distribution of propensity scores in the unmatched and matched cohorts, a) CT-SS pre-match, b) CT-SS post-match, c) SIG pre-match, d) SIG post-match.

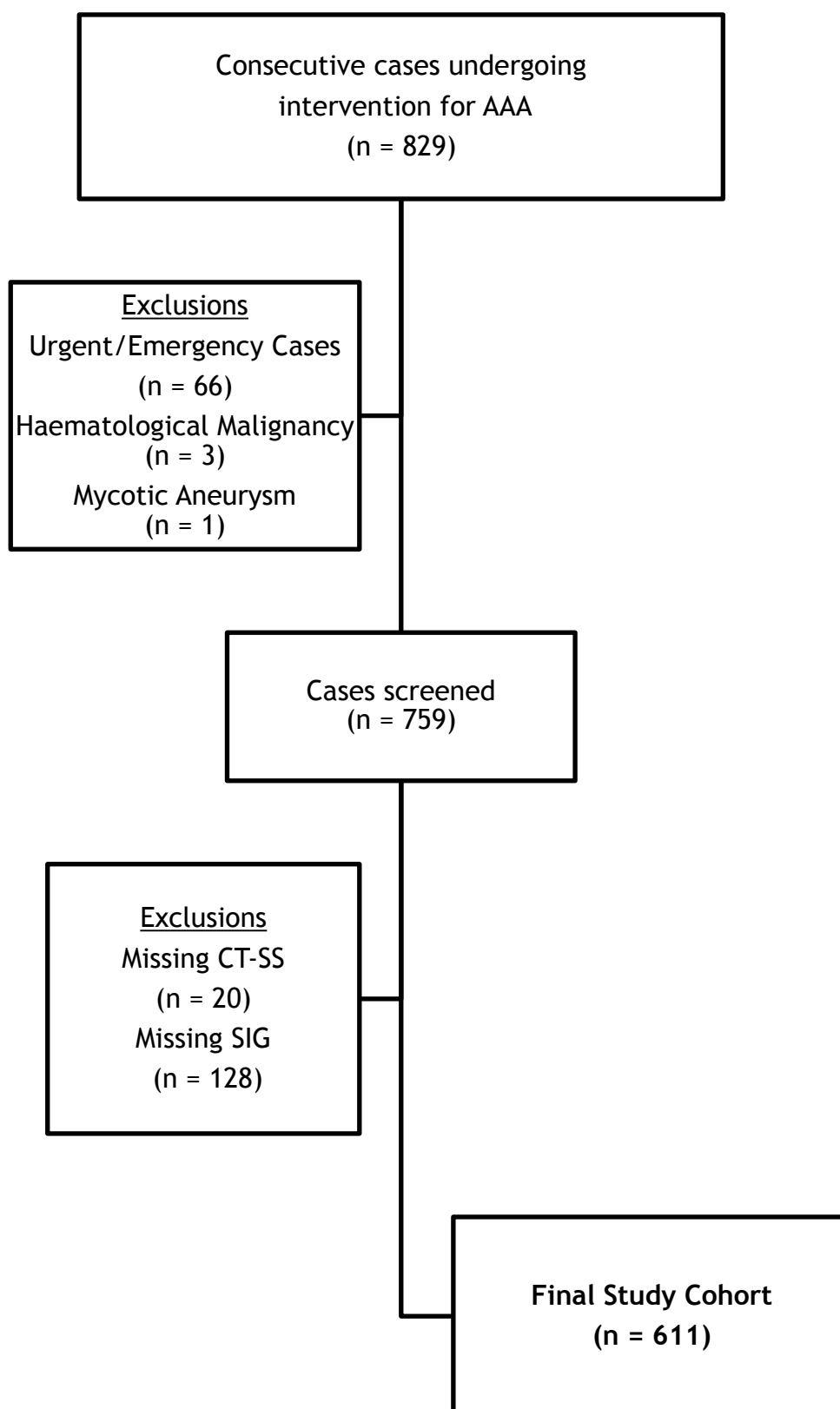
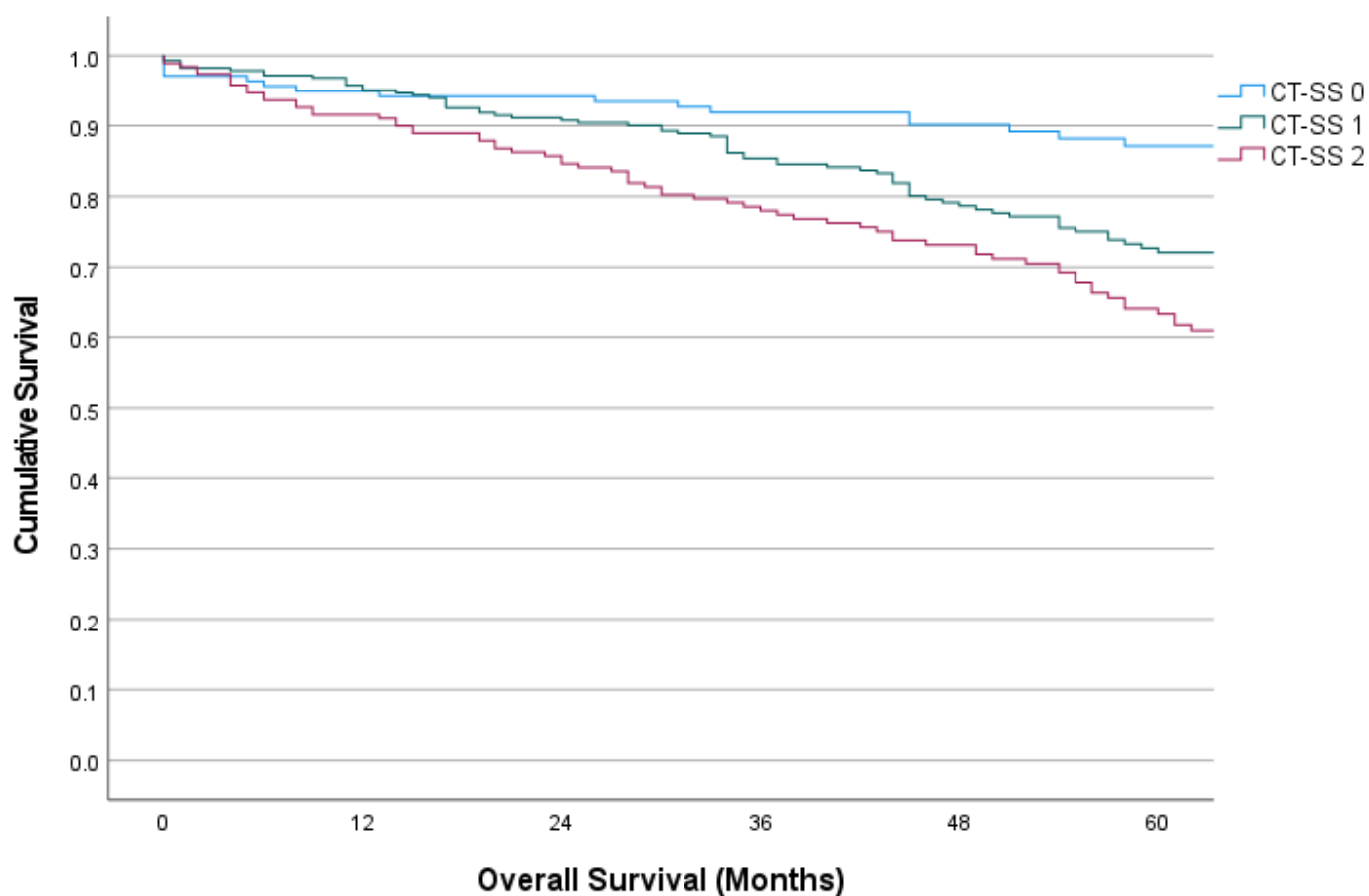
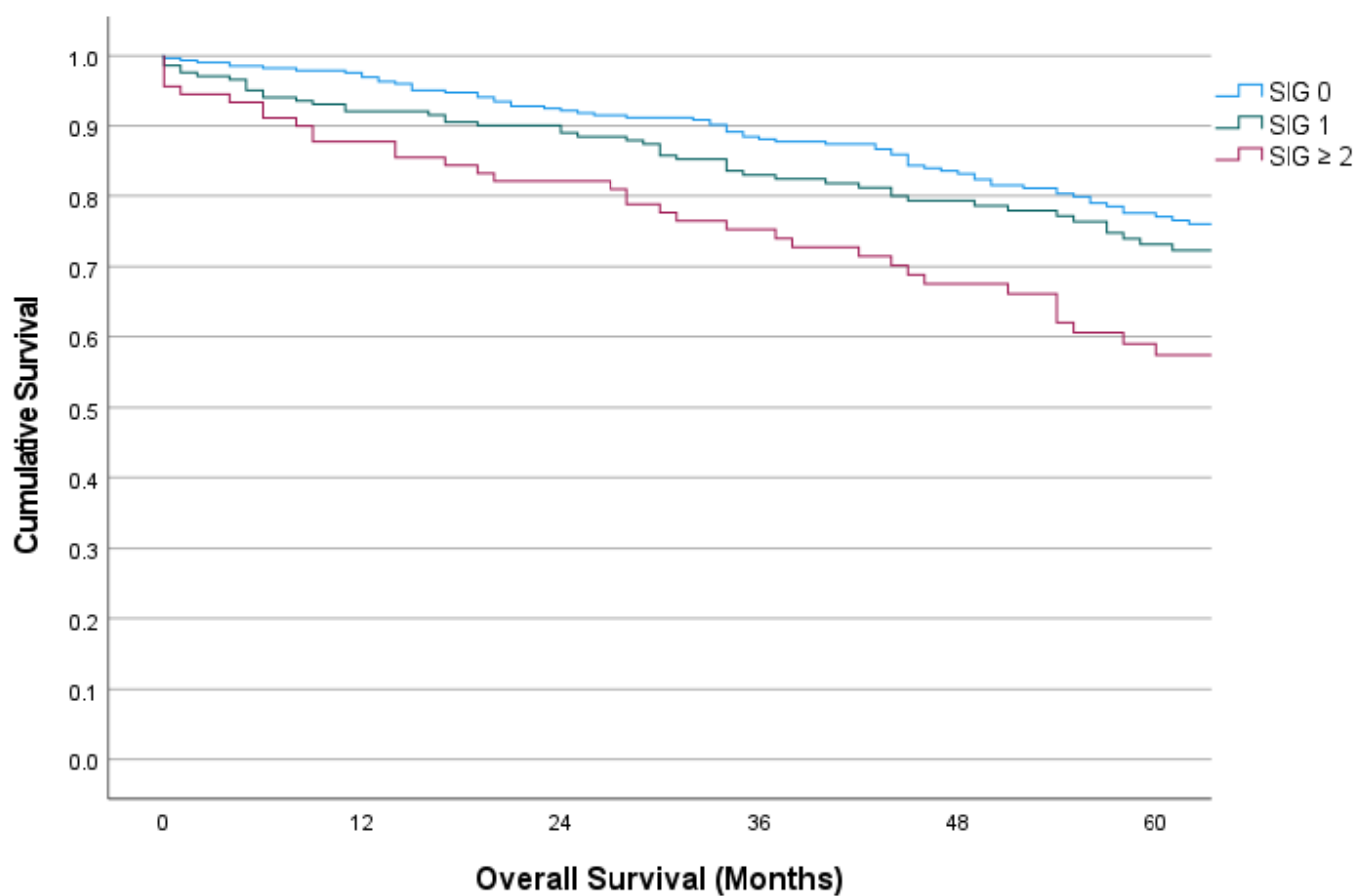


Figure 6.1 patient selection into the study



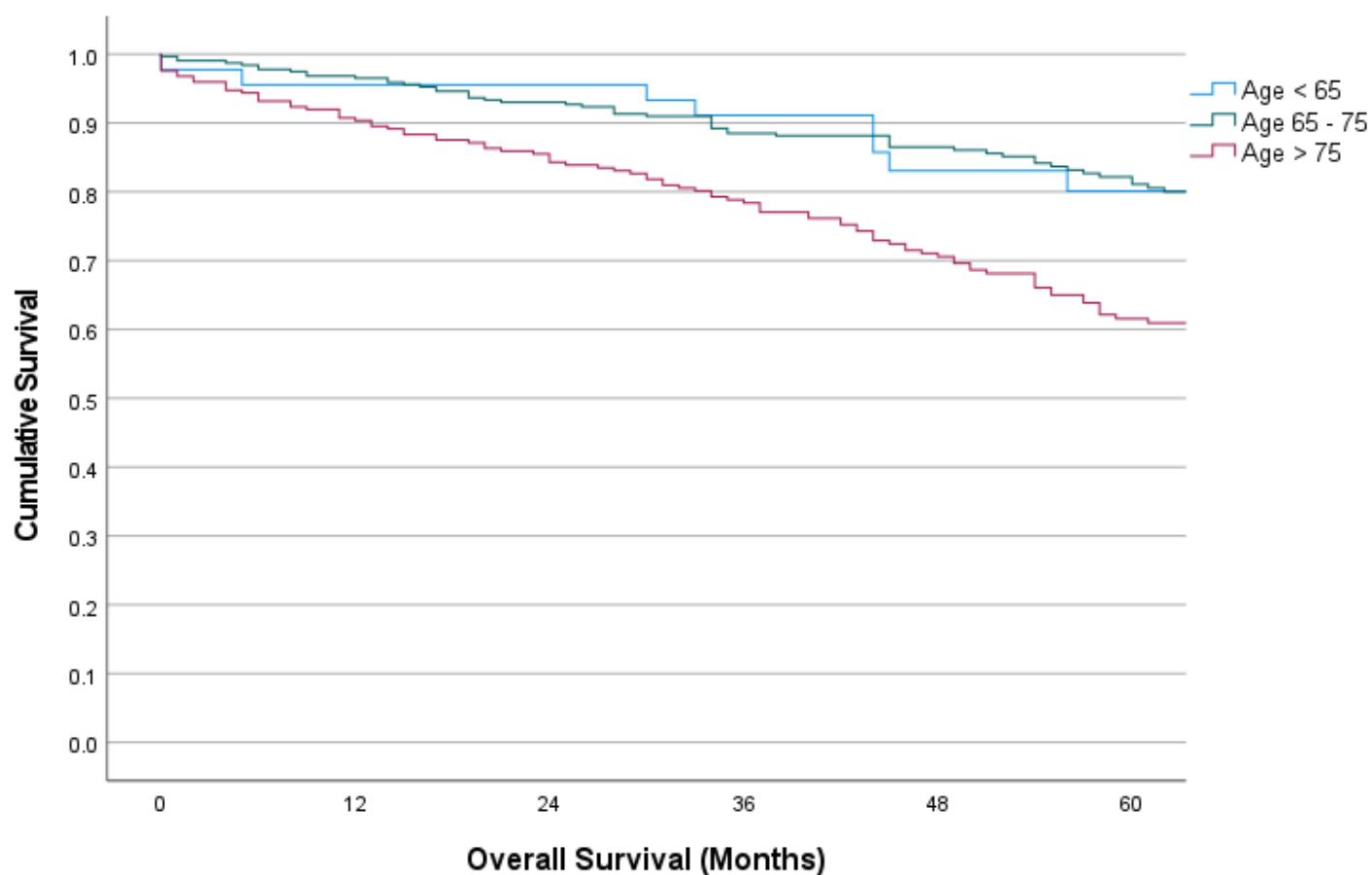
	Number at Risk					
Months	0	12	24	36	48	60
CT-SS 0	138	131	128	118	98	77
CT-SS 1	283	271	251	214	164	119
CT-SS 2	190	174	158	139	112	84

Figure 6.2 Kaplan-Meier survival plots and life table for CT-SS (0 / 1 / 2) subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method)



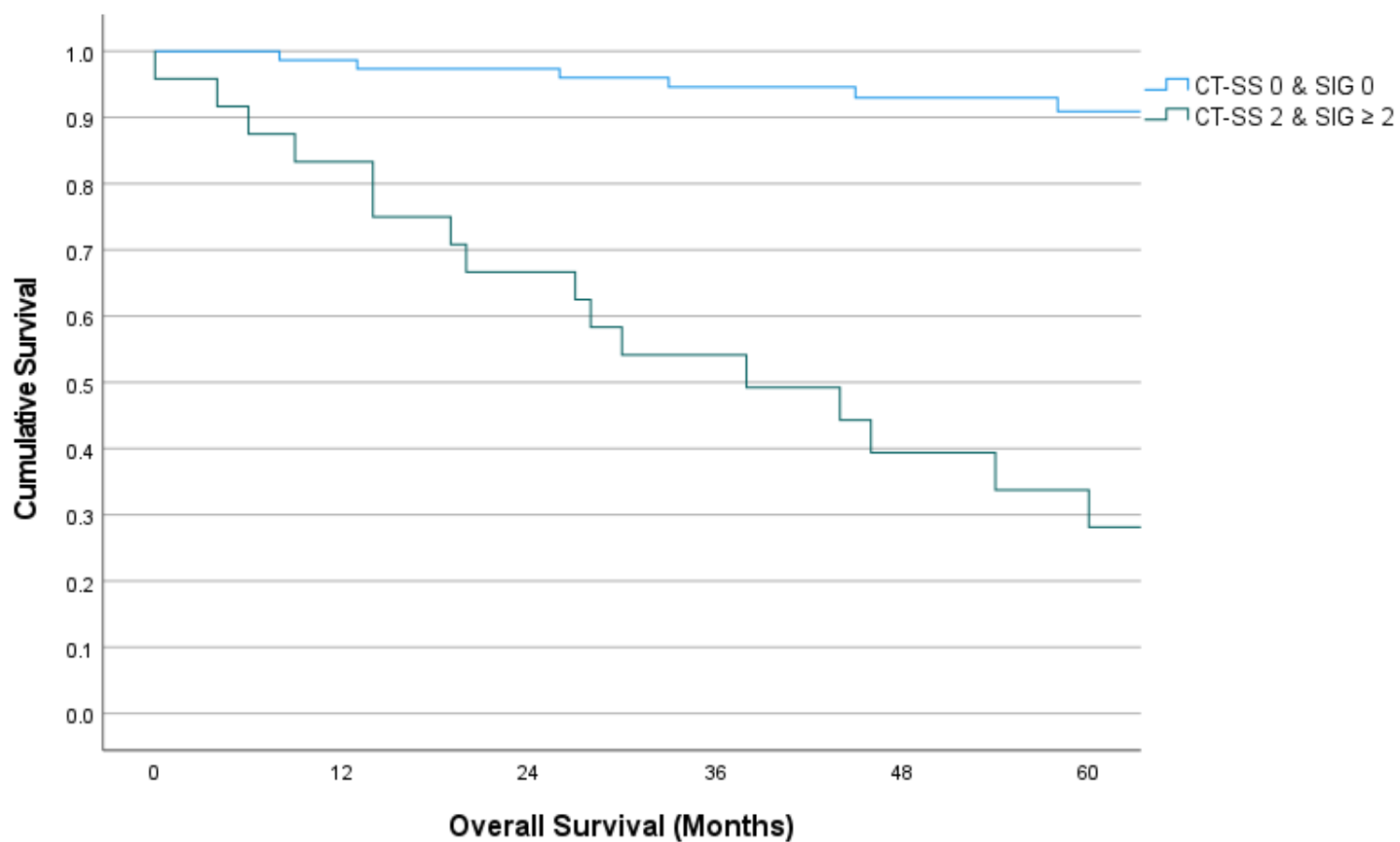
	Number at Risk					
Months	0	12	24	36	48	60
SIG 0	320	312	289	262	210	154
SIG 1	201	185	174	147	112	89
SIG ≥ 2	90	79	74	62	52	37

Figure 6.3 Kaplan-Meier survival plots and life table for SIG (0 / 1 / ≥ 2) subgroups in patients undergoing elective intervention for AAA. $p < 0.05$ (log-rank method)



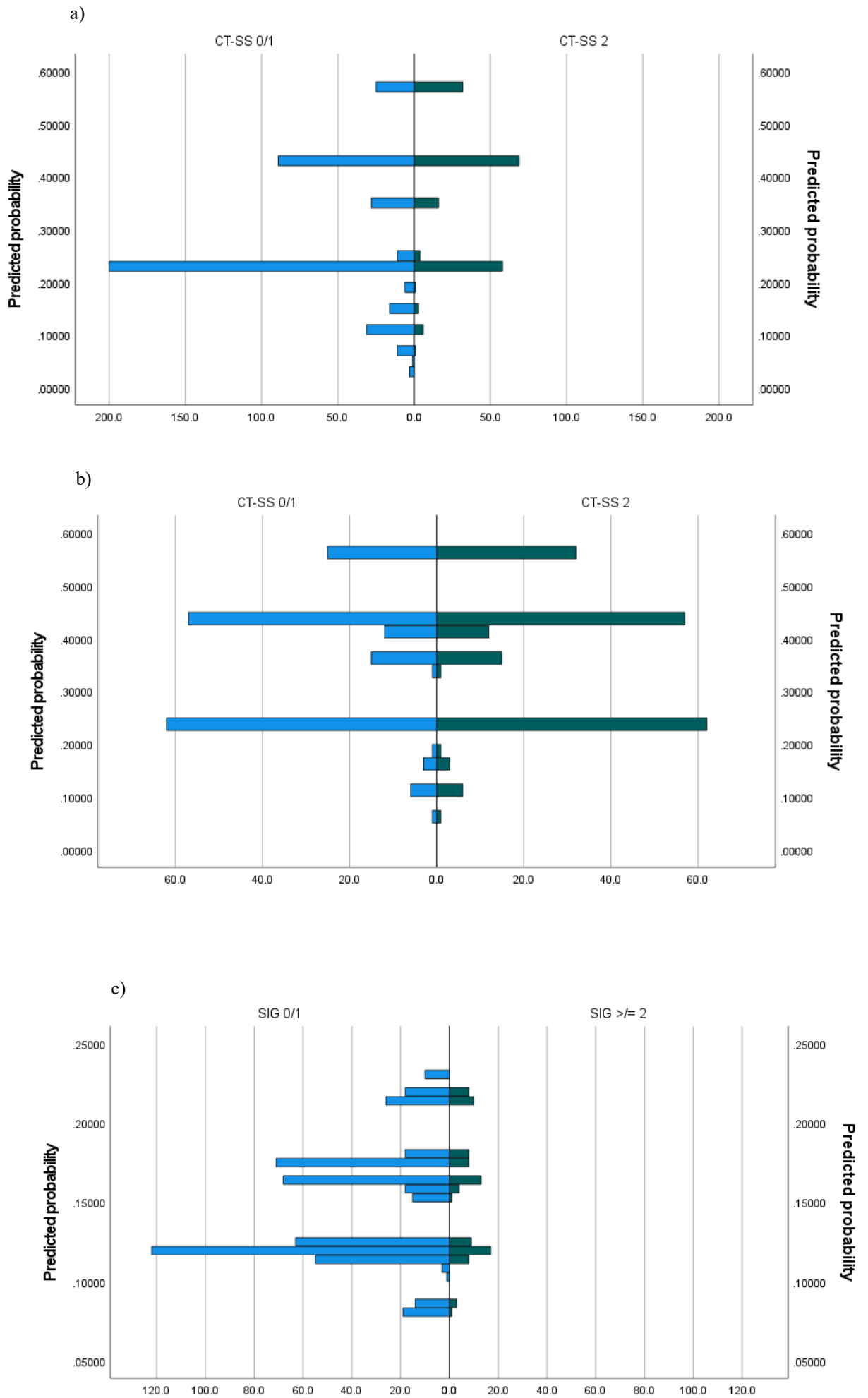
	Number at Risk					
Months	0	12	24	36	48	60
Age < 65	45	43	43	41	30	23
Age 65 - 75	317	307	284	251	196	156
Age > 75	249	226	210	179	148	101

Figure 6.4 Kaplan-Meier survival plots and life table for age (< 65 / 65 - 75 / > 75) subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method)



Months	Number at Risk					
	0	12	24	36	48	60
CT-SS 0 & SIG 0	75	74	73	67	54	40
CT-SS 2 & SIG ≥ 2	24	20	16	12	8	6

Figure 6.5 Kaplan-Meier survival plots and life table for CT-SS 0 & SIG 0 vs. CT-SS 2 & SIG ≥ 2 subgroups in patients undergoing elective intervention for AAA. $p < 0.001$ (log-rank method)



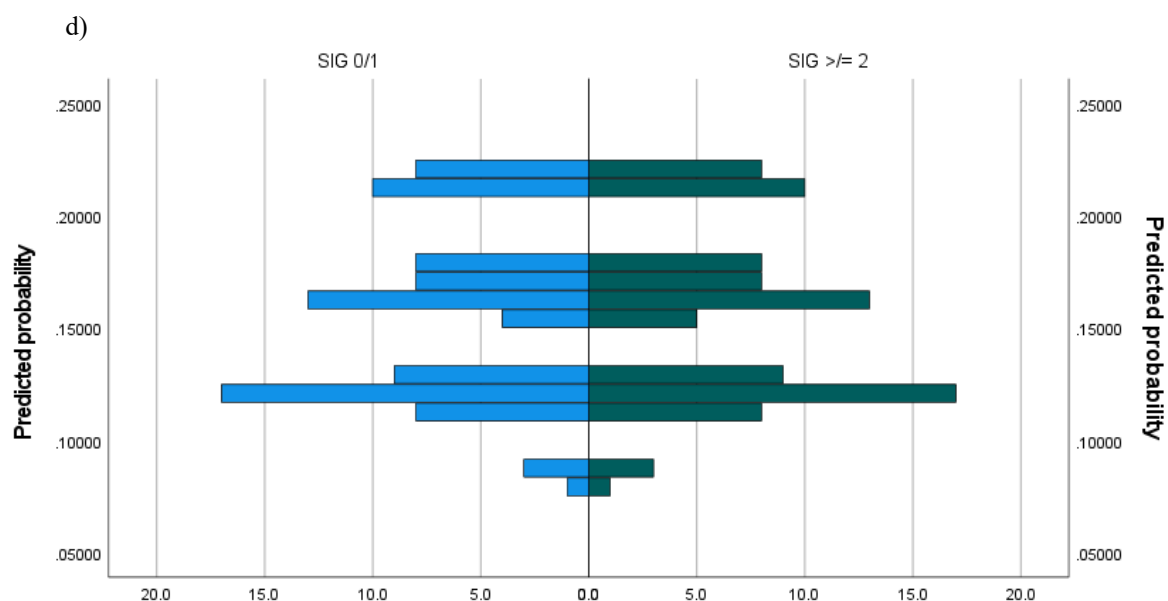


Figure 6.6 Distribution of propensity scores (x axis) plotted against predicted probability (y axis) in the unmatched and matched cohorts, a) CT-SS pre-match, b) CT-SS post-match, c) SIG pre-match, d) SIG post-match in a cohort of patients undergoing elective intervention for AAA, matched 1:1 based on Age, Sex, BMI, and CT-SS (c) and d)), or SIG (a) and b))

7 AN OBSERVATIONAL STUDY DESCRIBING THE ASSOCIATION BETWEEN CARDIOPULMONARY EXERCISE TESTING PARAMETERS, CT-DERIVED BODY COMPOSITION, SYSTEMIC INFLAMMATION, AND SURVIVAL IN PATIENTS UNDERGOING ELECTIVE ABDOMINAL AORTIC ANEURYSM REPAIR

7.1 INTRODUCTION

Cardiopulmonary exercise testing (CPEX) can be used to provide measures of physiological fitness and reserve and is commonly used to risk stratify patients prior to major surgical intervention²¹⁸. In patients with AAA, CPEX parameters have been shown to predict early and mid-term mortality in patients undergoing OSR and EVAR^{219–221}. NICE guidance recommends the use of CPEX to assist in clinical decision making for choice of procedure in patients being assessed for AAA intervention²².

In previous chapters we have described the associations between CT-BC parameters, in particular SMI and SMD, and outcomes following repair of AAA. Moreover, the potential prognostic role of markers of the systemic inflammatory response, and the associations with skeletal muscle parameters, was assessed. These associations are in keeping with those reported in the wider literature, largely in patients with cancer.

Despite the wealth of literature in a range of disease states reporting on CT-BC parameters as prognostic factors, the mechanism by which altered body composition leads to inferior outcomes is poorly understood and is likely a complex interaction between reduced physiological reserve, increasing comorbidity, and chronic activation of the SIR²²². The relationship between objective measures of physiological fitness derived from CPEX and CT-BC parameters has been previously investigated in patients undergoing hepatobiliary resection^{83,223}. More recently, McGovern et al report an association between radiological sarcopenia (CT-sarcopenia score; CT-SS), CPEX parameters (VO₂Peak and VO₂ at anaerobic threshold (AT)), systemic inflammation, and survival in a cohort of patients undergoing neoadjuvant therapy for upper gastrointestinal cancer²²⁴. VO₂Peak has previously been shown to be weakly correlated with CT-derived pectoralis muscle area but not erector spinae muscle area in Japanese patients with COPD²²⁵. In cardiovascular

populations, the literature describing an association between CPEX values and body composition parameters is limited to published abstracts²²⁶.

This study therefore aimed to describe the association between pre-operative CT-BC parameters, CPEX parameters, systemic inflammation, and survival in patients undergoing elective intervention for AAA.

7.2 MATERIALS & METHODS

7.2.1 PATIENT SELECTION

The recruitment of the AAA cohort is described in 1.7.2.1. Due to unavailable CPEX data from two (NHS Grampian, NHS Lanarkshire) of the centres, only patients from a single centre (NHS Tayside) were included in the present study.

7.2.2 OUTCOMES OF INTEREST

The primary outcome was all-cause mortality during the follow-up period. The secondary outcome was 2-year survival, chosen as all cases completed this minimum follow-up interval. Community Health Index (CHI) registries, which are maintained at a national level and populated by patients' community health records, were used to access outcome data and identify deaths.

7.2.3 CPEX PARAMETERS

Institutional practice during the study period was to perform CPEX on all patients with AAA eligible for OSR or F/B-EVAR, and to use CPEX selectively in patients eligible for standard EVAR at the discretion of a specialist vascular anaesthetist. Patients who were being considered for open repair of juxta- or para-renal AAA were referred to the national centre for these cases rather than undergoing intervention locally. In NHS Tayside AAA repair is performed at a single site acting as a tertiary referral centre, therefore some CPEX investigations performed locally to the patient which were available at the time of surgery were not available for retrospective interrogation. These patients were excluded from analysis. Patients with early termination of CPEX were also excluded from analysis. A specialist pre-operative assessment team provided a metabolic equivalence of tasks score (METs) as a subjective marker of cardiorespiratory fitness, with patients sub-grouped as high or low risk ($\text{METs} \leq 4$ / $\text{METs} > 4$) in keeping with evidence-based guidelines^{227,228} and institutional practice.

CPEX was performed at a single respiratory function laboratory using a VMAX Encore V29 (© 2014 CareFusion, Ca, USA) with a standardised 15-watt incremental ramp protocol. Several variables were recorded including electrocardiography, blood pressure, oxygen uptake, and inspiratory and expiratory gas analysis. Patients were exposed to an incremental physical exercise protocol to their maximally tolerated level, which was

determined by exhaustion, symptomatic breathlessness, or pain. The measured variables along with the exercise protocol allowed weight-adjusted VO_2 at maximal exercise and at AT to be quantified. On preliminary analysis, thresholds for VO_2Peak (≤ 19 and >19 ml/kg/min) and AT (≤ 11 and >11 ml/kg/min) as defined in previous literature²²⁴ were explored and found not to offer association with survival. Moreover, it was apparent that these thresholds were not rigorously adhered to clinically and that at MDT patient fitness was considered holistically on a case-by-case basis. For example, 17% and 15% of patients with low VO_2Peak and AT respectively ultimately underwent OSR. This practice is reflected in a similar recently reported UK cohort²⁰⁷. Therefore, CPEX parameters were considered as continuous variables and subgroup analyses between tertiles performed. Patients with suboptimal CPEX testing due to early termination of the test were excluded.

7.2.4 CT-BC ANALYSIS

CT-BC analysis was performed on pre-operative CTs as described in section 1.7.3. In keeping with prior reports from McGovern *et al*²²⁴, abnormal skeletal muscle parameters were analysed by CT-SS, calculated as described in section 6.2.3.

7.2.5 SYSTEMIC INFLAMMATION

In order to minimise the amount of missing data, the systemic inflammation-based prognostic score with the most complete dataset in the final study cohort (mGPS) was chosen for investigation. mGPS was calculated based on routine pre-operative bloods as described in table 5.1.

7.2.6 STATISTICAL ANALYSES

General statistical techniques employed in the present study are described in section 1.7.4. Specifically in the present study, the correlation between CT-BC and CPEX parameters was assessed using Pearson Correlation Coefficients (PCC). Owing to the use of multiple comparisons, $p < 0.01$ were considered statistically significant. Missing data were selectively excluded from relevant analyses.

7.3 RESULTS

There were 336 eligible procedures performed during the study period. Following exclusions for missing height, corrupted CT, ruptured AAA, or missing CPEX data, there were 176 patients (130 EVAR, 46 OSR) with recorded METS, VO₂Peak, and AT available for analysis in the final study cohort (figure 7.1), of which 168 had CT-BC data available. Median (IQR) follow-up was 60.5 (27) months. All patients completed a minimum of 2 years follow-up. Mean (95% CI) survival in the entire cohort was 72.9 (68.3 – 77.5) months. There were 54 deaths during the follow-up period, 30-day mortality was 0.6%, and 2-year survival was 92%. 156 (89%) of patients were male.

The association between CT-SS, cardiopulmonary exercise testing parameters, systemic inflammation, and 2-year survival in the study cohort is shown in table 7.1. Patients with greater CT-SS had a lower 2-year survival ($p < 0.01$), whilst other parameters were similar between CT-SS subgroups.

When METS, VO₂Peak, and AT were considered as tertiles, sub-groups for analysis were generated as follows; METS < 5 (tertile 1, $n = 18$), METS $5 - 7$ (tertile 2, $n = 118$), and METS > 7 (tertile 3, $n = 40$), VO₂Peak < 16.1 ml/kg/min (tertile 1, $n = 57$), VO₂Peak $16.1 - 19.3$ ml/kg/min (tertile 2, $n = 62$), VO₂Peak > 19.3 ml/kg/min (tertile 3, $n = 57$), AT < 10.8 ml/kg/min (tertile 1, $n = 57$), AT $10.8 - 12.3$ ml/kg/min (tertile 2, $n = 63$), and AT > 12.3 ml/kg/min (tertile 3, $n = 56$). The association between CPEX parameters (tertiles), CT-BC parameters, systemic inflammation, and 2-year survival in the study cohort is shown in table 7.2. Regarding METS, patients in the higher METS tertile were more likely to be male ($p < 0.001$), had a lower ASA ($p < 0.01$), and were more likely to have an open procedure ($p < 0.001$), whilst other parameters were similar between METS tertiles. Regarding VO₂Peak, patients in the higher VO₂Peak tertile were more likely to be male ($p < 0.01$), had a lower BMI ($p < 0.001$), had a lower ASA ($p < 0.05$), and were more likely to have an open procedure ($p < 0.001$), whilst other parameters were similar between VO₂Peak tertiles. Regarding AT, patients in the higher AT tertile were more likely to be male ($p < 0.05$), had a lower BMI ($p < 0.01$), had a lower ASA ($p < 0.01$), and were more likely to have an open procedure ($p < 0.001$), whilst other parameters were similar between AT tertiles.

The relationships between CT-derived SMD and CPEX parameters are shown in figure 7.2. SMD was significantly directly correlated with VO₂Peak (PCC = 0.30, $p < 0.001$) and

AT (PCC = 0.31, $p < 0.001$). SMI was not significantly correlated with either CPEX parameter ($p > 0.05$).

The relationships between CT-BC fat parameters, BMI, and CPEX parameters are shown in figure 7.3. SFI was significantly inversely correlated with VO₂Peak (PCC = -0.39, $p < 0.001$) and AT (PCC = -0.43, $p < 0.001$). VFI was significantly inversely correlated with VO₂Peak (PCC = -0.25, $p < 0.01$) and AT (PCC = -0.26, $p < 0.001$). BMI was significantly inversely correlated with VO₂Peak (PCC = -0.34, $p < 0.01$) and AT (PCC = -0.36, $p < 0.001$).

Kaplan-Meier survival plots in subgroups of CT-SS and mGPS parameters are shown in figure 7.4. Mean (95% CI) survival in the CT-SS 0 vs. CT-SS 1 vs. CT-SS 2 subgroups was 80.1 (73.6 – 86.6) months vs. 70.3 (63.5 – 77.1) months vs. 63.8 (53.4 – 74.2) months ($p < 0.05$, figure 2).

Table 7.3 shows the relationship between baseline clinical characteristics, CPEX parameters, pre-operative CT-derived body composition parameters, systemic inflammation, and overall survival in the study cohort. On univariate analysis, increasing age ($p < 0.01$), and elevated CT-SS ($p < 0.01$) were associated with poorer survival. On multivariate analysis elevated CT-SS (HR 1.83, 95% CI 1.16 – 2.89, $p < 0.01$) remained significantly associated with poorer survival whilst increasing age (HR 1.59, 95% CI 0.97 – 2.63, $p = 0.07$) was not. METS ($p = 0.21$), VO₂Peak ($p = 0.31$) and AT ($p = 0.40$) were not significantly associated with survival.

7.4 DISCUSSION

This chapter describes the, at time of writing, novel relationship between CPEX parameters, body composition, systemic inflammation, and outcomes in a cohort of patients undergoing elective intervention for AAA. Our analyses suggest that there was no significant difference in the proportion of patients with clinically relevant thresholds of CPEX parameters between CT-SS subgroups. Therefore, the present results question the relationship between muscle mass/quality and physiological function in patients with AAA.

The relationship between CPEX and CT-BC has been previously explored in patients with cancer; McGovern et al report on a cohort of 232 patients receiving neoadjuvant chemotherapy for upper gastrointestinal malignancy²²⁴, and West et al report on a cohort of 123 patients undergoing hepatobiliary surgery for malignancy⁸³. The former study reported an association between CPEX parameters and CT-SS, whilst the latter observed an association between CPEX parameters and SMD, but not SMI, supporting the previously described association between SMD and muscle function⁸⁰. It is important to note that these studies had a lower proportion of males (75% and 63% respectively) than the present study (89% male), and the sexual dimorphism within both CPEX performance (as observed by the present study) and CT-BC should be considered. Therefore, in cancer at least, there would appear to be an inconsistent relationship between muscle mass/ density and physical function. The present results in another chronic disease confirm this and therefore the relationship is likely to be complex²²⁹. Further large studies of this relationship, adjusting for potential confounding factors, are warranted.

A somewhat surprising observation in the present study was the trend towards increased prevalence of low SMI associated with increasing tertile of VO₂Peak (30% vs. 35% vs. 52%, $p < 0.05$), though this did not reach statistical significance using the adjusted p values. Interestingly the inverse relationship was seen between low SMD and VO₂Peak, where the prevalence of low SMD decreased with increasing VO₂Peak tertile, however this trend also did not reach statistical significance ($p = 0.08$). These strange observations highlight the complex relationships between muscle mass, density, and physical function, which require further investigation with large prospective studies.

Of particular interest, the present study observed an independent potential prognostic role for CT-SS but not for any individual CPEX parameter. The use of CPEX as a pre-operative

risk stratification tool in patients undergoing intervention for AAA is controversial, with limited high quality evidence available²³⁰. METS is well established as a prognostic tool, and is supported by a body of evidence in non-cardiac surgery^{227,228,231}, however recently its role has been challenged, with Wijeyesundera and colleagues advocating for the less subjective, more structured Duke Activity Status Index (DASI) questionnaire²³². In their model based on patients undergoing major non-cardiac surgery, DASI score was independently associated with 30-day post-operative death or myocardial infarction, whilst CPEX and METS were not. These findings highlight the clinical equipoise regarding optimal strategy of pre-operative risk stratification, and the need for objective, quantifiable markers. CT-BC shows promise in this field, as discussed in chapter 3. Importantly, predicting perioperative mortality is a key component of any prospective risk stratification tool. In the present study, the low (0.6%) 30-day mortality precludes meaningful analysis of peri-operative mortality, highlighting the need for further investigation. Elective AAA repair is a prophylactic procedure, and the use of prognostic tools to identify patients in whom long-term outcomes are inferior may allow for more robust selection into conservative management pathways and better resource allocation.

In the present study BMI was inversely associated with VO₂Peak and AT. The association of high BMI with inferior physical fitness has been previously described^{233–235}, however the controversial “obesity paradox” observed in a range of patient groups, including those with AAA^{157,236}, questions the conventional thinking that higher BMI is associated with inferior outcomes in surgery. The results of the present study highlight the complex relationship between body composition, obesity, fitness, and outcomes, which require further characterisation.

The present study did not observe an association between body composition and systemic inflammation, contrasting with the findings of McGovern and colleagues²²⁴, as well as the data presented in chapter 6. Furthermore, the relationship between CT-BC and systemic inflammation has been described in wider cohorts of patients with cancer^{103,212}. It may be that in the present study the relatively small sample size and low absolute numbers of patients in the more inflamed subgroup resulted in a lack of statistical power to observe such a difference. Additionally, the median values of CPEX parameters were overall lower than expected in the present study. This may reflect selection bias, as cases of juxta/para-renal AAA suitable for OSR were not managed locally, or may reflect the high level of socioeconomic deprivation and comorbidity prevalent in the catchment area of our unit.

Indeed, 75 (42%) of patients in the present study were in the two most deprived quintiles as measured by Scottish Index of Multiple Deprivation (SIMD).

Our results are limited by a single-centre retrospective study design, lack of a control group, small sample size, and missing data for some patients. The small sample size results in low absolute numbers in certain subgroups, reducing the validity of conclusions drawn from these analyses. Regarding the limitations of CPEX parameters; VO_2Peak describes the highest value of VO_2 achieved during CPEX by an individual, however is limited to the effort of the individual during the test, therefore may not reflect the highest value of VO_2 which an individual could potentially achieve ($\text{VO}_{2\text{max}}$) and therefore bias may be introduced into our results due to submaximal effort which was not identified on CPEX reports. The thresholds of CPEX parameters were derived from a cohort of patients with oesophageogastric cancer rather than repair of AAA (as quoted in the NICE guidelines²³⁷) as they were more widely used in the centre that patients were recruited from, however this is a potential source of bias. The thresholds used to define CT-BC parameters in the present study were derived from a wider cohort including emergency cases, which is a potential source of bias. Longitudinal analyses of CT-BC parameters are of particular interest in the present patient cohort, however the majority of patients underwent ultrasound follow-up rather than CT, therefore low numbers precluded meaningful analysis. This is an important area for further investigation.

In a cohort of patients undergoing intervention for AAA, CT-derived body composition does not appear to be associated with physiological fitness as measured by CPEX performance. CPEX parameters do not appear to be associated with survival in this cohort, and the role of CPEX in predicting outcomes in patients with AAA remains uncertain and requires further investigation. CT-SS may be a clinically useful tool for future risk stratification and prognostication, though further large studies are required to confirm this.

7.5 TABLES

Table 7.1: The association between CT Sarcopenia Score, cardiopulmonary exercise testing parameters, and systemic inflammation in patients undergoing elective intervention for AAA (n = 168).

Table 7.2: The association between CPEX parameters (tertile), CT-derived body composition, systemic inflammation in patients undergoing elective intervention for AAA (n = 176).

Table 7.3: The relationship between baseline clinical characteristics, pre-operative CT Sarcopenia Score, cardiopulmonary exercise testing parameters, systemic inflammation and overall survival in patients undergoing elective intervention for AAA (n=176).

Table 7.1 The association between CT Sarcopenia Score, cardiopulmonary exercise testing parameters, and systemic inflammation in patients undergoing elective intervention for AAA (n = 168).

	CT-SS 0 (n = 44)	CT-SS 1 (n = 91)	CT-SS 2 (n = 33)	p
Age				
< 65	4 (9%)	9 (10%)	3 (9%)	0.20
65 - 75	27 (61%)	48 (53%)	14 (42%)	
> 75	13 (30%)	34 (37%)	16 (49%)	
Sex				
Male	38 (86%)	86 (94%)	32 (97%)	0.06
Female	6 (14%)	5 (6%)	1 (3%)	
BMI				
< 25 kg/m ²	6 (14%)	17 (19%)	9 (27%)	0.14
≥ 25 kg/m ²	38 (86%)	74 (81%)	24 (73%)	
ASA				
≤ 2	31 (70%)	53 (59%)	24 (73%)	0.98
> 2	13 (30%)	37 (41%)	9 (27%)	
Technique				
Endovascular	29 (66%)	65 (71%)	28 (85%)	0.07
OSR	15 (34%)	26 (29%)	5 (15%)	
High SFI				
Yes	37 (90%)	74 (86%)	28 (85%)	0.48
No	4 (10%)	12 (14%)	5 (15%)	
High VFI				
Yes	29 (66%)	72 (79%)	25 (76%)	0.26
No	15 (34%)	19 (21%)	8 (24%)	
METS				
median (IQR)	7 (2)	7 (3)	7 (2)	0.71
VO₂Peak				
median (IQR)	17.7 (5.6)	17.3 (5.0)	18.2 (5.0)	0.53
AT				
median (IQR)	11.8 (2.6)	11.5 (2.2)	11.7 (2.3)	0.91
mGPS				
0	30 (88%)	60 (88%)	23 (92%)	0.60
1	3 (9%)	5 (7%)	2 (8%)	
2	1 (3%)	3 (5%)	0 (0%)	
Two-year Survival	97% (SE 3%)	91% (SE 3%)	86% (SE 6%)	< 0.01
Length of stay (days)				
median (IQR)	6 (7)	6 (5)	6 (3)	0.85

Yes	7(41%)	41(36%)	18(46%)		16(30%)	20(35%)	29(52%)		16(30%)	25(42%)	25(46%)	
No	10(59%)	72(64%)	21(54%)	0.50	37(70%)	37(65%)	27(48%)	0.02	38(70%)	35(58%)	30(54%)	0.09
Low SMD												
Yes	9(53%)	76(65%)	18(46%)		36(67%)	37(62%)	28(50%)		36(67%)	40(63%)	27(49%)	
No	8(47%)	41(35%)	21(54%)	0.25	18(33%)	23(38%)	28(50%)	0.08	18(33%)	24(38%)	28(51%)	0.06
CT-SS												
0	5(29%)	29(26%)	10(26%)		14(26%)	15(27%)	14(25%)		13(24%)	16(27%)	15(27%)	
1	9(53%)	59(53%)	23(59%)		29(55%)	33(59%)	28(50%)		32(59%)	29(49%)	30(55%)	
2	3(8%)	24(21%)	6(15%)	0.91	10(19%)	8(14%)	14(25%)	0.55	9(17%)	14(24%)	10(18%)	0.90
mGPS												
0	11(79%)	73(88%)	34(94%)		35(81%)	40(91%)	41(93%)		37(82%)	39(91%)	42(93%)	
1	2(14%)	7(8%)	2(6%)		6(14%)	3(7%)	2(5%)		6(13%)	3(7%)	2(4%)	
2	1(7%)	3(4%)	0(0%)	0.08	2(5%)	1(2%)	1(2%)	0.13	2(4%)	1(2%)	1(2%)	0.14
Two-year Survival	88% (SE 8%)	90% (SE 3%)	95% (SE 4%)	0.08	91% (SE 4%)	91% (SE 4%)	91% (SE 4%)	1.00	96% (SE 3%)	88% (SE 4%)	89% (SE 4%)	0.44
T1 – tertile 1. T2 – tertile 2. T3 – tertile 3.												

Table 7.3 The relationship between baseline clinical characteristics, pre-operative CT Sarcopenia Score, cardiopulmonary exercise testing parameters, systemic inflammation and overall survival in patients undergoing elective intervention for AAA (n=176).

	Univariate			Multivariate		
Covariate	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age (<65 / 65-75 / > 75)	1.95	1.21 – 3.14	<0.01	1.59	0.97 – 2.63	0.07
Female Sex	1.10	0.40 – 3.05	0.86	-	-	-
BMI ≥ 25	0.69	0.37 – 1.29	0.24	-	-	-
ASA > 2	0.86	0.48 – 1.52	0.59	-	-	-
OSR	0.59	0.26 – 1.19	0.13	-	-	-
CT-SS (0 / 1 / 2)†	1.76	1.19 – 2.61	<0.01	1.83	1.16 – 2.89	<0.01
High SFI	0.55	0.27 – 1.11	0.10	-	-	-
High VFI	0.81	0.45 – 1.46	0.48	-	-	-
Low SMI†	1.68	1.03 – 2.74	0.04	1.89†	1.04 – 3.43	0.04
Low SMD†	1.68	0.98 – 2.90	0.06	-	-	-
METS	0.88	0.74 – 1.07	0.21	-	-	-
VO ₂ Peak	0.96	0.89 – 1.04	0.31	-	-	-
AT	0.94	0.82 – 1.08	0.40	-	-	-
mGPS (0 / 1 / 2)	1.77	0.99 – 3.16	0.05	1.77	0.94 – 3.31	0.07

For covariates with >2 subgroups, the first category was considered as the reference category. METS, VO₂Peak, and AT considered as continuous variables. †CT-SS and low SMI/low SMD modelled separately in the multivariate model to avoid multicollinearity, values for other covariates pertain to the multivariate model using CT-SS.

7.6 FIGURES

Figure 7.1: Patient selection into the study.

Figure 7.2: Correlations between CT-derived SMD and CPEX parameters in patients undergoing elective intervention for AAA. a) SMD vs. VO2Peak ($p < 0.001$), b) SMD vs. AT ($p < 0.001$).

Figure 7.3: Correlations between CT-BC fat parameters, BMI, and CPEX parameters in patients undergoing intervention for AAA. a) SFI vs. VO2Peak ($p < 0.001$), b) SFI vs. AT ($p < 0.001$), c) VFI vs. VO2Peak ($p < 0.001$), d) VFI vs. AT ($p < 0.01$), e) BMI vs. VO2Peak ($p < 0.001$), f) BMI vs. AT ($p < 0.001$).

Figure 7.4: Kaplan-Meier survival plots and life tables of overall survival in patients undergoing elective intervention for AAA sub-grouped by CT-SS 0 vs. CT-SS 1 vs. CT-SS 2 ($p < 0.05$).

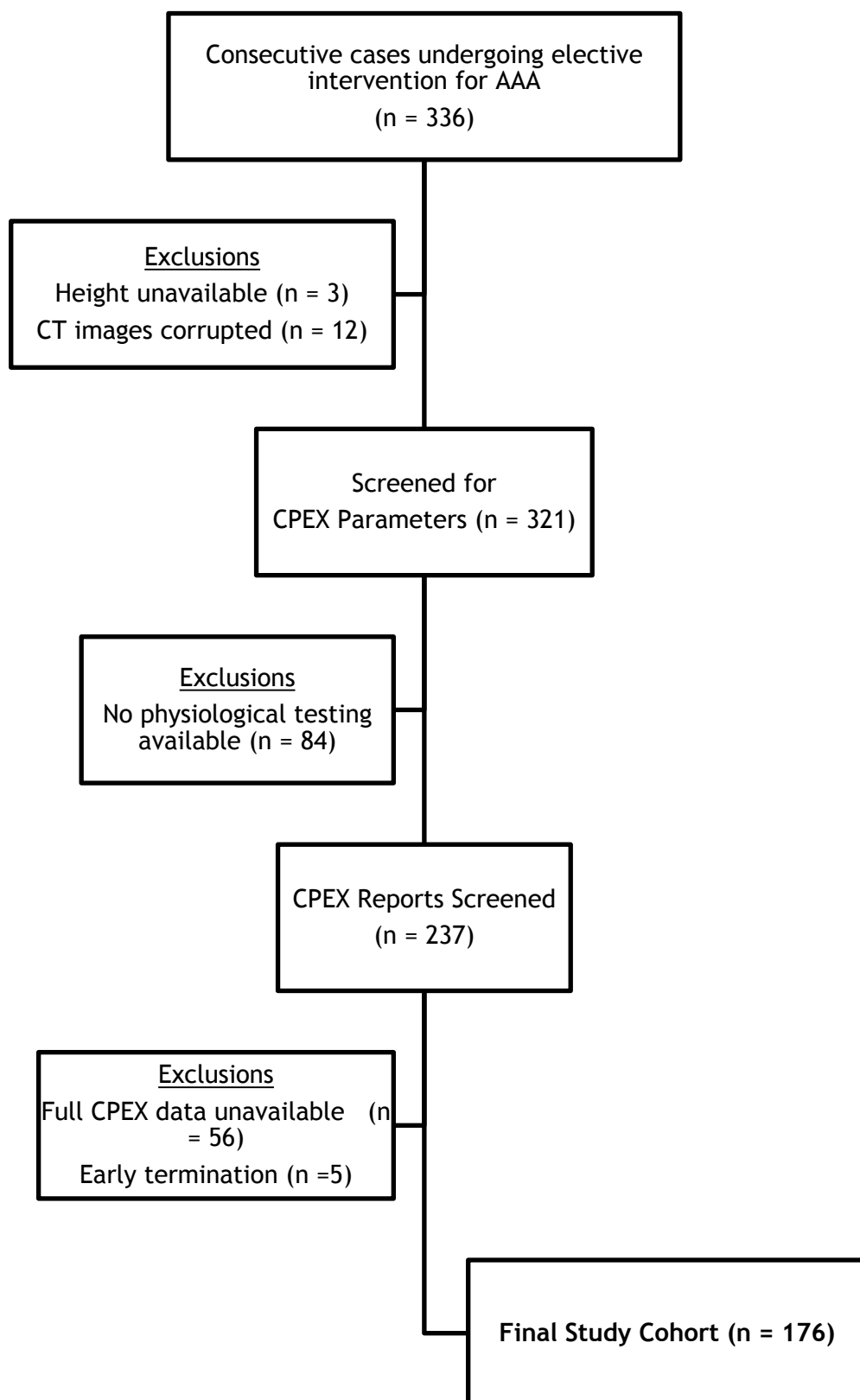


Figure 7.1 Patient selection into the study

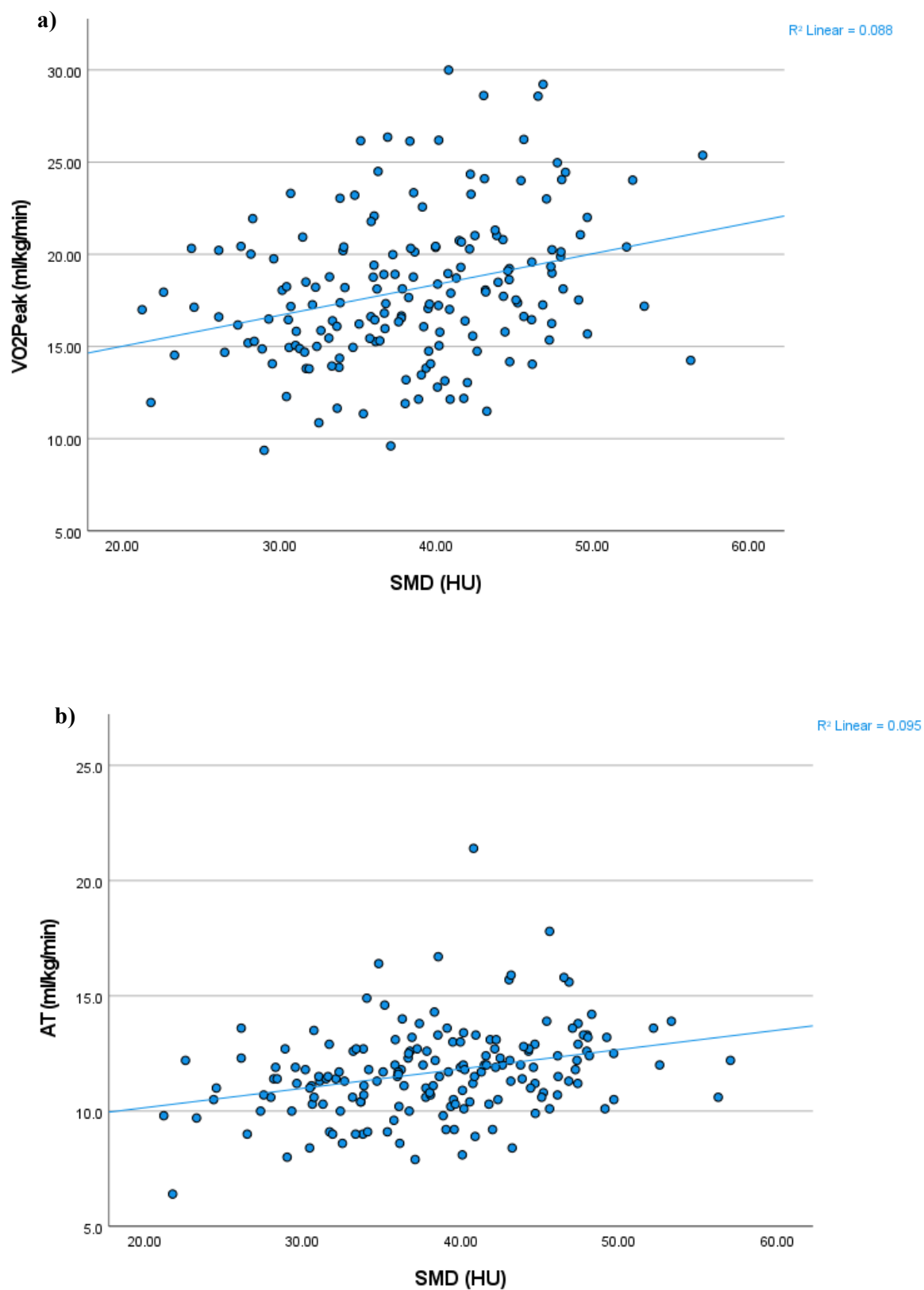
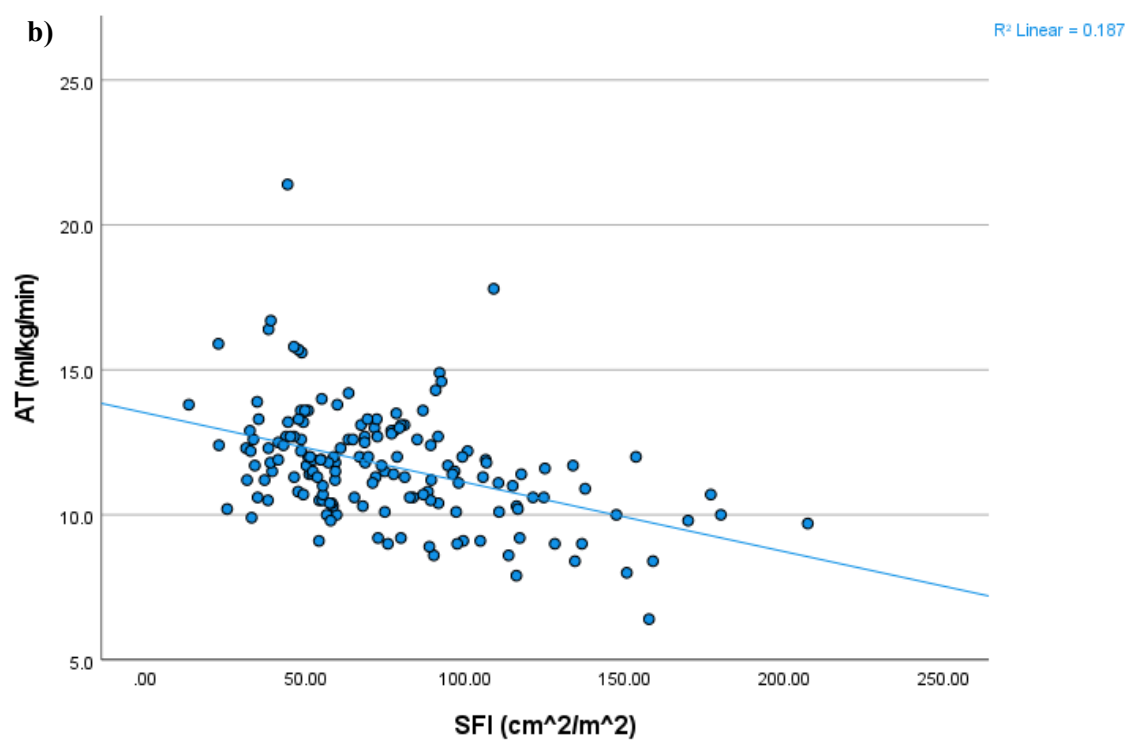
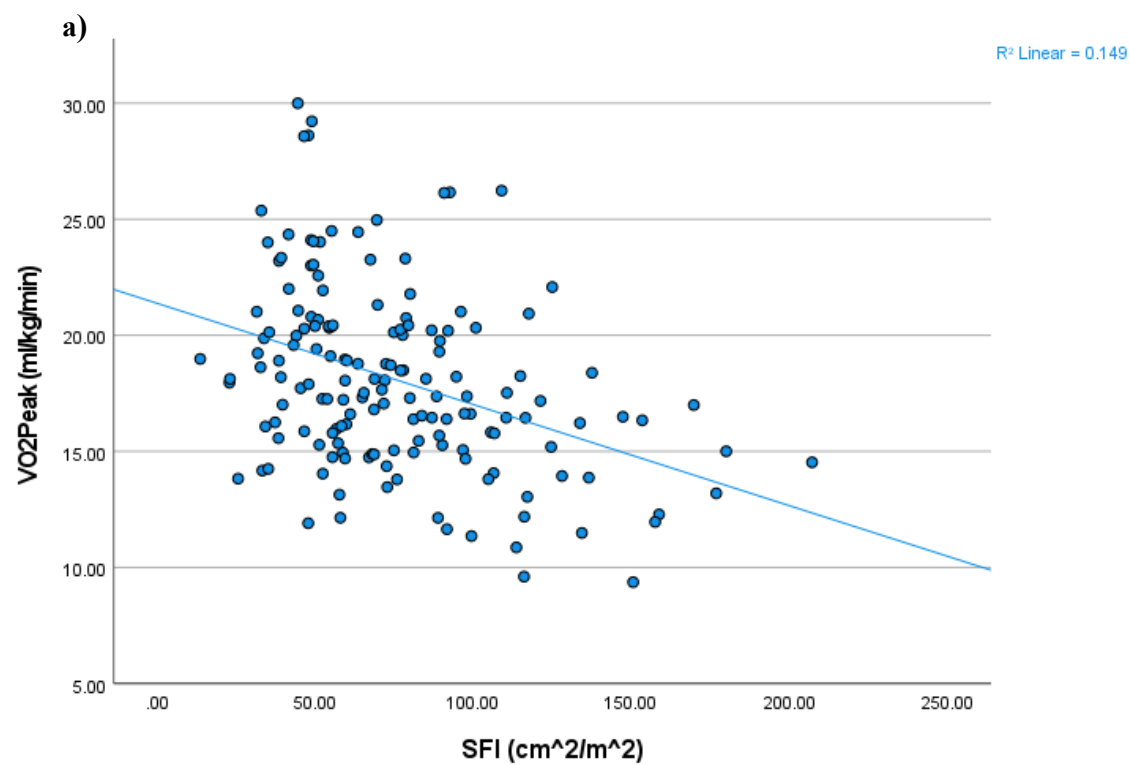
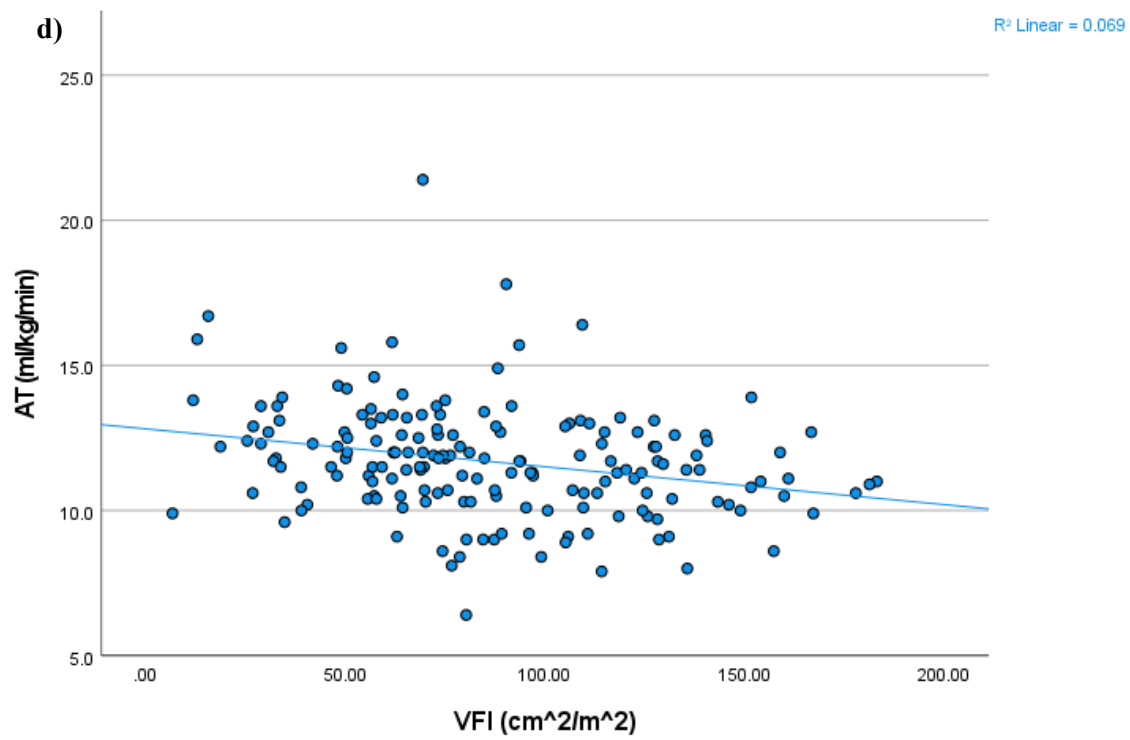
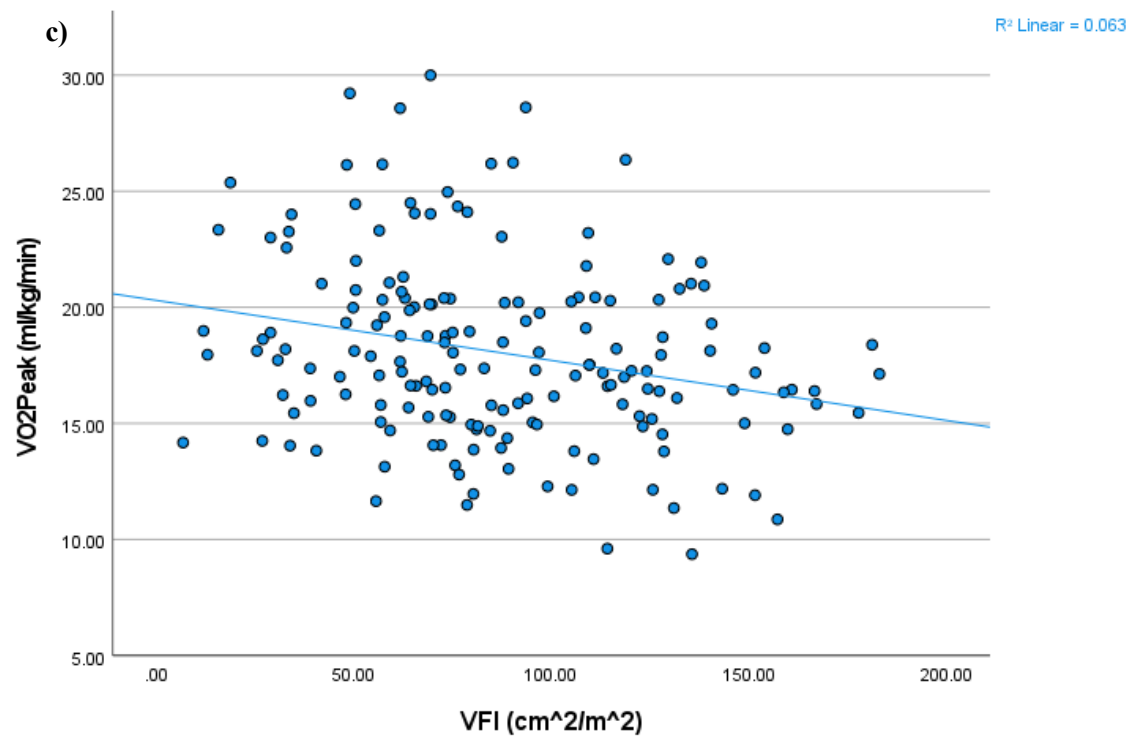


Figure 7.2 Correlations between CT-derived SMD and CPEX parameters in patients undergoing elective intervention for AAA. a) SMD vs. VO₂Peak ($p < 0.001$), b) SMD vs. AT ($p < 0.001$).





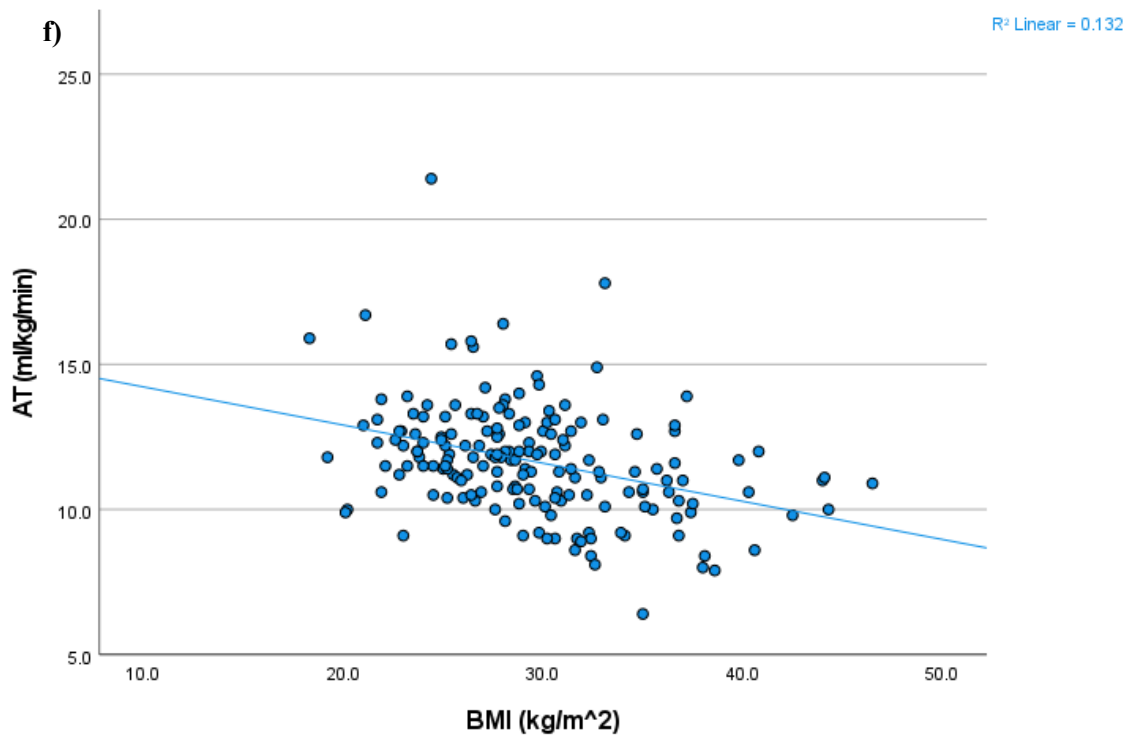
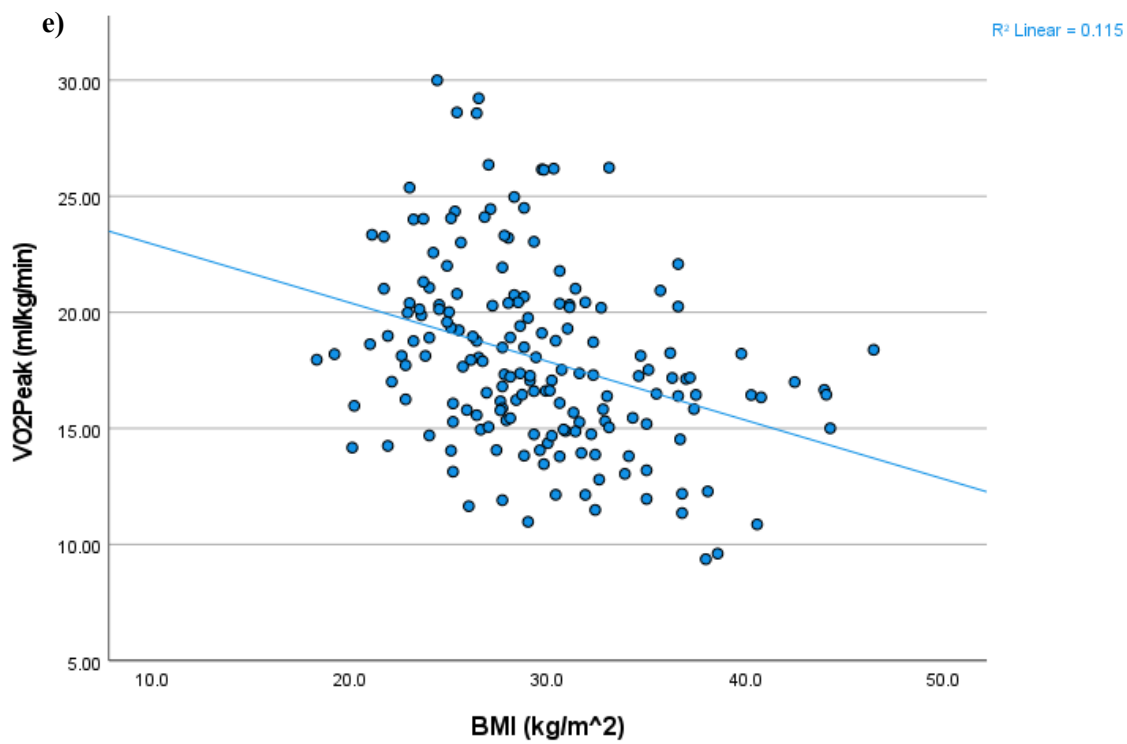
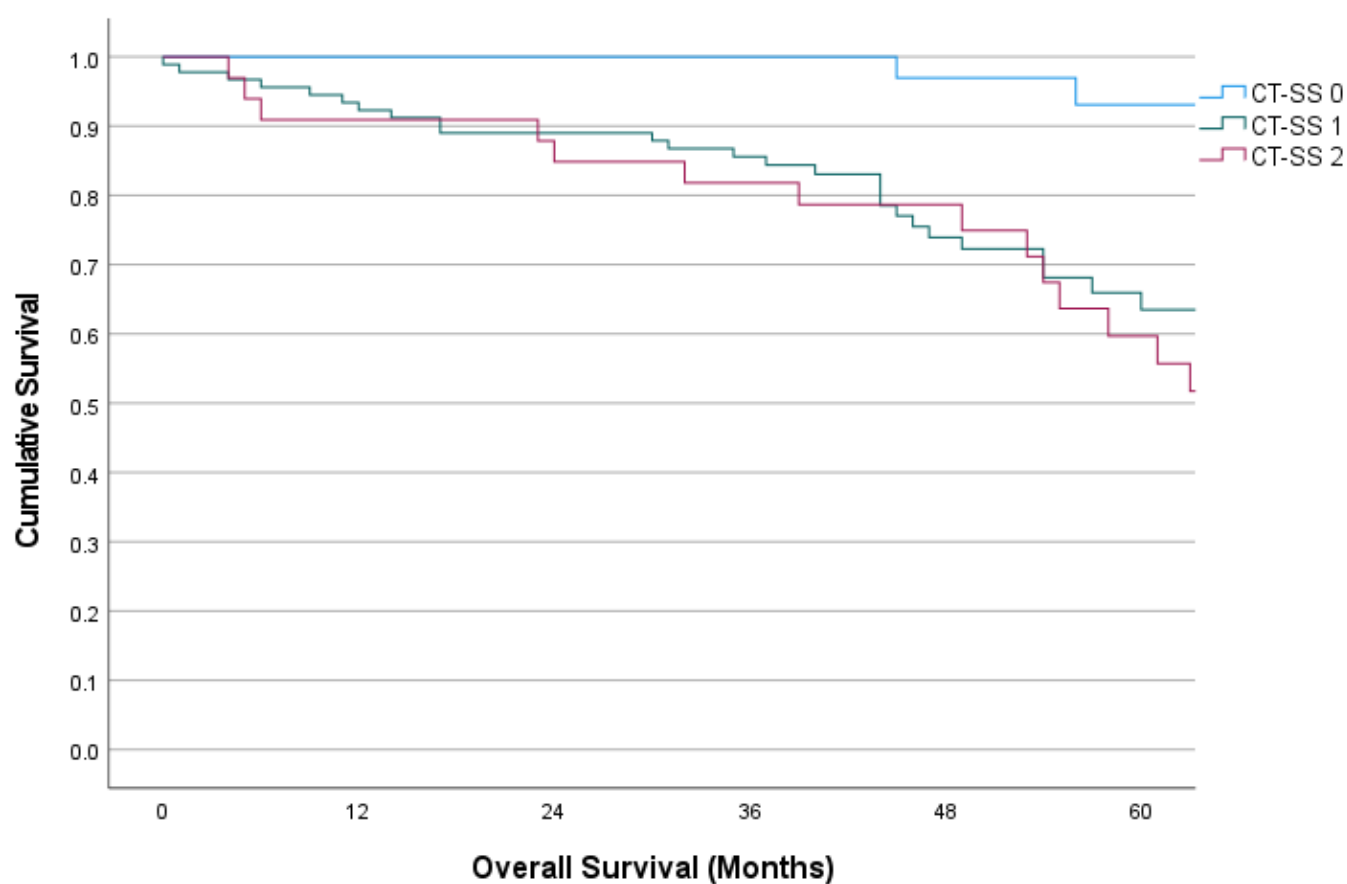


Figure 7.3 Correlations between CT-BC fat parameters, BMI, and CPEX parameters in patients undergoing intervention for AAA. a) SFI vs. VO₂Peak ($p < 0.001$), b) SFI vs. AT ($p < 0.001$), c) VFI vs. VO₂Peak ($p < 0.001$), d) VFI vs. AT ($p < 0.01$), e) BMI vs. VO₂Peak (<0.001), f) BMI vs. AT (<0.001).



		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	CT-SS 0	44	44	44	41	29	20
	CT-SS 1	91	85	80	71	46	27
	CT-SS 2	33	31	30	28	22	16

Figure 7.4 Kaplan-Meier survival plots and life tables of overall survival in patients undergoing elective intervention for AAA sub-grouped by CT-SS 0 vs. CT-SS 1 vs. CT-SS 2 ($p=0.01$)

8 CT-DERIVED BODY COMPOSITION: DIFFERENTIAL ASSOCIATION WITH DISEASE, AGE AND INFLAMMATION IN A RETROSPECTIVE COHORT STUDY

8.1 INTRODUCTION

To date, the prognostic effect of both body composition and systemic inflammation has been reported focussing on cohorts of patients based on a single disease state. Historically, the presence of sarcopenia (and the closely related phenomenon of cachexia) was considered a hallmark feature of malignant disease, and was largely ignored in other non-malignant chronic illnesses. The emergence of sarcopenia and systemic inflammation as important factors in non-malignant conditions requires that the traditional dogma, where these phenomena were considered to be exclusively related a cancer diagnosis, be challenged.

Specifically, this raises the question of whether body composition is primarily constitutional and related to shared risk factors, or whether it results from disease specific factors. For example, a recent systematic review suggested that CT-derived sarcopenia has a similar prevalence across a range of different cancers and disease stages¹⁵⁸. There have been attempts to define normal values of CT-BC parameters using “healthy” control populations^{238,239}, however when comparing these cohorts to clinically relevant disease entities such as CRC, there are likely to be potentially confounding factors.

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer worldwide, with an increased incidence in males and in older adults²⁴⁰. CRC is staged using the AJCC TNM (8th Edition) staging system²⁴¹, with curative surgical resection the gold standard of treatment for early stage resectable disease²⁴². Both AAA and CRC are considered to occur on a background of older age, obesity, comorbid disease and functional decline^{243,244}.

The aim of the present study was to compare CT-derived body composition and systemic inflammation in two large cohorts of patients undergoing elective intervention for AAA and elective curative resection for colorectal cancer. In particular, the role of increasing age as a determinant of altered body composition was examined.

8.2 MATERIALS & METHODS

8.2.1 PATIENTS

The present study included 2 large multicentre cohorts of patients. Recruitment of the AAA cohort is described in section 1.7.2.1.

The CRC cohort was recruited from prospectively recorded cancer network data; within Scotland, basic clinicopathological data for all new cases of colorectal cancer are prospectively collected and held within regional Managed Clinical Network (MCN) datasets. The West of Scotland Cancer Network (WoSCAN) dataset incorporates four health boards (Ayrshire and Arran, Forth Valley, Lanarkshire and Greater Glasgow and Clyde) and includes approximately half of the population of Scotland. These patients receive treatment in line with national guidelines and are followed up for a period of 3–5 years. Patients diagnosed with colon cancer between January 2011 and December 2014 were identified from the West of Scotland MCN database. Patients undergoing curative elective surgery for a diagnosis of AJCC stage I–III²⁴¹ colon cancer were included. Ethical approval was granted for this project from the Public Benefit and Privacy Panel (PBPP) for Health and Social Care (NHS Scotland) and Caldicott Guardian Approval.

In both cohorts, comorbidity was assessed using ASA derived from preoperative anaesthetic assessment. Age (< 60 , $60 - 69$, $70 - 79$, ≥ 80), ASA (≤ 2 and > 2), and BMI (< 25 and ≥ 25 kg/m²) were considered as categorical variables. Haemoglobin and creatinine were recorded from routine pre-operative blood tests and defined as “normal” or “high/low” based on local laboratory sex-specific reference values.

8.2.2 SIR

The SIR was assessed using SIG, calculated as described in table 5.1 Patients were sub-grouped based on SIG into SIG 0 (non-inflamed), SIG 1 (mildly inflamed) and SIG ≥ 2 (inflamed).

8.2.3 CT-BC

CT-BC was performed on pre-operative CTs as described in section 1.7.3. CT-BC parameters were then sub-grouped based on previously reported thresholds derived from patients with cancer^{78,79,151}, chosen as these thresholds have been validated in cancer

cohorts. Analysis was performed on arterial phase scans (AAA cohort) and portal venous phase scans (CRC) cohort; in order to mitigate the potential risk of bias in SMD readings between these 2 phases SMD analyses were repeated using values in the AAA cohort transformed from arterial phase to comparable portal venous phase as per Rollins et al ($SMD_{Rollins}$)²⁴⁵.

8.2.4 STATISTICAL ANALYSES

General statistical analyses are described in section 1.7.4. Analyses were performed on the entire study cohort, and subsequently sub-group analyses were performed on patients aged 70 - 79 years (chosen as the sub-group of age with maximal patient numbers), to control for potential confounding due to differences in age distribution between the AAA and CRC cohorts. The association between baseline factors and outcome variables of interest (CT-BC parameters recorded as dichotomous categorical variables) was investigated using binary logistic regression to generate odds ratios and confidence intervals. This allowed for comparison of associations between the two large cohorts. AAA repair strategy (EVAR/OSR) and AJCC stage were not included in multivariate models to avoid excluding the entire sub-group of CRC or AAA patients respectively. Missing parameters were selectively excluded from relevant analyses on a case-by-case basis.

8.3 RESULTS

Following exclusions there were a total of 1695 patients who underwent elective intervention for either AAA or CRC included; 759 patients with AAA and 936 patients with CRC. In the AAA cohort, 604 (80%) underwent EVAR compared with 155 (20%) undergoing OSR. In the CRC cohort, 224 (24%) were AJCC stage I, 380 (41%) were AJCC stage II, and 332 (35%) were AJCC stage III. When sub-group analyses based on age were performed, there were 672 patients included in the age 70 - 79 sub-group analysis; 359 patients with AAA and 313 patients with CRC (Figure 8.1).

The difference in baseline demographic and clinicopathological characteristics, CT-BC parameters, markers of the SIR, and survival between AAA and CRC in the entire study cohort is shown in table 8.1. Compared with the AAA cohort, patients with CRC were younger ($p < 0.001$), more likely to be female ($p < 0.001$), had a lower ASA ($p < 0.001$), had a lower BMI ($p < 0.001$), had a lower haemoglobin ($p < 0.001$), and were less likely to have a raised creatinine ($p < 0.001$). High VFA (79% vs. 73%, $p < 0.01$) was more prevalent in the AAA cohort, whilst high SFI (74% vs. 81%, $p < 0.001$) and low SMD (33% vs. 66%, $p < 0.001$) were more prevalent in the CRC cohort. Low SMI prevalence was similar in both cohorts (51% vs. 51%, $p = 0.80$). Compared with the AAA cohort, the CRC cohort had a higher prevalence of raised SIG ($p < 0.001$). 30 day and 1-year outcomes were similar between groups, however the AAA cohort had decreased 3-year survival (76% vs. 83%, $p < 0.01$).

The difference in baseline demographic and clinicopathological characteristics, markers of the SIR, and survival between AAA and CRC in the age 70-79 sub-group is shown in table 8.2. In these sub-groups, median age was similar ($p = 0.55$) between patients with AAA and CRC. Compared with the AAA cohort, patients with CRC were more likely to be female ($p < 0.001$), and had a lower haemoglobin ($p < 0.001$). Compared with the AAA cohort, the CRC cohort had a higher prevalence of raised SIG ($p < 0.001$). 1-year and 3-year outcomes were similar between groups; however the AAA cohort had decreased 30-day survival (98% vs. 100%, $p < 0.05$).

The difference in BMI and CT-BC parameters between AAA and CRC in the entire study cohort sub-grouped by age is shown in table 8.3. Low SMD was more prevalent in the CRC cohort across all age sub-groups. BMI was significantly higher in patients with AAA apart from those aged < 60 , where a non-significant trend was observed ($p = 0.07$). High

SFI was more prevalent in the CRC sub-group in patients aged 60 – 69 ($p < 0.05$), however was similar between patients with AAA and CRC of other age groups.

The binary logistic regression models for the association between baseline demographic and clinicopathological characteristics, systemic inflammation, and CT-BC muscle parameters is shown in table 8.4. On univariate analysis, increasing age ($p < 0.001$), AJCC Stage II/III ($p < 0.05$), and elevated SIG ($p < 0.001$) were associated with increased odds of low SMI, whilst BMI ≥ 25 kg/m² ($p < 0.05$) was associated with decreased odds of low SMI. On multivariate analysis, increasing age (OR 1.54, 95% CI 1.38 – 1.72, $p < 0.001$) and elevated SIG (OR 1.23, 95% CI 1.09 – 1.40, $p = 0.001$) were independently associated with increased odds of low SMI, whilst BMI ≥ 25 kg/m² (OR 0.78, 95% CI 0.62 – 0.98, $p < 0.05$) was independently associated with decreased odds of low SMI. On univariate analysis, increasing age ($p < 0.001$), CRC diagnosis ($p < 0.001$), ASA > 2 ($p < 0.01$), and elevated SIG ($p < 0.001$) were associated with increased odds of low SMD, whilst BMI ≥ 25 kg/m² ($p < 0.05$) and OSR ($p < 0.001$) were associated with decreased odds of low SMD. On multivariate analysis, increasing age (OR 1.90, 95% CI 1.66 – 2.17, $p < 0.001$) CRC diagnosis (OR 5.89, 95% CI 4.55 – 7.62, $p < 0.001$), ASA > 2 (OR 1.37, 95% CI 1.08 – 1.73, $p < 0.05$), and elevated SIG (OR 1.19, 95% CI 1.03 – 1.37, $p < 0.05$) were independently associated with increased odds of low SMD, whilst BMI ≥ 25 kg/m² (OR 0.51, 95% CI 0.39 – 0.66, $p < 0.001$) was independently associated with decreased odds of low SMD.

Figure 8.2 displays the proportion of patients with abnormal BMI and CT-BC parameters sub-grouped by age (figure 8.2a) and SIG (figure 8.2b) in the entire study cohort. The prevalence of low SMI and SMD was associated with increasing age in both the AAA and CRC cohorts, with a greater magnitude of association between age and SMD in patients with CRC compared to AAA. As SIG increased, there was a trend towards a higher proportion of patients with low SMD in both AAA and CRC cohorts. Compared with the AAA cohort, the proportion of patients with low SMD in the CRC cohort was consistently higher across each SIG subgroup.

Figure 8.3 displays the proportion of patients with abnormal BMI and CT-BC parameters sub-grouped by SIG in the age 70-79 sub-group. As SIG increased, there was a trend towards a higher proportion of patients with low SMI in the CRC cohort, and a low SMD in both AAA and CRC cohorts. Compared with the AAA cohort, the proportion of patients with low SMD in the CRC cohort was consistently higher across each SIG subgroup.

When the SMD analyses were repeated using $SMD_{Rollins}$, low SMD was less prevalent in the AAA cohort (21% vs. 66%, $p < 0.001$). To account for potential categorical misclassification based on phase of scan, continuous values of SMD and $SMD_{Rollins}$ were analysed. Median (IQR) SMD in the AAA vs. CRC cohorts was 37.8 (9.5) HU vs. 31.8 (12.7) HU ($p < 0.001$). Median (IQR) $SMD_{Rollins}$ in the AAA vs. CRC cohorts was 40.2 (9.3) HU vs. 31.8 (12.7) HU ($p < 0.001$).

8.4 DISCUSSION

The data presented in this chapter are the first to directly compare baseline demographic and clinicopathological characteristics CT-BC parameters and systemic inflammation between large cohorts of patients with AAA and CRC. The results of the present study describe similar rates of low SMI in the AAA and CRC cohorts. In contrast, low SMD and elevated magnitude of the SIR were more prevalent in patients with CRC compared with AAA, despite the greater BMI in the AAA cohort. An association between age and both low SMI and low SMD was also observed, in both patients with AAA and CRC. Therefore, loss of skeletal muscle mass appears to be endemic across multiple chronic illnesses, however loss of skeletal muscle density exhibits greater disease-specific variation. Moreover, it would appear that increasing age and systemic inflammation predominates in determining loss of skeletal muscle mass and quality.

The present results support the “common soil” hypothesis of shared aetiology and risk factors producing similar host phenotypes despite different disease entities²⁴⁶. These results are consistent to those in patients with cancer, McGovern et al¹⁵⁸ reported similar rates of low skeletal muscle mass in different cancer subtypes and disease stages. Therefore, taken together these results would suggest that sarcopenia is endemic across a range of common, life-limiting diseases, and highlight age and systemic inflammation as key determinants of altered body composition and a host response rather than disease-specific entity. The disease-specific differences in SMD observed in the present study may be in part explained by tumour mediated inflammation, however these differences were independent of inflammatory status. It may be that the inflammatory cascade in patients with cancer include alternative pathways which are not entirely captured through SIG. Further prospective analysis, including cytokine analysis, is required to more accurately define these pathways.

Increasing age is a risk factor for sarcopenia, though it is also recognised that skeletal muscle loss can occur in younger populations^{247,248}. There appears to be an association between increasing age and elevated magnitude of the systemic inflammatory response, which is a potential underlying mechanism explaining loss of skeletal muscle with age²²². However, the sub-group analyses in the present study support a mechanistic role for elevated magnitude of the SIR independent of age. Moreover, both age and SIG are independently associated with both low SMI and low SMD, irrespective of disease state.

The basis of the relationship between SMD and systemic inflammation is incompletely understood. However, it may be that systemic inflammation primarily influences muscle quality rather than quantity. If this were to prove to be the case then it might explain the profound effect of the SIR on physical function in patients with cancer²⁴⁹. These results also have implications for our understanding of the aetiology and definition of cachexia syndromes. For example, if such results are confirmed across disease states it may that more priority, compared with SMI, should be given to SMD and the importance of fat infiltration into skeletal muscle in determining clinical outcome. Clearly, this would suggest that muscle density (quality) rather than muscle mass would become a more meaningful therapeutic targets to optimise prognosis in a range of conditions.

The relationship between inflammation and muscle density has been reported in non-cancer populations, and attempts to define the mechanistic pathways suggest that cytokines such as TNF, IL-6, and IL-1 β may stimulate proteolysis and inhibit anabolism, leading to muscle breakdown and wasting²¹⁵. IL-1 β blockade has been shown to reduce cardiac morbidity in patients with established cardiovascular disease¹⁷³. Further prospective interventional studies investigating these potential therapeutic targets are required. In particular, SMD measurement appears to be associated with intramuscular lipid content²⁵⁰. Furthermore, intramyocellular lipid content is increased in the presence of cancer, and increased further in patients with clinical features of the cancer cachexia syndrome²⁵¹. White adipose tissue, the predominant form of mammalian adipose tissue, is known to play an active role in the inflammatory response, potentially through the expression of adipokines which act as pro-inflammatory mediators²⁵². Additionally, an association between inflammation and ectopic fat deposition in both liver and skeletal muscle has been described²⁵³. To date, radiological hepatic architecture in relation to inflammation has not been directly compared between non-cancer and cancer cohorts, and investigation of this potential association may allow for greater understanding of the differences in CT-BC.

Mitochondria are the predominant organelles found in skeletal muscle, and have a role in inflammatory signalling²⁵⁴, with potential pathways via reactive-oxygen species and the NLRP3 inflammasome²⁵⁵. Mitochondrial loss “mitophagy” has been described in relation to aging and chronic illness^{256,257}. The response of mitochondria to systemic inflammation in patients with cancer is uncertain. Downregulation of mitochondria, and mitophagy with amino acid release in response to both age and tumour-mediated inflammation may result in mitochondrial loss with preservation of the sarcomere, and subsequent fat deposition may explain the preferential SMD loss compared to SMI loss in the CRC cohort.

CT-BC parameters may vary depending on the phase of CT which is analysed, though there is uncertainty around the effects of phase and contrast on recorded values²⁴⁵. It appears that SMD is the most susceptible CT-BC parameter to such potential confounding. In order to mitigate this, we repeated our analyses using transformed SMD values as per the formula proposed by Rollins et al²⁴⁵, which did not alter results. Given the uncertainty around the true effect that phase has on SMD values, we chose to report the non-transformed values in the main analysis. Rollins et al report that, as compared to the portal venous phase, arterial phase CTs may underestimate SMD values²⁴⁵. Given the present study observed lower SMD in the CRC cohort (portal venous phase) as compared to the AAA cohort (arterial phase) it is therefore likely that the effect of phase is underestimating rather than overestimating the strength of our observations. However, the conflicting results from previously published small series warrant further investigation to better understand the role of CT phase.

The potentially confounding effect of pharmacological therapies such as steroids, chemotherapy, statins on muscle tissue and the systemic inflammatory response may be considered. These data were not available for the present study cohorts, and is therefore a potential source of bias. However, typical UK practice does not advocate neoadjuvant steroid or chemotherapy for colonic cancer, therefore any effect is likely to be small. The association between statins and the results of interest in the present study would be an important area for further research. Nevertheless, it is clear from the present work that aging and systemic inflammation are important determinants of loss of muscle mass and content, independent of disease setting.

In the present study nutritional status may have been a potential confounding factor, however, the patient groups studied (i.e. patients undergoing intervention for AAA and patients undergoing surgery for colorectal cancer) are not recognised to be at high nutritional risk. For example, Chaar and colleagues reported that in patients undergoing intervention for AAA the mean (SE) pre-operative Nutritional Risk Index was 103.6 (1.4); with values less than 100 conferring malnutrition²⁵⁸. Similarly, in a cohort of 363 patients undergoing surgery for CRC, 79% were classed as low risk of malnutrition based on MUST score²⁵⁹. Additional limitations include retrospective study design and missing data for some participants, however the present study is the largest comparative study of CT-BC in non-cancer and cancer patients to date.

Low SMI was prevalent and similar non-cancer and cancer cohorts (AAA and CRC). Low SMD and systemic inflammation were more prevalent in patients with CRC than with AAA. Increasing age and systemic inflammation appear to be important determinants of loss of skeletal muscle mass and quality.

8.5 TABLES

Table 8.1: The difference between demographic and clinicopathological characteristics, CT-BC and systemic inflammation in patients undergoing elective EVAR or OSR for AAA or curative resection for CRC (n = 1695).

Table 8.2: The difference between demographic and clinicopathological characteristics and systemic inflammation in patients aged 70 - 79 undergoing elective EVAR or OSR for AAA or curative resection for CRC (n = 672).

Table 8.3: The difference between BMI and CT-BC parameters in patients undergoing elective EVAR or OSR for AAA or curative resection for CR, sub-grouped by age (n = 1695).

Table 8.4: The association between baseline demographic and clinicopathological covariates, systemic inflammation, and CT-BC parameters in patients undergoing elective intervention for AAA or curative resection for CRC (n = 1695).

Table 8.1 The difference between demographic and clinicopathological characteristics, CT-BC and systemic inflammation in patients undergoing elective EVAR or OSR for AAA or curative resection for CRC (n = 1695)

	AAA (n=759)	Curative CRC (n=936)	<i>p</i>
Age			
< 60	12 (2%)	207 (22%)	<0.001
60 – 69	222 (29%)	295 (32%)	
70 - 79	359 (47%)	313 (33%)	
≥ 80	166 (22%)	121 (13%)	
Sex			
Male	703 (93%)	520 (55%)	<0.001
Female	56 (7%)	416 (45%)	
ASA			
≤ 2	418 (55%)	614 (66%)	<0.001
> 2	337 (45%)	322 (34%)	
BMI			
< 25 kg/m ²	158 (21%)	320 (34%)	<0.001
≥ 25 kg/m ²	596 (79%)	616 (66%)	
AJCC Stage			
I	-	224 (24%)	-
II	-	380 (41%)	
III	-	332 (35%)	
Repair Strategy			
EVAR	604 (80%)	-	-
OSR	155 (20%)	-	
Haemoglobin			
Normal	606 (81%)	515 (61%)	<0.001
Low	146 (19%)	327 (39%)	
Creatinine			
Normal	588 (78%)	724 (88%)	<0.001
High	165 (22%)	103 (12%)	
SFI (Ebadi)			
Normal	184 (26%)	180 (19%)	<0.001
High	522 (74%)	756 (81%)	
VFA (Doyle)			
Normal	157 (21%)	250 (27%)	<0.01
High	594 (79%)	686 (73%)	
SMI (Martin)			
Normal	357 (49%)	461 (49%)	0.80
Low	377 (51%)	475 (51%)	
SMD (Martin)			
Normal	495 (67%)	316 (34%)	<0.001
Low	244 (33%)	620 (66%)	
SIG			
0	331 (52%)	408 (44%)	<0.001
1	207 (33%)	236 (25%)	
≥ 2	93 (15%)	286 (31%)	
30-Day Mortality			
Yes	10 (1%)	6 (1%)	0.15
No	749 (99%)	930 (99%)	
1-Year Survival			
Yes	717 (95%)	881 (94%)	0.76
No	43 (5%)	55 (6%)	
3-Year Survival			
Yes	580 (76%)	775 (83%)	

No	179 (24%)	161 (17%)	<0.01

Table 8.2 The difference between demographic and clinicopathological characteristics and systemic inflammation in patients aged 70 - 79 undergoing elective EVAR or OSR for AAA or curative resection for CRC (n = 672)

	AAA (n=359)	Curative CRC (n=313)	<i>p</i>
Median (IQR) Age (years)	74 (5)	74 (5)	0.55
Sex			
Male	330 (92%)	173 (55%)	<0.001
Female	29 (8%)	140 (45%)	
ASA			
≤ 2	194 (54%)	176 (56%)	0.60
> 2	164 (46%)	137 (44%)	
AJCC Stage			
I	-	76 (24%)	-
II	-	124 (40%)	
III	-	113 (36%)	
Repair Strategy			
EVAR	292 (81%)	-	-
OSR	67 (19%)	-	
Haemoglobin			
Normal	276 (78%)	159 (57%)	<0.001
Low	80 (22%)	118 (43%)	
Creatinine			
Normal	281 (79%)	230 (83%)	0.23
High	75 (21%)	48 (17%)	
SIG			
0	147 (51%)	125 (40%)	<0.001
1	102 (35%)	85 (27%)	
≥ 2	39 (14%)	103 (33%)	
30-Day Mortality			
Yes	7 (2%)	0 (0%)	<0.05
No	352 (98%)	313 (100%)	
1-Year Survival			
Yes	339 (94%)	291 (93%)	0.44
No	20 (6%)	22 (7%)	
3-Year Survival			
Yes	279 (78%)	251 (80%)	0.44
No	80 (22%)	62 (20%)	

Table 8.3 The difference between BMI and CT-BC parameters in patients undergoing elective EVAR or OSR for AAA or curative resection for CR, sub-grouped by age (n = 1695)

	AAA	Curative CRC	p
< 60 Years	n = 12	n = 207	
BMI			
< 25 kg/m ²	1 (8%)	69 (33%)	0.07
≥ 25 kg/m ²	11 (92%)	138 (67%)	
SFI (Ebadi)			
Normal	1 (8%)	48 (23%)	0.23
High	11 (92%)	159 (77%)	
VFA (Doyle)			
Normal	2 (17%)	73 (35%)	0.19
High	10 (83%)	134 (65%)	
SMI (Martin)			
Normal	10 (83%)	132 (64%)	0.17
Low	2 (17%)	75 (36%)	
SMD (Martin)			
Normal	11 (92%)	118 (57%)	<0.05
Low	1 (8%)	89 (43%)	
60 – 69 Years	n = 222	n = 295	
BMI			
< 25 kg/m ²	33 (15%)	85 (29%)	<0.001
≥ 25 kg/m ²	187 (85%)	210 (71%)	
SFI (Ebadi)			
Normal	44 (22%)	42 (14%)	0.03
High	158 (78%)	253 (86%)	
VFA (Doyle)			
Normal	39 (18%)	66 (22%)	0.20
High	181 (82%)	229 (78%)	
SMI (Martin)			
Normal	127 (59%)	158 (54%)	0.20
Low	87 (41%)	137 (46%)	
SMD (Martin)			
Normal	163 (76%)	115 (39%)	<0.001
Low	52 (24%)	180 (61%)	
70 – 79 Years	n = 359	n = 313	
BMI			
< 25 kg/m ²	70 (20%)	108 (35%)	<0.001
≥ 25 kg/m ²	287 (80%)	205 (65%)	
SFI (Ebadi)			
Normal	79 (24%)	57 (18%)	0.09
High	255 (76%)	256 (82%)	
VFA (Doyle)			
Normal	74 (21%)	72 (23%)	0.53
High	279 (79%)	241 (77%)	
SMI (Martin)			
Normal	162 (47%)	134 (43%)	0.30
Low	184 (53%)	179 (57%)	
SMD (Martin)			
Normal	237 (68%)	72 (23%)	<0.001
Low	112 (32%)	241 (77%)	
≥ 80 Years	n = 166	n = 121	
BMI			
< 25 kg/m ²	54 (33%)	58 (48%)	<0.001
≥ 25 kg/m ²	111 (67%)	63 (52%)	
SFI (Ebadi)			
Normal	60 (38%)	33 (27%)	0.06
	98 (62%)	88 (73%)	

High			
VFA (Doyle)			
Normal	42 (25%)	39 (32%)	
High	124 (75%)	82 (68%)	0.20
SMI (Martin)			
Normal	58 (36%)	37 (31%)	
Low	104 (64%)	84 (69%)	0.36
SMD (Martin)			
Normal	84 (52%)	11 (9%)	
Low	79 (48%)	110 (91%)	<0.001

Table 8.4 The association between baseline demographic and clinicopathological covariates, systemic inflammation, and CT-BC parameters in patients undergoing elective intervention for AAA or curative resection for CRC (n = 1695)

	N (%)	Low SMI (Martin)		Low SMD (Martin)	
		Univariate	Multivariate	Univariate	Multivariate
Age (< 60, 60 – 69, 70 – 79, ≥ 80)	219 (13%) / 517 (30%) / 672 (40%) / 287 (17%)	1.55 1.39 – 1.73 $p < 0.001$	1.54 1.38 – 1.72 $p < 0.001$	1.41 1.27 – 1.57 $p < 0.001$	1.90 1.66 – 2.17 $p < 0.001$
CRC (Yes / No)	936 (55%) / 759 (45%)	0.98 0.80 – 1.18 $p = 0.80$	-	3.98 3.24 – 4.88 $p < 0.001$	5.89 4.55 – 7.62 $p < 0.001$
ASA (≤ 2 / > 2)	1032 (61%) / 659 (39%)	1.07 0.88 – 1.30 $p = 0.52$	-	1.31 1.08 – 1.60 $p < 0.01$	1.37 1.08 – 1.73 $p < 0.05$
BMI (<25 kg/m² / ≥ 25 kg/m²)	478 (28%) / 1212 (72%)	0.76 0.61 – 0.94 $p < 0.05$	0.78 0.62 – 0.98 $p < 0.05$	0.40 0.32 – 0.50 $p < 0.001$	0.51 0.39 – 0.66 $p < 0.001$
OSR† (Yes / No)	155 (20%) / 604 (80%)	0.87 0.61 – 1.25 $p = 0.87$	-	0.45 0.29 – 0.69 $p < 0.001$	-
AJCC Stage† (I / II & III)	224 (24%) / 712 (76%)	1.45 1.07 – 1.96 $p < 0.05$	-	1.27 0.93 – 1.74 $p = 0.13$	-
SIG (0 / 1 / ≥ 2)	739 (47%) / 443 (28%) / 379 (25%)	1.27 1.13 – 1.44 $p < 0.001$	1.23 1.09 – 1.40 $p < 0.01$	1.43 1.26 – 1.62 $p < 0.001$	1.19 1.03 – 1.37 $p < 0.05$
For covariates with >2 subgroups, the first category was considered as the reference category. † - OSR and AJCC stage not included in multivariate analyses to avoid complete exclusion of CRC/AAA patients respectively.					

8.6 FIGURES

Figure 8.1: Participant flow chart and inclusion into the study.

Figure 8.2: The proportion of patients with abnormal BMI and CT-BC parameters grouped by a) age and b) SIG in patients with AAA and CRC, $n = 1695$.

Figure 8.3: The proportion of patients with abnormal BMI and CT-BC parameters grouped by SIG in patients with AAA and CRC age 70 - 79, $n = 672$.

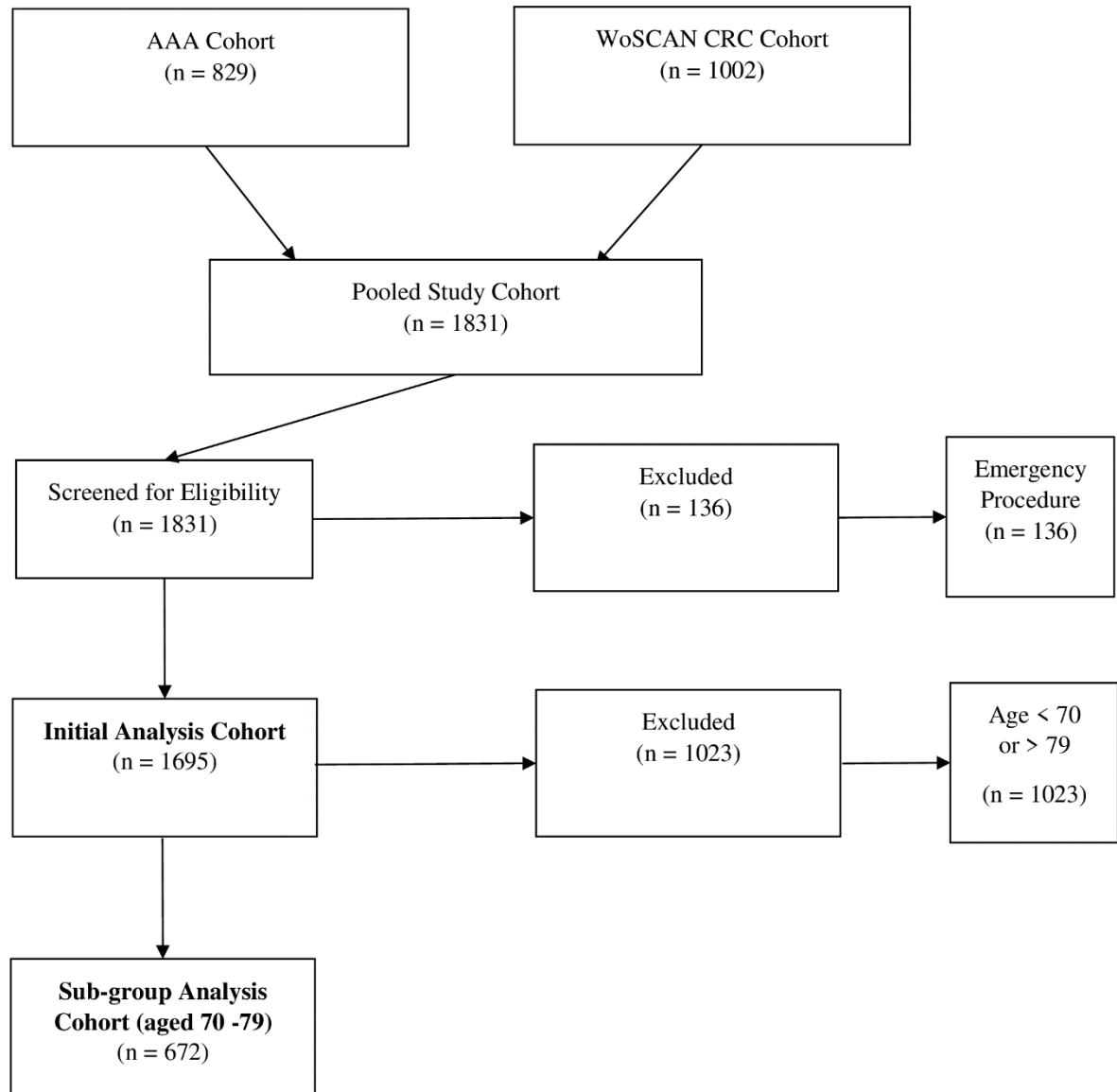
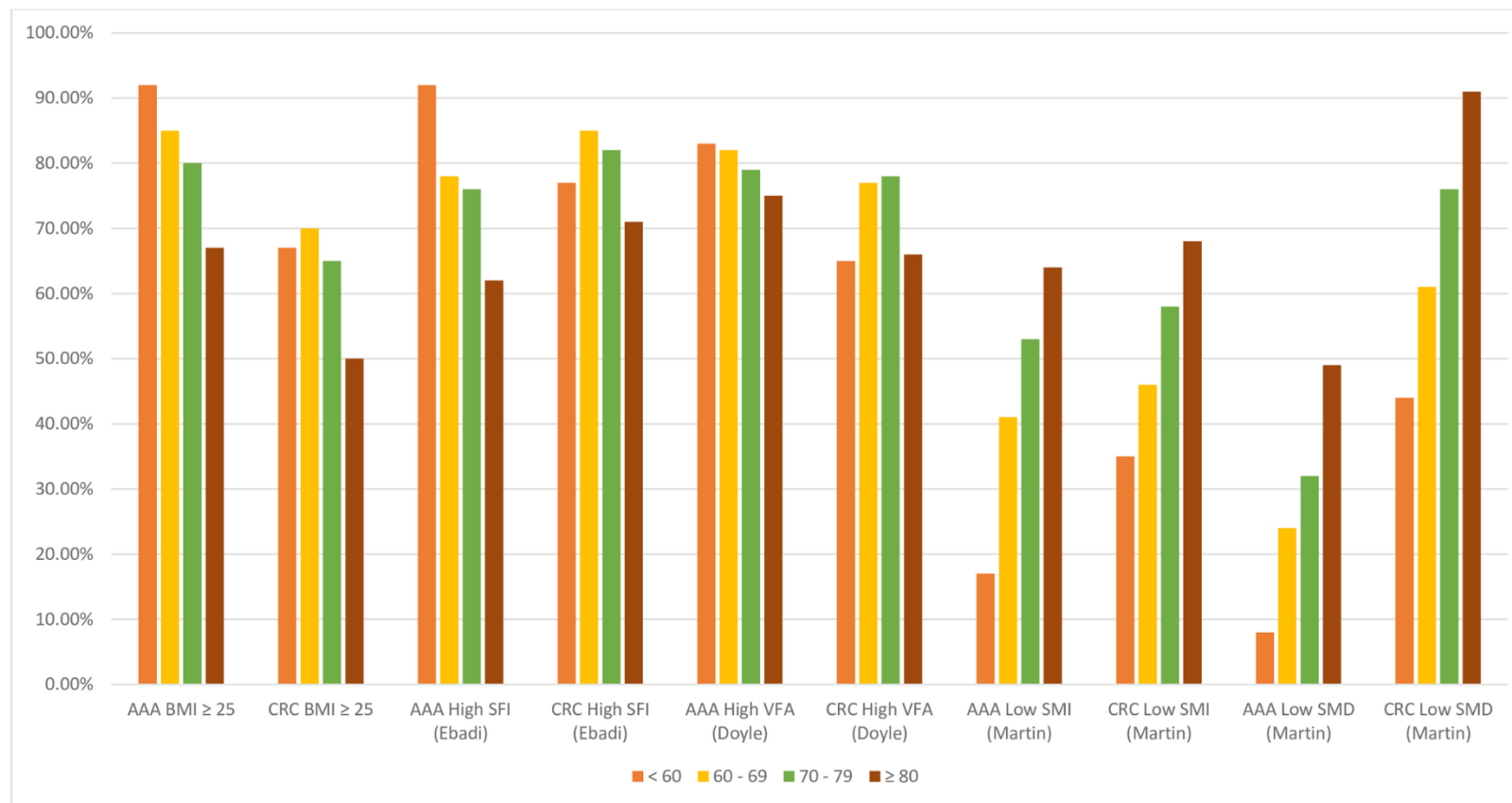


Figure 8.1 Participant flow chart and inclusion into the study. AAA: Abdominal aortic aneurysm. CRC: Colorectal cancer. WoSCAN: West of Scotland Cancer Network.

1

1 a)

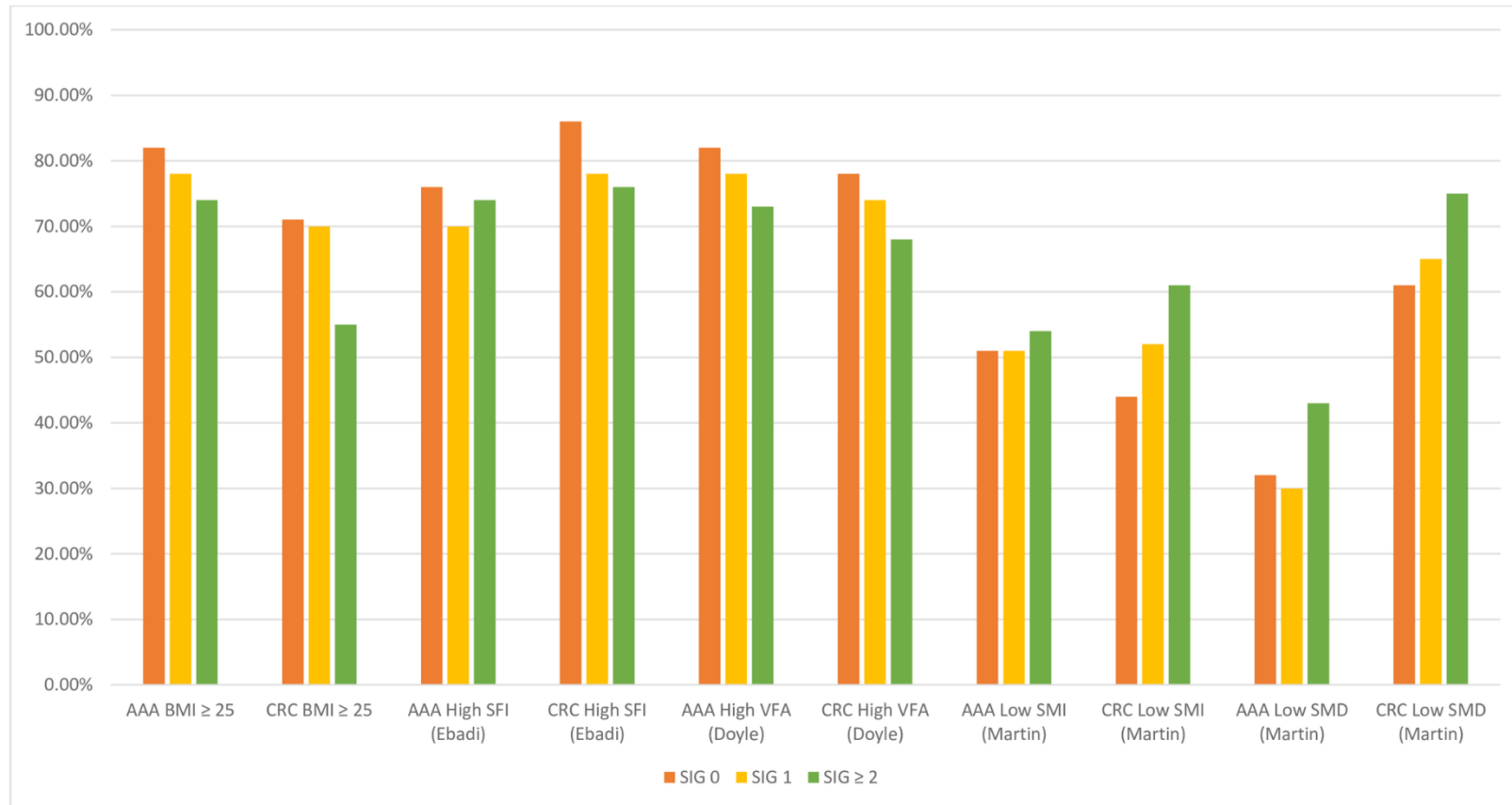


3

4

1

1 b)



6

2

Figure 8.2 The proportion of patients with abnormal BMI and CT-BC parameters grouped by a) age and b) SIG in patients with AAA and CRC, n = 1695.

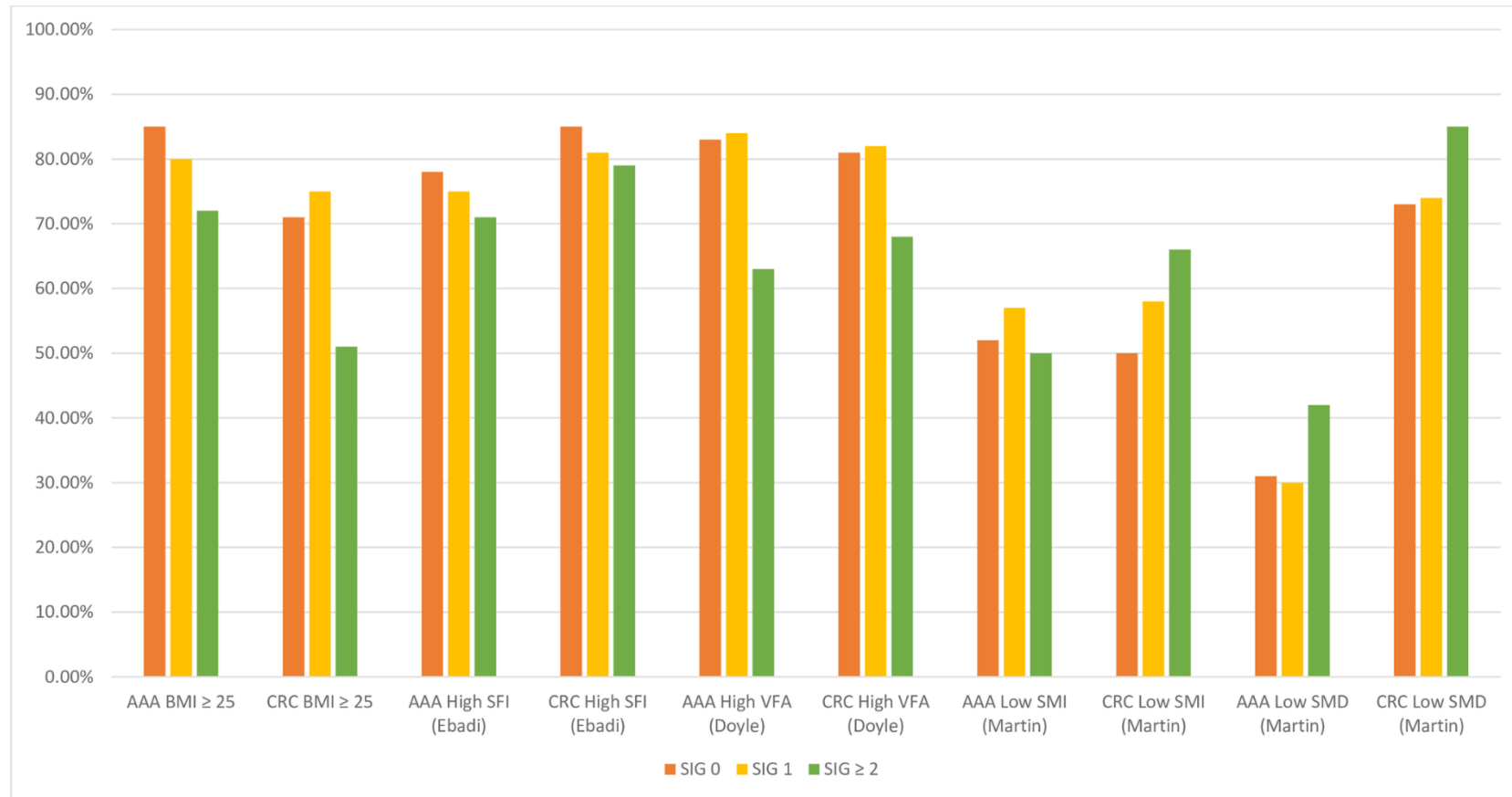


Figure 8.3 The proportion of patients with abnormal BMI and CT-BC parameters grouped by SIG in patients with AAA and CRC age 70 - 79, n = 672.

9 THE RELATIONSHIP BETWEEN POST-OPERATIVE SYSTEMIC INFLAMMATION AND MORTALITY IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

9.1 INTRODUCTION

Throughout the present thesis the SIR has been investigated based on a range of scoring system, all calculated using pre-operative blood results, with the rationale that this likely reflects chronic activation of the SIR rather than an acute inflammatory response. The prognostic value of the post-operative SIR is generally less well reported in all conditions as compared to the pre-operative SIR, likely due to the confounding effect that a surgical insult has on systemic inflammation. The post-operative Glasgow Prognostic Score (poGPS) describes the acute phase response following major surgical intervention²⁶⁰. There appears to be an association between poGPS and survival (both short-term and long-term) in patients undergoing resection for colorectal cancer, as well as in non-surgical conditions^{260,261}. Watt *et al* describe a prognostic role for poGPS measured on the third post-operative day, corresponding to a typically expected peak in post-operative CRP²⁶⁰. Additionally, they report predictors of an elevated poGPS, which include pre-operative systemic inflammation, and tumour site²⁶². Furthermore, maximal CRP appears to confer inferior survival in an unselected cohort of elderly patients presenting to acute medical services²⁶³. It appears that the magnitude of the SIR following aortic surgery is much greater than following colorectal cancer surgery, therefore the use of poGPS in an AAA cohort may be limited²⁶⁴.

The relationship between skeletal muscle mass and density, and the magnitude of the post-operative SIR is poorly reported across all disease states. The prognostic role of the post-operative SIR remains unreported in patients with AAA. The present study therefore aimed to describe a potential prognostic role of the peri-operative SIR in patients undergoing both emergency and elective intervention for AAA, to evaluate potential factors associated with elevated magnitude of the post-operative SIR, and to evaluate the association between the peri-operative SIR and pre-operative CT-BC muscle parameters.

9.2 MATERIALS & METHODS

9.2.1 PATIENT ELIGIBILITY AND DATA COLLECTION

Recruitment and data collection for the AAA cohort is described in section 1.7.2.1. In this chapter, an additional cohort was recruited, of patients with emergency presentation (section 11.2.2). Age (<75 , ≥ 75 years), BMI ($<25\text{kg/m}^2$, $\geq 25\text{kg/m}^2$), and haemoglobin ($<135\text{g/L}$, $\geq 135\text{g/L}$ in males, $<120\text{g/L}$, $\geq 120\text{g/L}$ in females) were considered as categorical variables. BMI was not available for emergency cases. Mesenteric ischaemia was defined as compromised viability at any level of the gastrointestinal tract necessitating resection, thought to be secondary to ischaemia, and diagnosed clinically by both a consultant vascular surgeon and consultant general surgeon. Patients with active malignancy, active infection, juxta- or para-renal aneurysms, isolated iliac aneurysms, or those prescribed immunomodulatory medications, were excluded due to the potential confounding. Additionally, patients with missing post-operative inflammatory parameters of interest were excluded.

9.2.2 EMERGENCY COHORT

Consecutive cases undergoing EVAR or OSR to treat infrarenal rAAA between 01/01/2011 and 31/12/2023 were screened for inclusion. rAAA was defined as CT-proven aneurysm rupture, confirmed by consultant radiologist; patients with “impending rupture” or symptomatic AAA were not eligible for inclusion. In addition, patients in whom repair was attempted but abandoned intra-operatively were excluded. All patients in the emergency cohort achieved a minimum follow-up of 30 days from the date of surgery.

9.2.3 ELECTIVE COHORT

Due to likely discharge prior to blood sampling on post-operative day 3, patients undergoing elective endovascular intervention were excluded. Therefore, consecutive cases undergoing elective OSR to treat infrarenal AAA were screened for inclusion as described in section 1.7.2.1. Patients with “impending rupture” of AAA on CT, symptomatic AAA, or clinical suspicion of inflammatory/mycotic AAA were excluded from this cohort. All patients in the elective cohort achieved a minimum follow-up of twelve-months from the date of surgery.

9.2.4 OUTCOMES OF INTEREST

The primary outcome in the emergency cohort was thirty-day mortality, and the primary outcome in the elective cohort was twelve-month mortality. Both of these outcomes were chosen as they were felt to represent a clinically relevant timepoint in each cohort, and all patients achieved the required minimum follow-up.

9.2.5 INFLAMMATORY PROFILING

The authors originally intended to examine the day 3 poGPS as the covariate of interest, however on preliminary analyses it became apparent that in excess of 95% of patients in both cohorts had a day 3 poGPS = 2, precluding any meaningful analyses. Therefore, day 3 CRP was chosen as the covariate of interest and patients were sub-grouped for analysis ($\leq 300\text{mg/L}$, $> 300\text{mg/L}$). These thresholds were chosen based on close relation to the median value in each cohort (table 11.1). The third post-operative day was chosen due to this being the typical peak value for CRP following major surgery^{265,266}. Day 3 albumin was also examined, with thresholds of $\leq 25\text{g/L}$, $> 25\text{g/L}$ chosen based on median values (table 11.1). Pre-operative activation of the SIR was assessed using the mGPS, calculated from admission blood results as described in section 1.3.2. All blood results were performed every day routinely as part of existing patient care. Patients with missing day 3 CRP were excluded.

9.2.6 CT-BC ANALYSIS

CT-BC analysis was performed on pre-operative planning CTs as described in section 1.7.3. Thresholds previously reported (Martin et al¹⁵¹) were applied to SMI and SMD to enable sub-grouping of patients for analysis. Due to the extent of retroperitoneal haematoma in rAAA limiting the measurement of skeletal muscle in $>90\%$ of cases, CT-BC analyses were only performed on the elective cohort.

9.2.7 STATISTICAL ANALYSES

Other than initial comparisons, separate analyses were performed on the emergency and elective cohorts. Differences between categorical variables were compared using the linear-by-linear Chi-Squared Test. Covariates of interest were examined using binary logistic regression, where covariates with univariate $p < 0.05$ were included in a multivariate model. Due to the risk of multicollinearity between pre- and post-operative measures of the SIR, in the multivariate models, the variance inflation factor (VIF) was

reported, with $VIF < 5$ considered acceptable in keeping with typical practice²⁶⁷. Statistical analyses were otherwise conducted as described in section 1.7.4.

9.3 RESULTS

There were 511 (222 emergency, 289 elective) procedures screened for inclusion during the study period. Following exclusions, the final study cohort consisted of 167 emergency cases and 207 elective cases. Median (IQR) follow-up was 85 (52) months in the emergency cohort and 63 (57) months in the elective cohort. During the follow-up period there were 92 deaths in emergency patients and 57 deaths in elective patients. The distribution of patients in day 3 CRP sub-groups between emergency and elective cases is shown in figure 9.1; the proportion of patients with day 3 CRP ≤ 300 mg/l vs. >300 mg/L was 56% vs. 44% of patients in the emergency cohort compared with 82% vs. 18% of patients in the elective cohort ($p < 0.001$).

Table 9.1 displays the clinical and pathological covariates sub-grouped by procedure priority and post-operative CRP. Compared with the elective cohort, the emergency cohort were typically older ($p < 0.001$), with a higher proportion of females ($p < 0.05$), a lower rate of diabetes mellitus ($p < 0.05$), cigarette smoking ($p < 0.05$) and statin use ($p < 0.001$), and had a greater rate of low pre-operative haemoglobin ($p < 0.001$), post-operative mesenteric ischaemia ($p < 0.001$), and thirty-day mortality ($p < 0.001$). Median (IQR) day 3 CRP was 292 (131) mg/L in emergency cases compared with 250 (89) mg/L in elective cases ($p < 0.001$), and median (IQR) day 3 albumin was 24 (6) g/L in emergency cases compared with 25 (4) g/L in elective cases ($p < 0.001$). In emergency cases, day 3 CRP >300 mg/L was associated with an increased rate of open surgical repair ($p < 0.001$) and with thirty-day mortality ($p < 0.05$). In elective cases, day 3 CRP >300 mg/L was associated with an increased rate of ischaemic heart disease ($p < 0.001$) and with increased thirty-day ($p < 0.05$) and twelve-month ($p < 0.001$) mortality.

Kaplan-Meier survival plots of are shown in figures 9.2, 9.3, and 9.4. In the combined emergency and elective cohorts, mean (95% CI) survival in the day 3 CRP ≤ 300 mg/l vs. >300 mg/L was 97.6 (89.4 – 105.8) months vs. 67.9 (56.9 – 78.8) months ($p < 0.001$, figure 9.2). In the elective cohort, mean (95% CI) survival in the day 3 CRP ≤ 300 mg/l vs. >300 mg/L was 112.0 (101.8 – 122.2) months vs. 67.2 (54.1 – 80.2) months ($p < 0.001$, figure 9.3). In the sub-group of patients in the elective cohort with low SMI, mean (95% CI) survival in the day 3 CRP ≤ 300 mg/l vs. >300 mg/L was 112.1 (97.9 – 126.4) months vs. 65.4 (47.3 – 83.4) months ($p < 0.01$, figure 9.4).

Table 9.2 displays the associations between clinicopathological factors and thirty-day mortality in the emergency cohort. In patients who suffered thirty-day mortality, there was an increased prevalence of open repair (86% vs. 68%, $p < 0.05$), pre-operative mGPS 2 (46% vs. 20%, $p < 0.05$), and post-operative mesenteric ischaemia (15% vs. 3%, $p < 0.01$). 63% of patients who suffered thirty-day mortality had day 3 CRP $> 300\text{mg/L}$, compared with 39% of thirty-day survivors ($p < 0.05$). On univariate binary logistic regression analyses, open repair ($p < 0.05$), pre-operative mGPS 2 ($p < 0.05$), post-operative mesenteric ischaemia ($p < 0.01$), and day 3 post-operative CRP $> 300\text{mg/L}$ ($p < 0.05$) were associated with increased odds of thirty-day mortality. On multivariate binary logistic regression analyses, only pre-operative mGPS 2 (OR 2.11, 95% CI 1.12 – 3.98, $p < 0.05$) retained independent association with thirty-day mortality.

Table 9.3 displays the associations between clinicopathological factors and twelve-month mortality in the elective cohort. Patients who suffered twelve-month mortality were typically older (age ≥ 75 ; 60% vs. 28%, $p < 0.05$), had a greater prevalence of comorbid ischaemic heart disease (50% vs. 22%, $p < 0.05$), and had a greater prevalence of low SMI (80% vs. 49%, $p < 0.05$). 70% of patients who suffered twelve-month mortality had day 3 CRP $> 300\text{mg/L}$, compared with 15% of twelve-month survivors ($p < 0.01$). On univariate binary logistic regression analyses, age ≥ 75 ($p < 0.05$), ischaemic heart disease ($p < 0.05$), and day 3 post-operative CRP $> 300\text{mg/L}$ ($p < 0.001$) were associated with increased odds of twelve-month mortality. On multivariate binary logistic regression analyses, both age ≥ 75 (OR 5.15, 95% CI 1.25 – 21.30, $p < 0.05$) and day 3 post-operative CRP $> 300\text{mg/L}$ (OR 15.68, 95% CI 3.61 – 68.15, $p < 0.001$) retained independent association with twelve-month mortality.

9.4 DISCUSSION

The results of the present study describe the novel association between peri-operative markers of the SIR and inferior mortality outcomes following intervention for AAA. In the emergency setting, pre-operative mGPS was independently associated with early mortality and in the elective open setting an elevated post-operative CRP was independently associated with late mortality. Therefore, both pre- and post-operative monitoring of the systemic inflammatory response may be warranted in patients undergoing surgery for AAA.

In the present study 24% of patients with an emergency presentation had mGPS 2 on admission, despite the likely relatively short time period between onset of symptoms and blood sampling. This highlights the marked inflammatory response produced by aneurysm rupture itself, even when the effect of surgical repair is not taken into consideration. Furthermore, 18% of patients with an elective presentation had an elevated day 3 CRP (>300 mg/l) and was independently associated with a poorer twelve-month survival. In this setting, the magnitude of inflammatory response was likely caused by the surgical insult is analogous to the acute severe illness in other cohorts. Indeed, an association between magnitude of systemic inflammation and short-term outcomes in cancer and critical illness has been described previously; Lobo and colleagues reported inferior survival and increased risk of organ failure associated with elevated CRP in an unselected cohort of patients admitted to intensive care²⁶⁸. Similarly, Ho and colleagues report increased risk of in-hospital death associated with high CRP in an unselected cohort of patients admitted to intensive care²⁶⁹. Furthermore, CRP appears to predict disease severity and outcomes in infective illnesses^{270–272}, and maximal CRP appears to influence prognosis in patients with pneumonia²⁷³. Lastly, the development of an acute severe illness necessitating critical care stay is known to influence long-term survival outcomes^{274–276}. Therefore, the magnitude of pre-operative and post-operative systemic inflammatory responses are likely to be important factors in determining clinical outcome.

In the present study the magnitude of the post-operative SIR in both emergency (44%) and elective (18%) cases was greater than previous reports of peak CRP following open aortic surgery²⁶⁴. However, the evidence base reviewed by Watt et al was limited by small numbers (234 patients in nine studies) and heterogenous post-operative sampling times. Irrespective, it appears that the CRP response following open aortic surgery exceeds that of the majority of abdominal surgery, and is comparable to major upper gastrointestinal

resection and cardiac surgery²⁶⁴. The extent of dissection, operative time, and requirement for a period of infrarenal ischaemia associated with open surgical repair of AAA are all likely to contribute to the significant inflammatory response to surgery. Therefore, alternative thresholds of day 3 CRP were used in the present study. The complexities of this acute phase protein response in different surgical settings highlight the importance of developing additional operation-specific inflammation-based prognostic scoring systems and monitoring this response, which may ultimately provide a measure by which innovations in treatment can be tested.

The mechanism by which activation of the SIR results in an inferior prognosis is poorly understood. The association between risk of cardiovascular event and inflammation is well described²⁷⁷, however this is typically described in patients with chronic low-grade inflammation which results in increased burden of systemic atherosclerosis. Whether a single major inflammatory insult, such as aneurysm repair or rupture, predisposes patients to increased risk of cardiovascular event is unknown. Similarly, the development of sustained low-grade inflammation following the initial insult is another potential mechanistic pathway.

The determinants of the post-operative SIR are poorly understood but provide a legitimate therapeutic target. In particular, the association between skeletal muscle mass and quality as measured by CT-BC, and the development of increased magnitude of the SIR in the acute and chronic setting, is poorly described. The present study did not demonstrate a relationship between the post-operative SIR and CT-BC parameters. Reisinger *et al* report on a cohort of patients undergoing elective resection colorectal cancer, where patients with low skeletal muscle mass developed a more marked post-operative inflammatory response as measured by calprotectin but not CRP or IL-6²⁷⁸. Calprotectin is not measured routinely in patients with AAA, however this may form the basis of future studies.

To date, immunomodulation in cardiovascular disease has primarily taken place in the non-emergency setting^{174,192}, with increased risk of infection the major drawback. Identifying patients at risk of a greater post-operative SIR may allow for peri-operative adjunctive therapy, such as steroid use, in an attempt to mitigate this response. Pre-operative methylprednisolone appears to reduce the rate of post-implantation syndrome and improve recovery following elective EVAR, however this has not yet translated to widespread clinical practice¹⁷⁶. Data on peri-operative steroid use in the present cohort were not available; this is a potential area for further investigation.

There are several limitations in the present study. The issue of reverse causality in measuring systemic inflammation is an important consideration and limitation of the present study, in particular in the emergency cohort. Whilst adjustments were made for presence of mesenteric ischaemia, the retrospective nature of the present study means that accurate data on infective complications were not available. If the patients with elevated CRP had a higher rate of infective complications, this may account for the survival disadvantage observed. The literature reporting infective complications after aneurysm surgery is limited to the elective setting, where infection rates following OSR may approach 7%²⁷⁹. Therefore, it may be anticipated that the presence of infection would not be a significant factor in the present results. The thresholds of post-operative CRP used for subgroup classification in the present study lack external validation. The present study reported 72% of patients in the emergency cohort undergoing OSR rather than EVAR as their repair strategy. This is slightly higher than contemporary UK data (60% rAAA OSR rate in 2021 across all UK units)³⁷, however is comparable to Scottish national data recorded during the time period of study recruitment. Given the expected difference in physiological insult caused by open or endovascular repair strategies, there is likely to be a difference in post-operative systemic inflammatory response. Finally, the present study is limited by retrospective study design, missing data for some parameters, and low absolute numbers in certain sub-groups

9.5 TABLES

Table 9.1: The association between clinicopathological factors, and survival in patients undergoing emergency or elective open surgical repair of infrarenal AAA (n = 374).

Table 9.2: The association between clinicopathological factors, day 3 post-operative CRP, and thirty-day mortality in patients undergoing emergency repair of ruptured infrarenal AAA (n = 167).

Table 9.3: The association between clinicopathological factors, day 3 post-operative CRP, and twelve-month mortality in patients undergoing elective open surgical repair of infrarenal AAA (n = 207).

Table 9.1: The association between clinicopathological factors, and survival in patients undergoing emergency or elective open surgical repair of infrarenal AAA (n = 374)

				Emergency repair (n = 167)			Elective open surgical repair (n = 207)		
	Emergency repair (n = 167)	Elective open surgical repair (n = 207)	p	Day 3 CRP ≤ 300 mg/L (n = 94, 56%)	Day 3 CRP > 300 mg/L (n = 73, 44%)	p	Day 3 CRP ≤ 300 mg/L (n = 170, 82%)	Day 3 CRP > 300 mg/L (n = 37, 18%)	p
Age ≥ 75	91 (55%)	61 (30%)	<0.001	53 (56%)	38 (52%)	0.58	51 (30%)	10 (27%)	0.72
Female Sex	26 (16%)	16 (8%)	<0.05	15 (16%)	11 (15%)	0.91	15 (9%)	1 (3%)	0.21
Ischaemic Heart Disease	35 (22%)	48 (23%)	0.80	19 (21%)	16 (23%)	0.78	31 (18%)	17 (46%)	<0.001
Diabetes Mellitus	13 (8%)	36 (18%)	<0.05	8 (9%)	5 (7%)	0.71	30 (18%)	6 (16%)	0.82
Cigarette Smoker	39 (25%)	71 (35%)	<0.05	18 (21%)	21 (30%)	0.15	56 (33%)	15 (41%)	0.39
Statin Use	88 (56%)	154 (75%)	<0.001	47 (54%)	41 (59%)	0.50	124 (74%)	30 (81%)	0.36
Open Surgical Repair	120 (72%)	-	-	51 (54%)	69 (95%)	<0.001	-	-	-
BMI ≥25kg/m²	-	146 (71%)	-	-	-	-	116 (69%)	30 (81%)	0.13
Low SMI†	-	102 (50%)	-	-	-	-	81 (48%)	21 (58%)	0.27
Low SMD†	-	46 (23%)	-	-	-	-	39 (23%)	7 (19%)	0.62
Low Pre-op Hb	107 (65%)	38 (19%)	<0.001	66 (70%)	41 (57%)	0.08	33 (20%)	5 (14%)	0.38

Table 9.2: The association between clinicopathological factors, day 3 post-operative CRP, and thirty-day mortality in patients undergoing emergency repair of ruptured infrarenal AAA (n = 167)

				Univariate‡			Multivariate‡			
	Thirty-Day Survivor (n = 132)	Thirty-Day Mortality (n = 35)	<i>p</i> †	OR	95% CI	<i>P</i>	OR	95% CI	<i>p</i>	Variance Inflation Factor
Age ≥ 75	71 (54%)	20 (57%)	0.72	1.15	0.54 - 2.43	0.72	-	-	-	-
Female Sex	22 (17%)	4 (12%)	0.48	0.67	0.21 – 2.08	0.48	-	-	-	-
Ischaemic Heart Disease	27 (21%)	8 (28%)	0.44	1.45	0.58 – 3.61	0.44	-	-	-	-
Diabetes Mellitus	8 (6%)	5 (17%)	0.06	3.03	0.91 – 10.02	0.07	-	-	-	-
Cigarette Smoker	33 (26%)	6 (21%)	0.57	0.75	0.28 – 2.01	0.57	-	-	-	-
Statin Use	71 (56%)	17 (61%)	0.61	1.24	0.54 – 2.86	0.61	-	-	-	-
Open Surgical Repair	90 (68%)	30 (86%)	<0.05	2.80	1.02 - 7.23	<0.05	1.51	0.43 – 5.34	0.53	1.279
Low Pre-op Hb	84 (64%)	23 (68%)	0.66	1.20	0.54 – 2.66	0.66	-	-	-	-
Pre-op mGPS										
0	43 (43%)	7 (29%)								
1	37 (37%)	6 (25%)								
2	19 (20%)	11 (46%)	<0.05	1.92*	1.08 – 3.43	<0.05	2.11*	1.12 – 3.98	<0.05	1.054
Post-op Mesenteric Ischaemia	4 (3%)	5 (15%)	<0.01	5.52	1.40 – 21.83	<0.01	1.91	0.37 – 10.02	0.44	1.060
Day 3 Albumin ≤25g/L	73 (58%)	24 (71%)								
>25g/L	53 (42%)	10 (29%)	0.18	0.57	0.25 – 1.30	0.18	-	-	-	-
Day 3 CRP ≤300mg/L	81 (61%)	13 (37%)								
>300mg/L	51 (39%)	22 (63%)	<0.05	2.69*	1.25 – 5.81	<0.05	2.14*	0.72 – 6.37	0.17	1.279

†: Data presented as absolute value (% of total). ‡: Data presented are odds of suffering thirty-day mortality, with risk of multicollinearity assessed using the VIF. * OR and 95% CI pertain to pre-op mGPS 2 and day 3 CRP > 300mg/L compared to the other categories as reference categories.

Table 9.3: The association between clinicopathological factors, day 3 post-operative CRP, and twelve-month mortality in patients undergoing elective open surgical repair of infrarenal AAA (n = 207).

				Univariate‡			Multivariate‡			
	Twelve-Month Survivor (n = 197)	Twelve-Month Mortality (n = 10)	<i>p</i> †	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	Variance Inflation Factor
Age ≥ 75	55 (28%)	6 (60%)	<0.05	3.87	1.05 – 14.25	<0.05	5.15	1.25 – 21.30	<0.05	1.001
Female Sex	16 (8%)	0 (0%)	0.35	-	-	-	-	-	-	-
Ischaemic Heart Disease	43 (22%)	5 (50%)	<0.05	3.56	1.00 – 12.86	0.05	-	-	-	-
Diabetes Mellitus	35 (18%)	1 (10%)	0.52	0.51	0.06 – 4.17	0.53	-	-	-	-
Cigarette Smoker	68 (35%)	3 (30%)	0.76	0.81	0.20 – 3.22	0.76	-	-	-	-
Statin Use	146 (75%)	8 (80%)	0.72	1.34	0.28 – 6.54	0.72	-	-	-	-
BMI ≥25kg/m²	139 (71%)	7 (70%)	0.95	0.96	0.24 – 3.83	0.95	-	-	-	-
Low SMI	94 (49%)	8 (80%)	<0.05	4.26	0.88 – 20.56	0.07	-	-	-	-
Low SMD	43 (22%)	3 (30%)	0.56	1.51	0.37 – 6.07	0.57	-	-	-	-
Low Pre-op Hb	36 (19%)	2 (20%)	0.91	1.10	0.22 – 5.39	0.91	-	-	-	-
Pre-op mGPS										
0	143 (88%)	9 (100%)								
1	18 (11%)	0 (0%)								
2	1 (1%)	0 (0%)	0.18	-	-	-	-	-	-	-
Day 3 Albumin										
≤25g/L	88 (49%)	7 (78%)								
>25g/L	90 (51%)	2 (22%)	0.09	0.28	0.06 – 1.38	0.12	-	-	-	-

9.6 FIGURES

Figure 9.1: A comparison of post-operative Day 3 CRP in patients undergoing emergency (n = 167) and elective open surgical (n = 207) repair of infrarenal AAA. $p < 0.001$. p value generated through linear-by-linear Chi-Squared analyses comparing absolute proportions within each sub-group based on Day 3 CRP.

Figure 9.2: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing emergency & elective open surgical repair of infrarenal AAA (n = 374). $p < 0.001$ (log-rank method).

Figure 9.3: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing elective open surgical repair of infrarenal AAA (n = 207). $p < 0.001$ (log-rank method).

Figure 9.4: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing elective open surgical repair of infrarenal AAA with low SMI (n = 102). $p < 0.01$ (log-rank method).

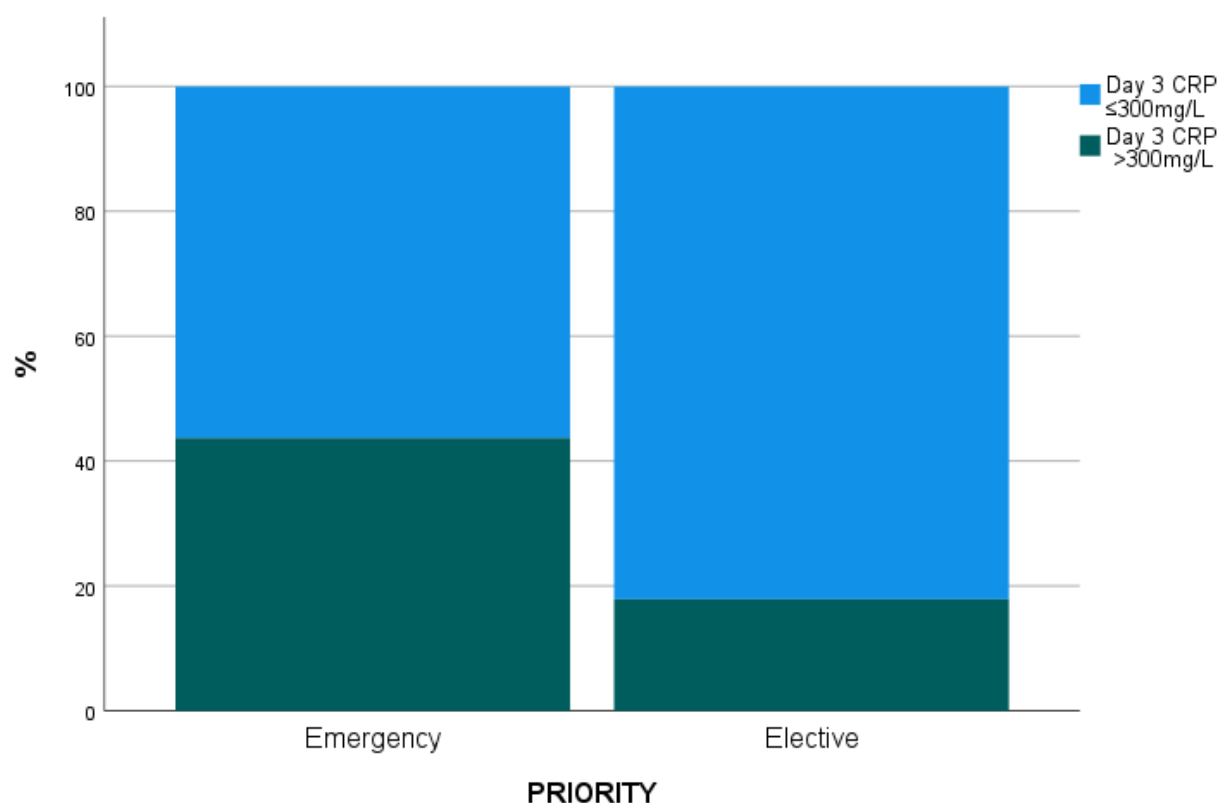
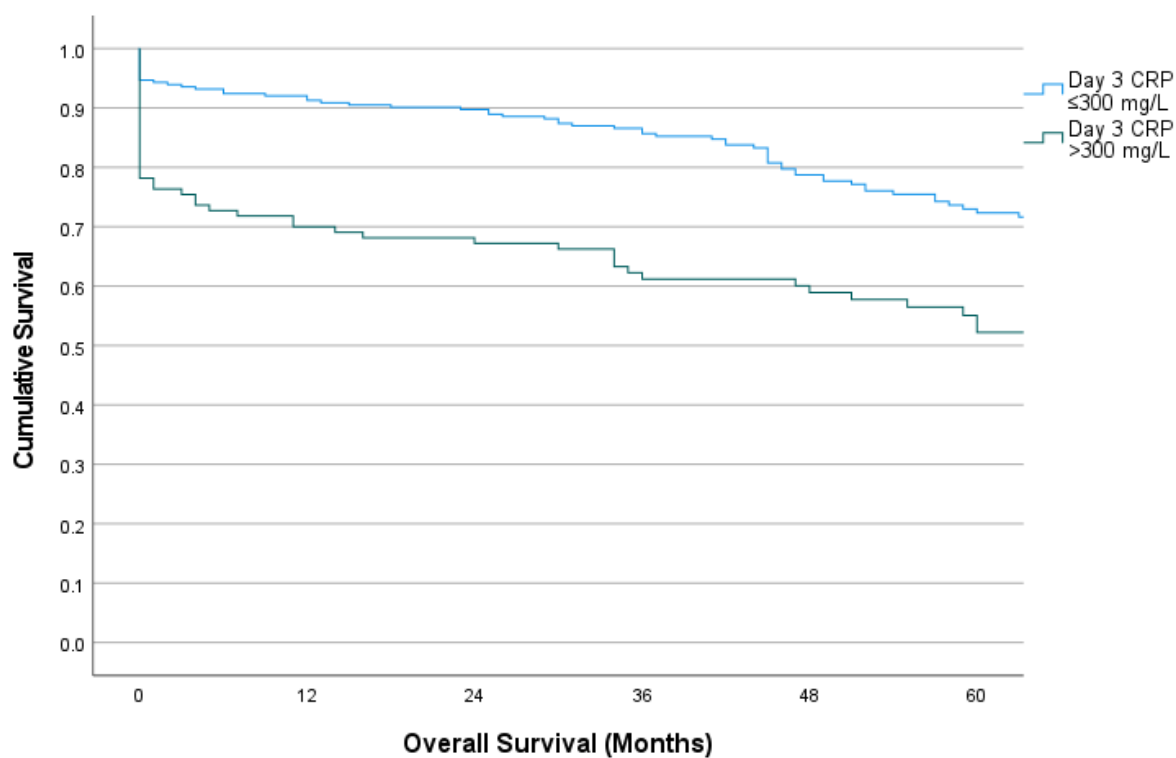
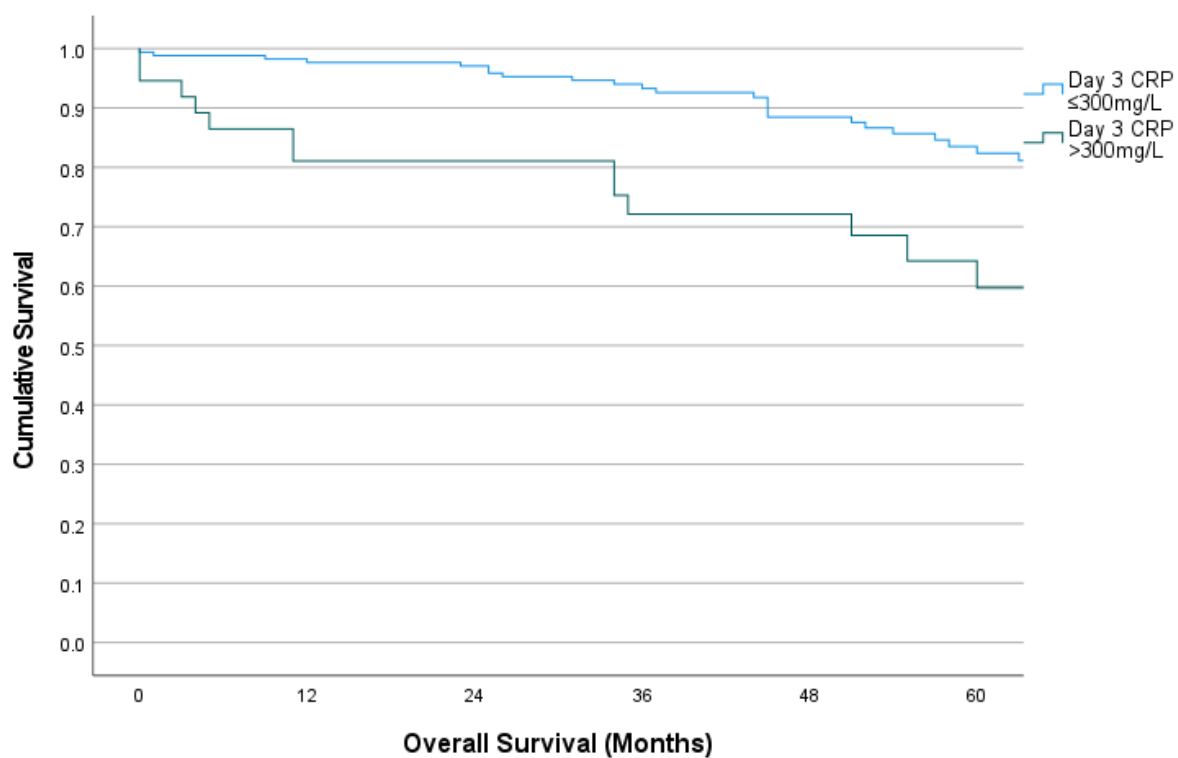


Figure 9.1: A comparison of post-operative Day 3 CRP in patients undergoing emergency ($n = 167$) and elective open surgical ($n = 207$) repair of infrarenal AAA. $p < 0.001$. p value generated through linear-by-linear Chi-Squared analyses comparing absolute proportions within each sub-group based on Day 3 CRP



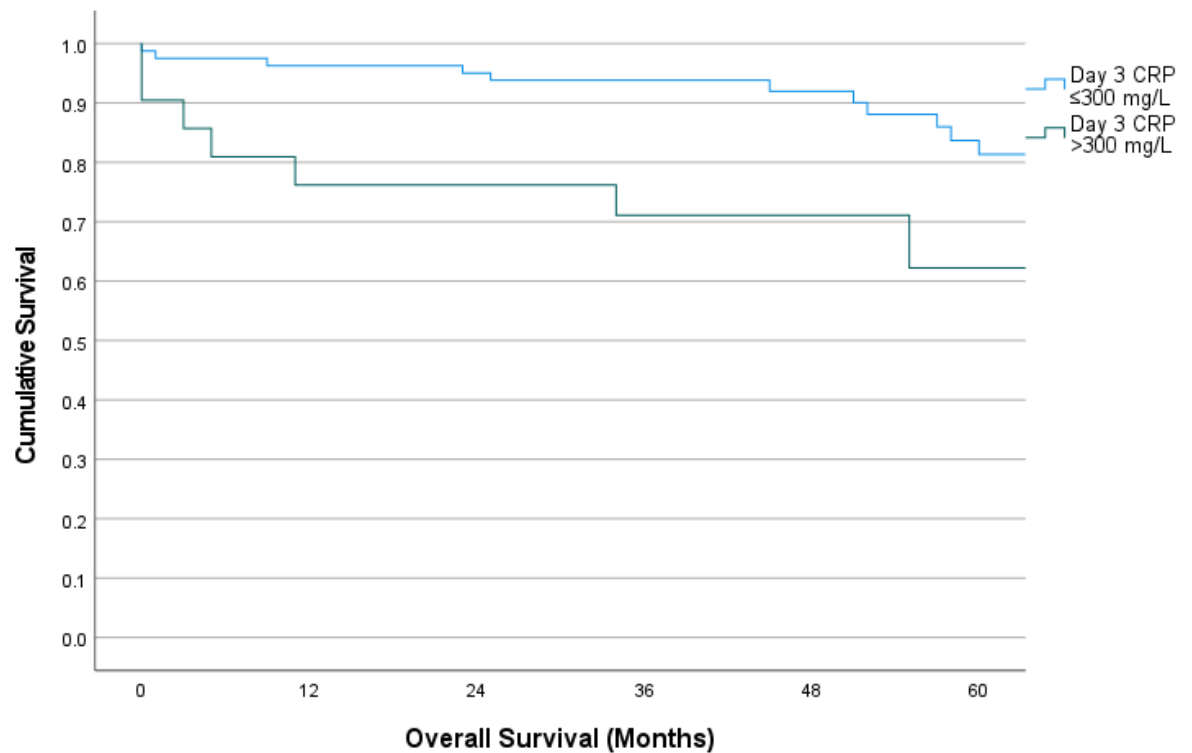
	Number at Risk					
Months	0	12	24	36	48	60
Day 3 CRP ≤300mg/L	264	241	233	194	154	112
Day 3 CRP >300mg/L	110	77	73	59	53	39

Figure 9.2: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing emergency & elective open surgical repair of infrarenal AAA (n = 374). $p < 0.001$ (log-rank method)



	Number at Risk					
Months	0	12	24	36	48	60
Day 3 CRP ≤300mg/L	170	167	165	132	105	73
Day 3 CRP >300mg/L	37	30	30	22	21	14

Figure 9.3: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing elective open surgical repair of infrarenal AAA (n = 207). $p < 0.001$ (log-rank method)



	Number at Risk					
Months	0	12	24	36	48	60
Day 3 CRP ≤ 300 mg/L & Normal SMI	81	78	77	60	49	36
Day 3 CRP > 300 mg/L & Low SMI	21	16	16	12	11	6

Figure 9.4: Kaplan-Meier survival plots and life table of day 3 CRP subgroups in patients undergoing elective open surgical repair of infrarenal AAA with low SMI ($n = 102$). $p < 0.01$ (log-rank method)

10 A SYSTEMATIC REVIEW OF THE NEUTROPHIL:LYMPHOCYTE AND PLATELET:LYMPHOCYTE RATIOS IN PATIENTS WITH LOWER EXTREMITY ARTERIAL DISEASE

10.1 INTRODUCTION

As discussed in section 1.1.2.2, LEAD refers to chronic atherosclerotic disease of the lower limb arteries. It is a common, with an estimated prevalence of 20% in individuals over the age of 50, though there is likely a significant amount of undiagnosed disease²⁸⁰. It is considered the peripheral arterial manifestation of generalised atherosclerosis, and as such there is significant overlap with other atherosclerotic conditions such as CVD and CAD²⁸¹. Atherosclerotic plaque buildup reduces blood flow to peripheral tissues, causing symptoms ranging from exertional ischaemic calf pain (intermittent claudication) to ischaemic rest pain and tissue breakdown/ulceration (CLTI). CLTI is considered the end-stage of LEAD and is associated with significant morbidity and mortality²⁶. Scoring systems based on clinical presentation, such as the Rutherford²⁸² and Fontaine²⁸³ scoring systems, allow classification of severity and can guide the need for intervention. Other scoring systems based on anatomic classification of lesions allow for planning of intervention based on the pattern of disease²⁸, for example the Transatlantic Inter-society Consensus (TASC-II) system which is widely used in both clinical and research settings²⁸⁴.

The management of LEAD is dictated by severity of symptoms and pattern of disease. Medical management consists of risk factor modification and administering appropriate secondary prevention agents²⁸⁵. Reconstruction options may be either open surgery or endovascular procedure (e.g. percutaneous transluminal angioplasty, PTA), with a variety of strategies available dependent on disease and patient factors²⁸⁶.

The role of systemic inflammation in the pathogenesis of atherosclerosis is discussed in chapter 1. NLR is associated with generalised atherosclerosis and impaired outcome in CVD and CAD¹⁷², though is less well described in LEAD. Whilst measures of the acute phase response (mGPS) appear to be associated with inferior survival in several conditions, including patients with cancer and cardiovascular disease^{100,287,288}, specifically in relation to LEAD there is a paucity of evidence.

This review therefore aimed to summarise the contemporary evidence base describing the potential prognostic value of NLR, PLR, and mGPS, in patients with LEAD.

10.2 MATERIALS & METHODS

General systematic review methodology is discussed in section 1.7.1. Both prospective and retrospective studies were included due to the lack of prospective data available. The review protocol was registered with the PROSPERO database (Registration Number: CRD42021292121).

10.2.1 OUTCOMES

The primary outcome of interest was the clinical outcome (measured as overall survival, or amputation-free survival, and rate of major adverse cardiovascular event; MACE or major adverse limb event; MALE) following diagnosis and management of LEAD (either medical, endovascular, surgical) in patients subgrouped by either NLR/PLR/mGPS measured as categorical or continuous variables. NLR, PLR and mGPS were chosen as markers of the SIR due to the body of evidence supporting their association with outcome in a range of conditions.

Secondary outcomes included severity of peripheral arterial disease (measured either as proportion of claudication vs. CLTI, or by objective scoring systems such as Fontaine, Rutherford classifications), and technical success rates in patients undergoing revascularisation (in-stent restenosis; ISR or target vessel revascularisation; TVR). Each secondary outcome was compared between the subgroups of inflammatory parameters.

10.2.2 SEARCH STRATEGY

Search methodology is described in section 1.7.1. The search was conducted on the 1st June 2022; any papers published after this date are not included in this review. The first studies reporting GPS (the precursor to mGPS), NLR, and PLR were published in 2003, 2001, and 2010 respectively^{161,162,289}, therefore studies published before 2001 were excluded. Review articles, case reports, editorials/comments, animal studies, and studies unavailable in English as a full text version were excluded.

Due to the significant overlap between patients suffering from peripheral arterial, cerebrovascular, and coronary artery diseases a broad initial search strategy was employed to ensure sufficient breadth of inclusion. Therefore, the following search string was used:

“(NLR) OR (neutrophil lymphocyte ratio) OR (PLR) OR (platelet lymphocyte ratio) OR (mGPS) OR (modified glasgow prognostic score) OR (GPS) OR (glasgow prognostic score)) AND ((CLI) OR (critical limb ischaemia) OR (CLTI) OR (chronic limb threatening ischaemia) OR (atherosclerosis) OR (coronary artery disease) OR (LEAD) or (lower extremity arterial disease) OR (LEAD) OR (peripheral arterial disease) OR (cerebrovascular disease) OR (CVA) OR (stroke) OR (STEMI) OR (NSTEMI) OR (myocardial infarction) OR (angina) OR (ischaemic heart disease) OR (revascularisation) OR (bypass) OR (angioplasty))”

This search term was applied to study title, key words, and Medical Subject Heading (MeSH) terms. Duplicate results were screened by identifying their PubMed Identifier (PMID), an integer value unique to each record. Relevant review articles underwent bibliography screening to identify additional relevant papers. Abstract screening was performed on the initial results to generate a list of studies to undergo full paper screening for final inclusion. Following initial abstract screening it was determined that there were no relevant studies investigating mGPS as the independent variable, therefore mGPS was not included in the subsequent final review.

10.2.3 DATA EXTRACTION

Data extracted from study documents include:

- Study design (centres, follow-up, prospective/retrospective) and study information (journal, authors, year).
- Baseline clinical and demographic data of patients.
- Classification of "inflamed" vs. "non-inflamed" i.e. cutoff of NLR/PLR (whether using data derived cut-offs or absolute values), or whether analysed as a continuous variable.
- Disease severity based on clinical assessment and using objective scoring systems detailed above.
- Technical success rate of revascularisation (in-stent restenosis, ISR, and target vessel revascularisation, TVR).

- Survival data for overall survival and amputation-free survival, where hazard ratio and 95% confidence intervals are reported these will be extracted.
- Rate of post-procedure major adverse cardiovascular event (MACE) and major adverse limb event (MALE), where hazard ratio and 95% confidence intervals are reported these will be extracted.

The risk of bias in each study was assessed using the Cochrane Quality in Prognostic Studies (QUIPS) tool to systematically assess and record bias. Preliminary literature review showed that due to significant heterogeneity between outcome measures reported and patient selection across all studies meaningful meta-analysis was impossible. Therefore, studies were grouped based on their reporting of each of the outcomes of this review and qualitative analysis performed.

10.3 RESULTS

The study selection process is summarised in the PRISMA diagram (figure 10.1). There were 35 studies included in the final review reporting outcomes on a total of 20396 patients. NLR was investigated in 21 studies, PLR was investigated in two studies, and both NLR & PLR were investigated in 12 studies. There were no studies investigating mGPS. Where reported outcomes qualified for both primary and secondary outcome analysis studies were included in multiple outcome categories. The characteristics of each study and main outcomes are studied in tables 10.1, 10.2, and 10.3.

10.3.1 STUDIES INVESTIGATING CLINICAL OUTCOMES IN LEAD

20 studies reported clinical outcomes in 10826 patients. Study design was prospective in one study, retrospective in 19 studies, and observational in all studies. Seven of these studies reported outcomes in pooled patients without subgrouping based on management strategy, one study reported outcomes following surgical revascularisation, Six studies reported outcomes following endovascular revascularisation, two studies reported outcomes following amputation, and four studies reported outcomes following conservative / medical management.

10.3.2 STUDIES REPORTING OUTCOMES FOLLOWING ALL REVASCUARISATION TECHNIQUES

Erturk et al²⁹⁰ used an NLR > 3.0 as a cutoff in 508 patients with symptomatic LEAD (77.8% claudication, 22.2% CLTI) with >50% angiographic stenosis who underwent medical (52.2%), surgical (15.0%), or endovascular (32.8%) management strategies. Median follow-up was 20 months. Multivariate analysis showed that NLR > 3.0 predicted cardiovascular mortality (HR 2.04, 1.26 – 3.30, $p = 0.004$), however the high NLR cohort had significantly more patients with CLTI than the low NLR cohort (28% vs. 19%, $p = 0.019$).

Spark et al²⁹¹ reported a patient cohort of 149 patients admitted with CLTI undergoing endovascular (22.1%) or open (28.9%) revascularisation, or amputation (21.5%), or conservative management (33.6%). ROC analysis was used to determine an NLR cutoff of ≥ 5.25 , which was associated with increased risk of mortality at a median follow-up of 8.7 months (HR 2.3, 1.2 – 4.2, $p = 0.007$).

González-Fajardo et al²⁹² reported outcomes on 561 patients with CLTI admitted for elective open or endovascular infrainguinal revascularisation, with a median follow-up of 31 months. High NLR was defined as $\text{NLR} > 5.0$. The high NLR cohort had a higher rate of coronary artery disease and congestive cardiac failure. There was a higher proportion of severe disease (Rutherford Category 5) in the High NLR cohort. Amputation-free survival was lower in the high NLR cohort on multivariate analysis (HR 2.325, 1.732 – 3.121).

Sanz et al²⁹³ included 672 patients with CLTI who underwent revascularisation (both surgical and endovascular), though excluded cases with early (<24 hours) post-operative deaths. At 12-month followup, AFS was inferior in patients with $\text{NLR} > 5$ (HR 2.325, 1.732 – 3.121, $p < 0.001$) on multivariate analysis. NLR was subsequently used as part of a larger risk prediction model in a validation cohort of patients.

Uzun et al²⁹⁴ included 602 patients with a clinical diagnosis of LEAD (18.3% CLTI, 81.7% claudication), subsequently diagnosed with $> 50\%$ angiographic stenosis, who then underwent surgical (16.8%), endovascular (34.4%), or medical (48.8%) management. They compared outcomes between patients with a PLR cutoff of 142 based on previously published results. $\text{PLR} > 142$ was associated with long-term cardiovascular mortality (HR 1.03, 1.01 – 1.04, $p = 0.001$).

Pourafkari et al²⁹⁵ retrospectively analysed 1228 patients with LEAD (67.2% CLTI, 22.8% claudication) undergoing both surgical and endovascular revascularisation. ROC analysis for each outcome was performed to determine a cutoff of NLR. High NLR cohort predicted MALE (HR 1.094, 1.071 – 1.118, $p < 0.001$) and 10-year mortality (HR 1.096, 1.072 – 1.120, $p < 0.001$).

Bath et al²⁹⁶ used retrospective registry interrogation to identify 3687 patients undergoing revascularisation (59% PTA, 41% surgical bypass) for LEAD (53.4% intermittent claudication, 14.5% rest pain, 32.1% tissue loss). High NLR (pre-operative) was defined as ≥ 3.65 based on ROC analysis. Pre-operative high NLR was associated with in hospital death (HR 5.359, 1.682 – 17.074, $p = 0.004$) and MACE (HR 2.907, 1.565 – 5.400, $p = 0.0007$) on multivariate analyses.

10.3.3 STUDIES REPORTING OUTCOMES FOLLOWING SURGICAL REVASCLARISATION

González-Hernandez et al²⁹⁷ included 150 patients undergoing surgical bypass to the below knee vessels for LEAD (93% CLTI) who were followed-up for 24 months. High NLR was defined by the 4th quartile. On multivariate analyses, the high NLR cohort was associated with inferior AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$).

10.3.4 STUDIES REPORTING OUTCOMES FOLLOWING ENDOVASCULAR REVASCULARISATION

Chan et al²⁹⁸ included 83 patients undergoing infrapopliteal PTA for CLTI, and defined high NLR as ≥ 5.25 based on previously published results. High NLR was associated with increased mortality at final followup of 12 months (HR 1.97, 1.08 – 3.62, $p = 0.03$).

Chen et al²⁹⁹ reported outcomes in a cohort of patients with LEAD (87.2% CLTI) who also had a diagnosis of chronic kidney disease (defined as $\text{CrCl} \leq 30\text{mL/min/1.73m}^2$) admitted for PTA. Multivariate analysis showed that $\text{NLR} \geq 3.76$ (based on previously published data) was associated with increased risk of death or major amputation (HR 2.07, 1.00 – 4.35, $p < 0.05$).

Huang et al³⁰⁰ reported amputation rates in 736 patients undergoing PTA for CLTI. NLR and PLR at baseline were higher in patients who subsequently underwent amputation following initial revascularisation.

Jhang et al³⁰¹ included 232 octogenarians with LEAD (83% CLTI) undergoing PTA. Baseline NLR and PLR were higher in patients who died at 24-month followup compared with those who were alive. $\text{NLR} > 3.89$ was associated with increased hazard of 24-month mortality (HR 2.679, 1.312 – 5.470, $p = 0.007$).

Lee et al³⁰² observed no difference baseline NLR and PLR between patients who suffered MACE ($n=7$) and those who did not ($n=88$) at 24-month prospective follow-up following PTA and stent placement for intermittent claudication.

Su et al³⁰³ reported outcomes on 195 patients with CLTI (defined as ≥ 4 on the Rutherford Classification) undergoing PTA, subgrouped into high (≥ 8) and low NLR based on receiver operating characteristics (ROC) analysis. The high NLR group had inferior one-year all-cause mortality, cardiac related mortality, MACE, and MALE. These associations were reproduced on multivariate analyses for all-cause mortality (HR 3.599, 1.818 – 7.123,

$p < 0.001$) and cardiac-related mortality (HR 5.286, 2.075 – 13.47, $p < 0.001$), however MACE and MALE were not significant.

10.3.5 STUDIES REPORTING OUTCOMES FOLLOWING AMPUTATION

Wang et al³⁰⁴ subgrouped patients with CLTI who underwent amputation into “poor prognosis” (MI, CVA, 30-day mortality) and control cohorts and reported high pre-operative NLR and PLR in the former. ROC analysis defined cutoffs of NLR and PLR. $\text{NLR} \geq 8.08$ (OR 26.228, 5.801 – 118.583, $p < 0.001$), and $\text{PLR} \geq 237.14$ (3.464, 1.289 – 9.308, $p = 0.014$) predicted “poor-prognosis” outcomes.

Pierre-Louis et al³⁰⁵ included 410 patients undergoing major (above- and below- knee) amputations for CLTI. Patients who went on to require revision of their amputation had a higher post-operative NLR at their initial amputation. Both pre- and post-operative NLR were higher in patients who suffered 30-day mortality, the association in post-operative NLR was reproduced on multivariate analysis.

10.3.6 STUDIES REPORTING OUTCOMES FOLLOWING CONSERVATIVE MANAGEMENT

Taşoğlu et al³⁰⁶ reported outcomes on a cohort of 104 patients with non-operable CLTI (due to technically impossible revascularisation, patient fitness, or patient declining intervention). $\text{NLR} \geq 3.2$ and $\text{PLR} \geq 160$ were determined as cutoffs using ROC analysis. High NLR (OR 5.6, 2.2 – 14.2, $p < 0.001$) and high PLR (OR 3.4, 1.4 – 8.2, $p = 0.005$) were associated with increased risk of amputation. When a composite measure of “high risk” status, defined as high NLR and high PLR was investigated, it was associated with amputation (OR 4.7, 1.7 – 12.6, $p = 0.002$).

Luo et al³⁰⁷ reported outcomes on 172 patients with CLTI without tissue loss who underwent conservative management alone (due to technically impossible revascularisation, patient fitness, or patient declining intervention). $\text{NLR} \geq 3.8$ was selected as a cutoff based on ROC analysis. High NLR predicted need for amputation on multivariate analysis (HR 1.140, 1.086 – 1.197, $p < 0.001$). 3-year AFS was 43.2% vs. 82.7% in the high vs. Low NLR groups ($p < 0.001$).

Amrock et al³⁰⁸ evaluated 556 participants who were part of a multicentre research registry, and diagnosed LEAD through measuring ankle:brachial pressure index (ABPI)

with a cutoff of ≤ 0.9 . These patients did not present with symptoms of LEAD as their means of entering into this study. At a median followup of 97.2 months, NLR (HR 1.20, 1.04 – 1.39, $p = 0.012$) predicted all-cause mortality.

Erdoğan et al³⁰⁹ reported outcomes on 268 patients with CLTI who were unable to undergo revascularisation and therefore received optimal medical therapy. Clinical progression of disease was used to define "non-response" as the primary outcome. ROC analysis determined cutoffs for NLR and PLR. Multivariate analyses showed that $\text{NLR} \geq 4.63$ (HR 3.983, 1.973 – 8.042, $p < 0.001$) and $\text{PLR} \geq 151.24$ (HR 2.254, 1.163 – 4.371, $p = 0.016$) were associated with non-response to medical therapy.

10.3.7 STUDIES INVESTIGATING SEVERITY OF LEAD

14 studies reported the severity of LEAD in 13632 patients (Table 10.2). Study design was prospective in one study, retrospective in 13 studies, and observational in all studies. Nine of these studies reported clinical measures of disease severity assessment; in the remaining five studies angiographic measures of disease severity assessment were reported.

10.3.8 STUDIES REPORTING CLINICAL ASSESSMENT OF SEVERITY

Bath et al²⁹⁶ used retrospective registry interrogation to identify 3687 patients undergoing revascularisation (59% PTA, 41% surgical bypass) for LEAD (53.4% intermittent claudication, 14.5% rest pain, 32.1% tissue loss). High NLR (pre-operative) was defined as ≥ 3.65 based on ROC analysis. There was a higher rate of more severe disease (tissue loss 56.47% vs. 27.33%, $p < 0.001$) in the high NLR vs. low NLR groups.

Velioglu et al³¹⁰ compared 75 patients with symptomatic LEAD (diagnosed by clinical assessment and ABPI) seen at outpatient clinics with 75 healthy controls. NLR was found to be higher in the LEAD cohort, however NLR did not predict LEAD on multivariate analysis.

Demirdal et al³¹¹ recruited 280 patients who were admitted to hospital for management of diabetic foot sepsis. LEAD was diagnosed following review by vascular surgeon and imaging. NLR was higher in the LEAD group ($p = 0.007$), and PLR demonstrated a non-significant trend towards being higher in the LEAD group.

Belaj et al³¹² calculated the “derived NLR” (dNLR) by dividing the neutrophil count by the difference between the leucocyte count and the neutrophil count. This was performed on 1995 patients who were managed for LEAD by any management strategy. ROC analysis was used to determine a cutoff of dNLR to predict CLTI. dNLR > 2.5 was associated with CLTI (OR 1.6, 1.3 – 2.0, $p < 0.01$).

Demirtas et al³¹³ prospectively recruited 82 consecutive patients undergoing investigation and management for LEAD. Disease severity was classified according to Fontaine’s stages, with baseline NLR similar between different stages.

Gary et al³¹⁴ retrospectively analysed 2121 patients treated for LEAD (32.1% CLTI, 67.9% claudication). PLR > 150 was determined as a cutoff based on ROC analysis. There was a higher proportion of patients with CLTI and tissue loss in the high PLR cohort. PLR > 150 was associated with CLTI on multivariate analysis (OR 1.9, 1.7 – 2.1, $p < 0.001$). The same patient population was subsequently analysed in terms of NLR³¹⁵. NLR > 3.95 was determined as a cutoff based on ROC analysis. There was a higher proportion of patients with CLTI in the high NLR cohort. NLR > 3.95 was associated with CLTI on multivariate analysis (OR 2.5, 2.3 – 2.7, $p < 0.001$).

Erturk et al²⁹⁰ used an NLR > 3.0 as a cutoff in 508 patients with symptomatic LEAD (77.8% claudication, 22.2% CLTI, defined by Fontaine classification). The high NLR cohort had significantly more patients with CLTI than the low NLR cohort (28% vs. 19%, $p = 0.019$).

Pourafkari et al²⁹⁵ retrospectively analysed 1228 patients with LEAD (67.2% CLTI, 22.8% claudication) undergoing both surgical and endovascular revascularisation. In the high NLR tertile there was a significantly higher proportion of patients with CLTI.

10.3.9 STUDIES REPORTING ANGIOGRAPHIC ASSESSMENT OF SEVERITY

Celebi et al²⁰³ reported outcomes in 280 patients referred for invasive angiography to confirm LEAD based on clinical suspicion. The pattern of disease as per TASC-II criteria was used to diagnose disease severity; TASC A/B were considered mild-moderate, TASC C/D were considered advanced. Patients without significant disease on angiography had lower baseline NLR. NLR was higher in TASC C/D patients compared to TASC A/B, and NLR predicted advanced disease on multivariate analysis (HR 0.896, 0.845 – 0.950, $p < 0.001$).

Teperman et al³¹⁶ retrospectively analysed 733 patients who had been referred for invasive angiography due to symptoms of LEAD (85.4% claudication, 14.6% CLTI). Patients were subgrouped based on tertiles of NLR. There was a higher proportion of CLTI in the high NLR tertile. Severe multilevel disease (defined as >70% stenosis in both supra- and infra-popliteal segments) was associated with high NLR tertile on univariate analysis (OR 1.11, 1.03 – 1.19, $p = 0.007$), however this was not reproduced on multivariate analysis (OR 1.07, 1.00 – 1.15, $p = 0.056$).

Hamur et al³¹⁷ reported outcomes on 211 patients with symptomatic LEAD (67.8% claudication, 32.1% CLTI) who were referred for invasive angiography with a primary outcome of angiographic chronic total occlusion (CTO). Baseline NLR was higher in patients with angiographic CTO, however this was not reproduced on multivariate analysis (OR 0.620, 0.220 – 1.745, $p = 0.365$).

Aykan et al²⁰⁴ retrospectively reported outcomes on 343 patients undergoing invasive angiography who were grouped based on TASC-II criteria of their disease. Patients with TASC A/B disease had significantly lower baseline NLR than those with TASC C/D disease. ROC analysis resulted in a cutoff of NLR > 3.05 to predict TASC C/D disease, which showed significant association on multivariate analysis (OR 1.914, 1.515 – 2.418, $p < 0.001$).

10.3.10 STUDIES INVESTIGATING TECHNICAL SUCCESS OF REVASCULARISATION

Eight studies reported technical success of revascularisation in 1587 patients (Table 10.3). Study design was prospective in one study, retrospective in seven studies, and observational in all studies. Seven of these studies reported outcomes in patients undergoing endovascular management, in the one remaining study patients underwent surgical management.

10.3.11 STUDIES REPORTING SUCCESS OF ENDOVASCULAR MANAGEMENT

Lee et al³⁰² reported TVR (>80% stenosis on colour-coded duplex sonography) on 95 patients undergoing PTA and stent placement for intermittent claudication with 24-month prospective follow-up. The absolute values of NLR and PLR were higher in patients who developed TVR than those who did not. ROC-derived cutoffs to predict TVR were NLR $\geq$

2.75 and $\text{PLR} \geq 91$. On multivariate analysis high NLR (HR 3.1, 1.3 – 7.7, $p = 0.01$) and high PLR (HR 3.0, 1.1 – 8.5, $p = 0.04$) were associated with $\text{TVR} < 24$ months.

Zhen et al³¹⁸ reported 6 month primary patency rates in 70 patients who underwent femoro-popliteal PTA with drug coated balloons for LEAD (42.9% CLTI and 57.1% claudication), with restenosis defined on colour-coded duplex sonography. In the group with primary patency < 6 months there was lower baseline PLR and a non-significant trend towards lower baseline PLR. Baseline PLR was associated with inferior 6-month primary patency on multivariate analysis (OR 1.008, 1.001 – 1.016, $p = 0.031$).

Zhen et al³¹⁹ also reported 6-month primary patency rates on a cohort of patients with LEAD (45.1% CLTI, 54.9% claudication) undergoing femoro-popliteal PTA with drug coated ($n = 44$) and uncoated ($n = 62$) balloons. Post-procedure NLR predicted 6-month primary patency on multivariate analysis, with a lower NLR conferring a superior result (OR 1.589, 1.078 – 2.343, $p = 0.019$).

Chang et al³²⁰ reported rates of ISR (< 12 months, early, and > 12 months, late) in patients undergoing PTA and stent insertion for femoropopliteal CTO. 180 patients with CTO were included (60 claudication, 120 CLTI), with ROC analysis producing a cutoff of $\text{NLR} \geq 3.62$. Multivariate analysis showed that high NLR predicted early ISR (OR 1.703, 1.521 – 2.063, $p = 0.002$).

Nakazawa et al³²¹ retrospectively assessed 479 patients with LEAD undergoing first-time stenting of the femoral-above knee popliteal arteries, with a primary outcome of ISR within 12 months on either colour-coded duplex sonography or angiography. NLR was similar between ISR and no-ISR groups, and multivariate analysis did not demonstrate NLR as a significant covariate.

Teperman et al³¹⁶ retrospectively analysed 733 patients who had been referred for invasive angiography due to symptoms of LEAD (85.4% claudication, 14.6% CLTI). Of these, 424 underwent intervention (PTA) and had followup data available. Patients were subgrouped based on tertiles of NLR. At a median followup of 10.4 months there was no difference in TVR between NLR tertiles.

Chan et al²⁹⁸ included 83 patients undergoing infrapopliteal PTA for CLTI, and defined high NLR as ≥ 5.25 based on previously published results. High NLR cohort was not associated with 12-month primary patency (HR 1.03, 0.74 – 1.43, $p = 0.87$).

10.3.12 STUDIES REPORTING SUCCESS OF SURGICAL MANAGEMENT

González-Hernandez et al²⁹⁷ included 150 patients undergoing surgical bypass to the below knee vessels for LEAD (93% CLTI) who were followed-up for 24 months. High NLR was defined as the 4th quartile. On multivariate analyses, the high NLR cohort was associated with inferior primary patency (HR 1.77, 1.01 – 3.10, $p = 0.04$), with a non-significant association with primary assisted patency (HR 1.70, 0.89 – 3.24, $p = 0.10$).

10.3.13 RISK OF BIAS ASSESSMENT

The summary of the risk of bias assessment using the QUIPS tool is shown in table 10.4. High risk of bias was judged in 17 of 204 (8%) domains, moderate risk in 119 of 204 (59%) domains, and low risk in 68 of 204 (33%) domains.

10.4 DISCUSSION

The present systematic review identified 20 studies that reported clinical outcomes in relation to NLR and PLR; all reported inferior clinical outcomes in patients with increased inflammatory parameters. Increased NLR and PLR were also associated with more severe LEAD in 13 of 14 studies (93%), and with inferior revascularisation outcomes in seven of eight studies (88%).

The precise mechanism by which elevated NLR or PLR confer inferior clinical outcomes is incompletely understood. Inflammatory cytokines such as interleukin-6 (IL-6) are known to have on the rate of cardiovascular events¹⁴⁷. Elevated IL-6 has been associated with increased levels of fatigue and poor quality of life, though this is not specifically described in LEAD patients³²². IL-6 is expressed by vascular endothelial cells in response to oxidative stress, which is a potential mechanism by which atherosclerotic disease may lead to increase morbidity and mortality³²³.

It appears that in patients with established atherosclerotic disease, the use of immunomodulation can reduce the future risk of cardiovascular events as well as lower the NLR. The CANTOS trial described promising results in patients with IHD undergoing IL-1 β blockade¹⁷³, however these results have not yet been reproduced in patients with LEAD. Follow-up studies with alternative immunomodulatory agents are eagerly awaited²¹⁷, and the results may prove transferable to patients with LEAD. Glucocorticoids have been used to suppress periprocedural inflammation in patients undergoing intervention for abdominal aortic aneurysm¹⁷⁶, however remain underreported in patients with LEAD.

The association between LEAD severity and NLR or PLR highlights the important role of inflammation as a key aetiopathological component of atherosclerosis⁴⁸. The rate of atherosclerotic progression appears to be related to levels of pro-inflammatory cytokines, though this has largely been demonstrated in pre-clinical studies³²⁴. Due to the established progression of LEAD, early identification of patients with increased NLR and PLR when presenting with less severe disease may allow for modulation of their chronic inflammation and resultant prevention of disease progression. Prospective evaluation of this relationship in LEAD patients with clinically meaningful outcomes such as AFS and MACE is lacking.

Treatment success rate following revascularisation is complex and multifactorial.

Neointimal hyperplasia is a key component of ISR³²⁵, which is modulated by the use of

drug-coated technology, however this is the subject of some current controversy³²⁶. Pre-clinical models of vein graft failure highlight a complex inflammatory insult to vascular endothelium resulting in accelerated atherosclerotic plaque deposition and a propensity to thrombosis³²⁷. Thrombus itself is known to promote inflammation due to a large pro-inflammatory cytokine content, in particular IL-6³²⁸, and additionally thrombosis is an established consequence of inflammation^{329,330}. Current secondary prevention measures focus on modulation of the coagulation cascade, with recent evidence supporting the concomitant use of both anti-coagulant and anti-platelet agents⁶⁶. Identification of patients with increased levels of NLR and PLR may allow for tailored secondary prevention strategies which focus on suppressing the inflammatory environment rather than platelet aggregation.

Historically studies reporting technical success of revascularisation have been criticised for reporting rates of graft or vessel patency whilst neglecting clinically meaningful outcomes such as limb salvage rates, quality of life, and functional performance. Whilst some of the studies in this review report patency rates alone, there are also seven studies included which report either MALE, AFS, or rate of amputations (the inverse of limb salvage rate). This strengthens the clinical application of their conclusions and supports the use of NLR and PLR as a meaningful clinical risk assessment tool. Furthermore, NLR and PLR are attractive options for use as prognostic markers as they are easily obtained through investigations which are already typically part of routine clinical practice.

The present review initially attempted to describe the effect that mGPS has on LEAD, however, the lack of any relevant studies made this impossible. As described in chapters 5 and 6, SIG is another potentially attractive option to quantify the systemic inflammatory response, as it may offer a more comprehensive assessment of systemic inflammation, however further evaluation in this patient cohort is required.

The majority of studies in this review employed a retrospective study design and as such the inherent limitations of retrospective studies apply to their findings.

A proportion of the studies included in this review include patients with intermittent claudication in their reporting of outcomes. Worldwide there is significant heterogeneity in management of claudication, with advocates for both conservative and more aggressive strategies. The inclusion of claudication by some authors limits the generalisability of these results.

A major limitation which affects all studies in this review is the lack of consensus definition on a cut-off for high/low NLR and PLR. Methods used include ROC analysis, data-derived cut-offs (e.g., tertiles), or absolute values based on previous studies. Each of these methods limits the generalisability of the results beyond the population studied.

Performing meaningful quantitative analysis is impossible given the significant heterogeneity in interventions, populations, and outcomes reported by the studies in this review.

Any inflammatory parameter measured in LEAD patients will be confounded by tissue loss with secondary infection. Whilst some studies specifically excluded these patients, this was not universal and so may impact upon the reliability of their results. Universal application of the Society for Vascular Surgery Wound, Ischaemia, and Foot Infection Score (SVS WIFI)³³¹ was not performed; this would enable more accurate assessment of heterogeneity between studies.

The studies included in this review support the role of elevated NLR and PLR as key components influencing the clinical outcomes, severity, and success of treatment in patients with LEAD. The use of these easily accessible, cost effective and routinely available markers is supported by the present review.

10.5 TABLES

Table 10.1: Studies investigating the association between clinical outcomes and NLR or PLR in patients with LEAD following A) all methods of management B) surgical revascularisation C) endovascular revascularisation D) amputation E) conservative management.

Table 10.2: Studies investigating the association between disease severity and NLR or PLR in patients with LEAD based on A) clinical assessment and B) angiographic assessment.

Table 10.3: Studies investigating the association between the technical success of revascularisation strategies and NLR or PLR in patients with LEAD in patients undergoing A) endovascular treatment and B) surgical treatment.

Table 10.4: Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review.

Table 10.1 Studies investigating the association between clinical outcomes and NLR or PLR in patients with LEAD following A) all methods of management B) surgical revascularisation C) endovascular revascularisation D) amputation E) conservative management

Author	PMID	Population	<i>n</i>	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Followup	Main Findings
A).										
Erturk et al (2014)	24685686	Symptomatic LEAD (77.8% IC, 22.2% CLTI) with >50% angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	High NLR associated with MACE on multivariate analysis (HR 2.04, 1.26 – 3.30, $p = 0.004$)
Spark et al (2010)	20573475	All CLTI admissions	149	Retrospective	Single	All-cause mortality	NLR	Tertiles, ROC (5.25)	8.7 months	Inferior OS in high NLR group, NLR > 5.25 associated with increased mortality on multivariate analysis (HR 2.3, 1.2 – 4.2, $p = 0.007$)
González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	AFS	NLR	Absolute value (5.0)	31 months	Inferior 5 year OS and AFS in high NLR group, high NLR associated with inferior 5-year AFS on multivariate analysis (HR 2.325, 1.732 – 3.121)
Sanz et al (2016)	26602223	All CLTI (Rutherford > 4) patients	672	Retrospective	Single	AFS 12 months post-procedure	NLR	NLR > 5 (data derived)	12 months	NLR > 5 predicted increased risk of amputation or death at

		undergoing open or endo revascularisation (excluded deaths <24hrs)								12 months on multivariate analysis (HR 2.325, 1.732 – 3.121, $p < 0.001$)
Uzun et al (2017)	28344615	LEAD with >50% angiographic stenosis (18.3% CLTI, 81.7% IC) undergoing open (16.8%), endo (34.4%), or medical (48.8%) management	602	Retrospective	Single	MACE	PLR	Absolute value of PLR	33.8 months	Rate of MACE higher in High PLR group, PLR > 142 associated with MACE on multivariate analysis (HR 1.03, 1.01 – 1.04, $p = 0.001$)
Pourafkari et al (2018)	29848209	All patients with LEAD (67.2% CLTI) undergoing PTA / bypass	1228	Retrospective	Multi	MALE, MACE, all-cause mortality	NLR	Tertiles, ROC	NR	High NLR tertile associated with CLTI, increased risk of MALE in high NLR tertile (HR 1.094, 1.071 – 1.118, $p < 0.001$), increased risk of 10-year mortality in high NLR tertile (HR 1.096, 1.072 – 1.120, $p < 0.001$)
Bath et al (2020)	31882318	Elective PTA (59%) / bypass (41%) for LEAD (53.4% IC, 14.5% rest pain, 32.1% tissue loss)	3687	Retrospective	Multicentre (registry interrogation)	Association between NLR and severity, in hospital death/cardiac event	NLR	ROC	NR	Higher NLR in more severe disease (TL vs. rest pain vs. IC), Baseline raised NLR associated with in hospital death (HR 5.359, 1.682 – 17.074, $p = 0.004$) and cardiac

										event (HR 2.907, 1.565 – 5.400, $p = 0.0007$)
B).										
González-Hernández et al (2021)	33496158	LEAD (93% CLTI, 7% claudicants) undergoing infragenicular vein bypass	150	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE), graft patency, AFS	NLR	Quartiles (Q4 = high, Q1-3 = low)	24 months	High NLR associated with worse AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$), patency loss (HR 1.77, 1.01 – 3.10, $p = 0.04$)
C).										
Chan et al (2014)	24816510	All patients undergoing infrapopliteal PTA for CLTI	83	Retrospective	Single	Technical success (<50% residual stenosis, restored perfusion), OS, 12-month primary patency, AFS	NLR	Absolute value (5.25)	12 months	High NLR associated with increased 1-year mortality (HR 1.97, 1.08 – 3.62, $p = 0.03$). NS values for primary patency and AFS
Chen et al (2016)	27713601	LEAD patients with CKD (CrCl ≤ 30 mL/min/1.73m ²) admitted for PTA (12.8% IC, 87.2% CLTI)	148	Retrospective	Single	AFS	NLR, PLR	Absolute value	8.6 months	High NLR cohort associated with increased risk AFS (HR 2.23, 1.03 – 4.82, $p = 0.04$)
Huang et al (2019)	31415395	CLTI undergoing PTA	736	Retrospective	Single	Amputation rate	NLR, PLR	-	NR	Higher NLR & PLR at baseline in patients who required amputation, PLR significant at

										predicting amputation in decision tree analysis
Jhang et al (2020)	33177036	LEAD (83% CLTI) undergoing lower limb PTA	232	Retrospective	Single	2-year “longevity”	NLR, PLR	ROC (NLR > 3.89)	24 months	High NLR cohort associated with increased 2 year mortality (HR 2.679, 1.312 – 5.470, $p = 0.007$)
Lee et al (2020)	32503291	IC patients undergoing SFA stent	95	Prospective	Single	Target Vessel Restenosis (TVR) on duplex within 2 years, MACE	NLR, PLR	ROC	24 months	NLR associated with TVR (HR 3.1, 1.3 – 7.7, $p = 0.01$), PLR associated with TVR (HR 3.0, 1.1 – 8.5, $p = 0.04$)
Su et al (2021)	34043672	CLTI undergoing PTA	195	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE)	NLR	ROC (NLR ≥ 8)	NR	High NLR associated with increased 1-year mortality, MALE, MACE ($p < 0.05$). Reproduced on multivariate analysis.
D).										
Wang et al (2017)	28042626	ALI (28.5%) and CLTI (71.5%, Rutherford V/VI) undergoing minor (11.1%) and major (88.9%) amputation	270	Retrospective	Single	“poor prognosis” group	NLR, PLR	ROC	NR	Higher NLR and PLR in “poor prognosis” group, reproduced on multivariate
Pierre-Louis et al (2019)	30339899	Patients undergoing major amputation	410	Retrospective	Multicentre	30-day mortality, need for revision	NLR	-	NR	Post-op NLR higher in patients requiring revision, Pre- and Post-op NLR higher in

										patients who died within 30-days, post-op NLR associated with 30-day mortality on multivariate analysis
E).										
Taşoğlu et al (2014)	23393289	CLTI patients with non-operable disease (due to non-reconstructable, fitness, declined)	104	Retrospective	Single	Amputation, overall survival	NLR, PLR	ROC, patients group into “low/medium/high risk” based on 0/1/2 being elevated	NR	Composite outcome of “High risk” (High NLR & High PLR) predicted amputation (OR 4.7, 1.7 – 12.6, $p = 0.002$)
Luo et al (2015)	26017794	CLTI patients without tissue loss undergoing medical management	172	Retrospective	Single	AFS at 36 months	NLR	ROC	36 months	Higher rate of total amputations, BKA, Toe amp in High NLR group, inferior survival in high NLR group, NLR predicted amputation on multivariate (HR 1.140, 1.086 – 1.197, $p < 0.001$)
Amrock et al (2016)	26762418	Patients with LEAD diagnosed by ABPI (<0.9)	556	Retrospective	Multicentre (registry interrogation)	All cause mortality and cardiovascular mortality	NLR	NR	97.2 months	NLR predicted all cause mortality (HR 1.20, 1.04 – 1.39, $p = 0.012$)
Erdoğan et al (2021)	33427105	CLTI with no revasc option, medical management	268	Retrospective	Single	Response to medical treatment (less pain, ulcer healing)	NLR, PLR	ROC (NLR ≥ 4.63 , PLR ≥ 151.24)	NR	High NLR associated with no response (HR 3.983, 1.973 – 8.042, $p < 0.001$), high PLR associated with no response (HR 2.254,

										$1.163 - 4.371, p = 0.016)$

Table 10.2 Studies investigating the association between disease severity and NLR or PLR in patients with LEAD based on A) clinical assessment and B) angiographic assessment

Author	PMID	Population	<i>n</i>	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
(A).										
Bath et al (2020)	31882318	Elective PTA (59%) / bypass (41%) for LEAD (53.4% IC, 14.5% rest pain, 32.1% tissue loss)	3687	Retrospective	Multicentre (registry interrogation)	Association between NLR and severity, in hospital death/cardiac event	NLR	ROC	NR	Higher NLR in more severe disease (TL vs. rest pain vs. IC), Baseline raised NLR associated with in hospital death (HR 5.359, 1.682 – 17.074, $p = 0.004$) and cardiac event (HR 2.907, 1.565 – 5.400, $p = 0.0007$)
Velioglu et al (2019)	30924393	OP clinic LEAD patients (CLTI vs. IC NR) and controls	75	Retrospective	Single	Difference in NLR/PLR in LEAD vs. control	NLR, PLR	Cases vs. controls	NR	NLR higher in LEAD patients ($p = 0.034$), NLR & PLR not significant at predicting LEAD on multivariate analysis
Demirdal et al (2018)	30176260	All patients hospitalised with foot sepsis and known diabetes	280	Retrospective	Single	Role of NLR/PLR in predicting LEAD	NLR, PLR	ROC		NLR significantly higher in patients with LEAD ($p = 0.007$)
Belaj et al (2015)	26058674	All patients treated for LEAD (27.6% CLTI)	1995	Retrospective	Single	Association of dNLR with CLTI	dNLR (derived NLR)	dNLR > 2.5 (ROC analysis)	NR	Higher rate of CLTI in patients with dNLR >2.5, dNLR >2.5 predicted CLTI on multivariate analysis (OR 1.6, 1.3 – 2.0, $p < 0.01$)

González-Fajardo et al (2014)	24559786	Patients admitted with CLTI for revascularisation (open or PTA)	561	Retrospective	Single	Association of NLR with Rutherford Category	NLR	Absolute value (5.0)	31 months	Higher proportion of Rutherford 5 disease in the NLR > 5.0 cohort (54.8% vs 71.4%, $p = 0.002$)
Demirtas et al (2014)	24522438	Consecutive LEAD patients without tissue loss (Fontaine I 36%, Fontaine II 28%, Fontaine III 36%)	50	Prospective	NR	Association between NLR and disease severity (Fontaine stage)	NLR	Fontaine stage	NR	No difference in NLR in different Fontaine stages (I-III)
Gary et al (2013)	23457609	LEAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between NLR and rate of CLTI	NLR	Tertiles, ROC	NR	Rate of CLTI higher in High NLR Tertile, NLR > 3.95 (ROC) associated with increased risk of CLTI in multivariate model (OR 2.5 2.3 – 2.7, $p < 0.001$)
Gary et al (2013)	23844064	LEAD patients diagnosed clinically, admitted for management, 32.1% CLTI, 67.9% IC	2121	Retrospective	Single	Association between PLR and rate of CLTI	PLR	Tertiles, ROC	NR	Rate of CLTI higher in High PLR Tertile, PLR > 150 (ROC) associated with increased risk of CLTI in multivariate model (OR 1.9, 1.7 – 2.1, $p < 0.001$)
Erturk et al (2014)	24685686	Symptomatic LEAD (77.8% IC, 22.2%)	508	Retrospective	Single	MACE	NLR	Absolute value (3.0)	20 months	Higher proportion CLTI in high NLR cohort

		CLTI) with >50% angiographic stenosis managed by medical (52.2%), open (15.0%), PTA (32.8%)								
Pourafkari et al (2018)	29848209	All patients with LEAD (67.2% CLTI) undergoing PTA / bypass	1228	Retrospective	Multi	Rate of CLTI	NLR	Tertiles	NR	Rate of CLTI 86.8% in high NLR tertile vs. 64.9% and 49.9% in mid and low tertiles ($p < 0.001$)
(B).										
Celebi et al (2020)	32445291	Patients referred for angiography to diagnose LEAD (TASC II definition)	280	Retrospective	Single	Presence of TASC II LEAD	NLR	-	NR	NLR predicted “advanced” (TASC C/D) LEAD (OR 0.896. 0.845 – 0.950, $p < 0.001$), NLR higher in TASC C/D vs. TASC A/B. NLR higher in LEAD vs. no LEAD.
Teperman et al (2016)	27865186	Symptomatic LEAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	733	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	Higher proportion of CLTI in high NLR tertile, higher proportion of multilevel disease in high NLR tertile, no difference in rates of target vessel revascularisation in NLR tertiles

Hamur et al (2016)	27059289	Symptomatic LEAD (67.8% IC, 32.1% CLTI) referred for angiography with ipsilateral lesion >50% stenosis	211	Retrospective	Single	Determinants of angiographic CTO	NLR	CTO yes or no	NR	Higher baseline NLR in CTO group, not reproduced on multivariate
Aykan et al (2016)	27004700	Patients undergoing angiography with suspected LEAD	343	Retrospective	Single	Complexity of disease (TASC-II classification)	NLR	TASC-A/B/C/D	NR	Higher baseline NLR in TASC-C&D vs. TASC-A&B, NLR predicted TASC-C&D category on multivariate (HR1.914, 1.515 – 2.418, $p < 0.001$)

Table 10.3 Studies investigating the association between the technical success of revascularisation strategies and NLR or PLR in patients with LEAD in patients undergoing A) endovascular treatment and B) surgical treatment

Author	PMID	Population	<i>n</i>	Design	Centres	Outcome(s)	Independent Variable(s)	Subgrouping	Follow up	Main Findings
(A).										
Lee et al (2020)	32503291	IC patients undergoing SFA stent	95	Prospective	Single	Target Vessel Restenosis (TVR) on duplex within 2 years, MACE	NLR, PLR	ROC	24 months	NLR associated with TVR (HR 3.1, 1.3 – 7.7, $p = 0.01$), PLR associated with TVR (HR 3.0, 1.1 – 8.5, $p = 0.04$)
Zhen et al (2020)	31918662	Patients undergoing drug-coated balloon PTA for fem-pop disease	70	Retrospective	Single	Primary patency (duplex) at 6 months	NLR, PLR	-	6 months	Higher baseline PLR in TVR group, similar baseline NLR in TVR group. Baseline PLR predicted 6-month primary patency (OR 1.008, 1.001- 1.016, $p = 0.031$)
Zhen et al (2019)	30221973	Fem-pop PTA (CLTI vs. IC NR), 41.5% DCB, 58.5% UCB	106	Retrospective	Single	6-month primary patency	NLR	ROC	6 months	Post-op NLR higher in DCB group ($p = 0.004$), primary patency higher in DCB ($p = 0.011$), low post-op NLR predicted superior primary patency (OR 1.589, 1.078 – 2.343, $p = 0.019$)
Chang et al (2018)	28635304	Patients undergoing stent for fem-pop CTO	180	Retrospective	Single	Early ISR (<12 months)	NLR	ROC, early ISR vs. no early ISR	NR	Baseline NLR higher in early ISR group ($p = 0.04$), high NLR associated with increased risk early ISR on multivariate analysis

Nakazawa et al (2017)	28259571	First time fem-AK pop segment stent (76.0% CLTI, 24.0% IC)	479	Retrospective	Single	ISR within 24 months (>50% narrowing / 2.5 x PSV)	NLR, PLR	ISR in 24 months vs. not	24 months	Absolute values of neutrophils and platelets higher in ISR-yes group but NLR and PLR similar. Reproduced on multivariate analyses.
Teperman et al (2016)	27865186	Symptomatic LEAD (85.4% IC, 14.6% CLTI) patients referred for angiography with ipsilateral lesion	424	Retrospective	Single	Prevalence of severe multi-level disease (>70% stenosis), target vessel revascularisation	NLR	Tertiles of NLR	10.4 months	No difference in rates of target vessel revascularisation in NLR tertiles
Chan et al (2014)	24816510	All patients undergoing infrapopliteal PTA for CLTI	83	Retrospective	Single	Technical success (<50% residual stenosis, restored perfusion), OS, 12-month primary patency, AFS	NLR	Absolute value (5.25)	12 months	High NLR associated with increased 1-year mortality (HR 1.97, 1.08 – 3.62, $p = 0.03$). NS values for primary patency and AFS
(B).										
González-Hernández et al (2021)	33496158	LEAD (93% CLTI, 7% claudicants) undergoing infragenicular vein bypass	150	Retrospective	Single	Mortality, major adverse limb/cardiac event (MALE/MACE), graft patency, AFS	NLR	Quartiles (Q4 = high, Q1-3 = low)	24 months	High NLR associated with worse AFS (HR 2.10, 1.06 – 4.14, $p = 0.03$), MALE (HR 2.04, 1.03 – 4.04, $p = 0.04$), patency loss (HR 1.77, 1.01 – 3.10, $p = 0.04$)

Table 10.4 Risk of bias summary judgements (from QUIPS tool) for the studies included in the final review

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Erturk et al (2014)						
Spark et al (2010)						
González-Fajardo et al (2014)						
Sanz et al (2016)						
Uzun et al (2017)						
Pourafkari et al (2018)						
Bath et al (2020)						
González-Hernandez et al (2021)						
Chan et al (2014)						
Chen et al (2016)						
Huang et al (2019)						
Jhang et al (2020)						
Lee et al (2020)						
Su et al (2021)						
Wang et al (2017)						
Pierre-Louis et al (2019)						
Taşoğlu et al (2014)						
Luo et al (2015)						
Amrock et al (2016)						
Erdoğan et al (2021)						
Velioglu et al (2019)						
Demirdal et al (2018)						
Belaj et al (2015)						

10.6 FIGURES

Figure 10.1: PRISMA diagram showing study inclusion.

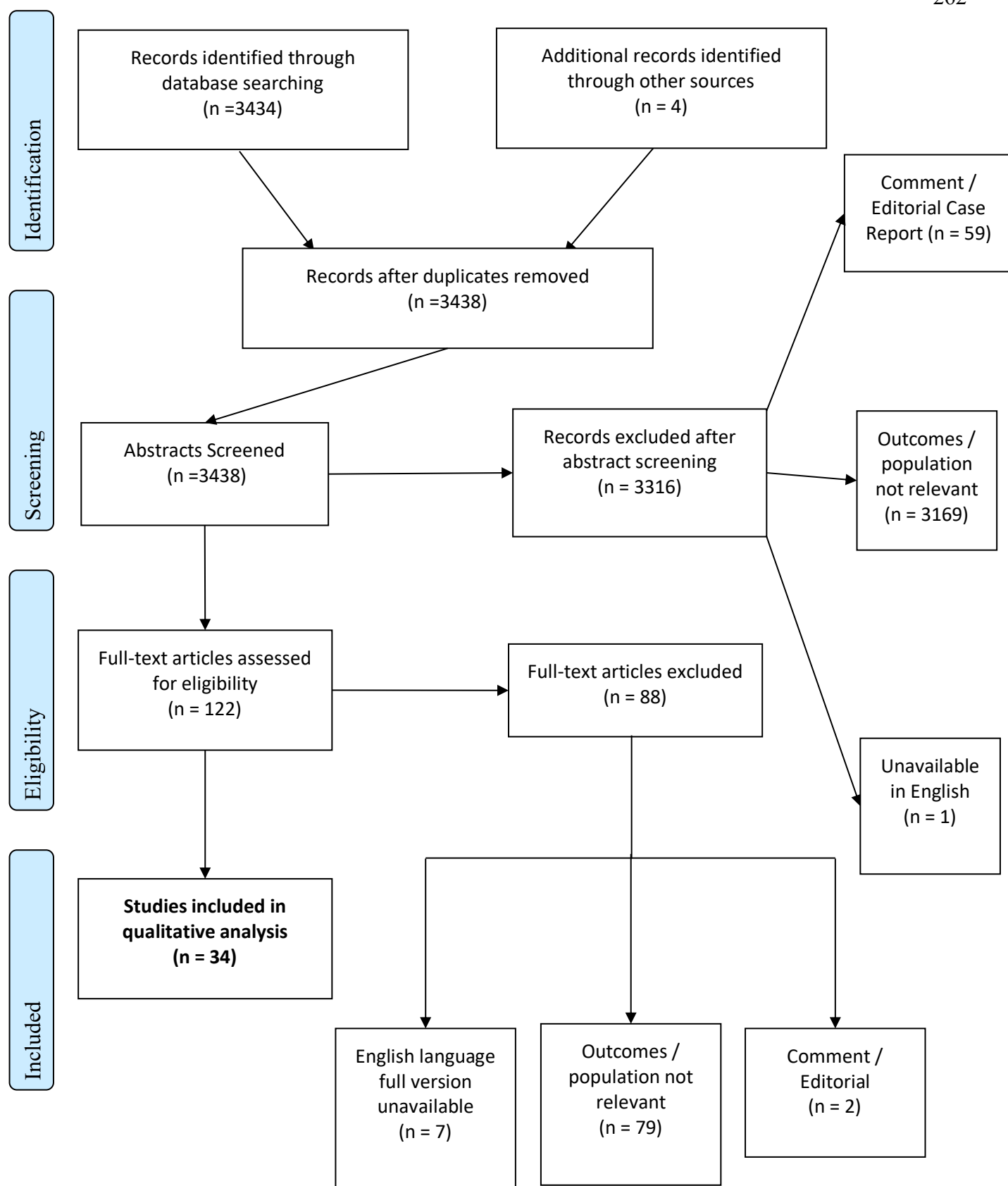


Figure 10.1 PRISMA diagram showing study inclusion

11 THE RELATIONSHIP BETWEEN CLINICAL FRAILITY SCORE, CT-DERIVED BODY COMPOSITION, SYSTEMIC INFLAMMATION, AND SURVIVAL IN PATIENTS WITH CHRONIC LIMB THREATENING ISCHAEMIA

11.1 INTRODUCTION

As discussed in section 1.1.2.2, CLTI is an important health condition with poor prognosis, and carries substantial morbidity. In prior chapters we discuss the limitations of the literature describing body composition in AAA. These limitations are similar when considering CLTI however the number of studies is even fewer. Similarly to AAA, literature describing CT-BC in patients CLTI is limited to small series with heterogenous methodology^{131,332–334}, chief of which (similarly to patients with AAA) is a lack of standardised thresholds to determine abnormal CT-BC parameters. Description of the prognostic role the SIR plays in patients with CLTI is also limited to small series, and mGPS has not been evaluated in this patient group^{292,296}.

Frailty is a complex multisystem disorder characterised by inferior functional status, loss of independence, and impaired physiological reserve³³⁵, which can be assessed using validated scoring systems such as the Clinical Frailty Scale (CFS). An association between frailty and outcomes in surgical patients has been described, though the literature specific to vascular surgery is limited by heterogeneity in assessment methodology³³⁶. Frailty and sarcopenia are discrete but closely related entities, with frailty a primarily clinical phenomenon and sarcopenia diagnosed on the basis of investigations³³⁷. Potential aetiological factors are similar for both clinical frailty and sarcopenia³³⁸. An association between clinical frailty and activation of the SIR has been reported³³⁹.

The present study examines the association between clinical frailty, CT-BC, systemic inflammation, and survival in patients with unscheduled CLTI presentations to a single tertiary vascular surgical unit.

11.2 MATERIALS & METHODS

11.2.1 PATIENT SELECTION

Recruitment of the CLTI cohort is described in section 1.7.2.2.

11.2.2 PRIMARY OUTCOME

The primary outcome was overall mortality during the follow-up period. The secondary outcomes were 1-year mortality, chosen as this reflected a clinically relevant outcome in this patient group and the minimum follow-up interval, and major amputation-free survival at 1 year.

11.2.3 BASELINE DATA COLLECTION

Data collection is described in section 1.5.2. Comorbidity was assessed using ASA, which was recorded from operative records and sub-grouped (≤ 2 / > 2) in keeping with previous literature¹⁸³. CFS was calculated on admission by the admitting medical team using an established institutional proforma, with visual prompts to aid clinicians' assessment as per Rockwood et al³⁴⁰. CFS ≤ 4 (considered non-frail) and > 4 (considered frail) was used to subgroup patients for comparison, in keeping with widely reported values from other studies, which are used in existing clinical practice³⁴¹. The presence of tissue loss was defined by the assessment made by the on-call vascular surgeon who documented presence of absence of tissue loss as part of their initial clinical review. Systemic inflammation was assessed by mGPS, calculated as described in table 5.1, based on the first blood sample taken on unscheduled admission. In order to control for the potentially confounding effect of tissue loss on mGPS, sub-group analyses on patients presenting with no tissue loss were performed. Nutritional state was assessed by Malnutrition Universal Screening Tool (MUST) score, which is routinely collected by nursing staff in NHS Health Boards as part of an admission proforma, with MUST ≥ 2 consider high risk for malnutrition.

11.2.4 CT-DERIVED BODY COMPOSITION ANALYSIS

Body composition analysis was performed on CTs performed as part of revascularisation planning, using methodology as described in section 1.7.3. To determine optimal thresholds for dichotomisation of body composition parameters into “High” and “Low” based on prognostic value, the “surv_cutpoint” function of the “survminer” R package (using RStudio 2022.02.01) was used, using the maximally selected rank statistic

technique. Sex-specific thresholds were derived to account for the established variation in body composition between males and females. Image compromise precluding CT-BC was assessed on a case-by-case and a parameter-by-parameter basis, and images selectively excluded if compromise deemed substantial. CT-SS was used to combine SMI and SMD, calculated as described in section 6.2.3.

11.2.5 STATISTICAL ANALYSIS

General statistical analyses are described in section 1.7.4. Specifically to the present data; 1-year survival and % standard error were calculated in CFS, CT-Sarcopenia Score, and mGPS subgroups using censored survival data, and absolute differences compared. The predictive value of covariates on CFS ($\leq 4 / > 4$) was assessed using a binary logistic regression model.

11.3 RESULTS

There were 190 patients included. Median (IQR) follow-up was 22 (6) months (range 15–32 months). CFS was recorded in all patients; 100 (53%) had a CFS > 4. When compromised images were excluded on a parameter-by-parameter basis, there were 185 cases (VFI), 176 cases (SFI), 185 cases (SMI), and 185 cases (SMD) available for analysis. There were 79 deaths during the follow-up period. Mean (95% CI) survival in the entire cohort was 21.1 (19.2 – 23.0) months. Thresholds of body composition parameters associated with survival which were used to sub-group patients, and the number within each sub-group, are shown in table 11.1. Scatter plots of body composition parameters sub-grouped by CFS are shown in figure 11.1a and 11.1b respectively.

The association between baseline clinicopathological characteristics, CT-derived body composition parameters, mGPS, and CFS > 4 is shown in table 11.2. Age ≥ 75 ($p < 0.001$), female sex ($p < 0.05$), MUST ≥ 2 ($p < 0.05$), ASA > 2 ($p < 0.001$), elevated CT-Sarcopenia Score ($p < 0.001$), and elevated mGPS ($p < 0.01$) were all more prevalent in patients with CFS > 4, whilst high VFI ($p < 0.01$) was less prevalent in patients with CFS > 4. On multivariate analysis, age ≥ 75 (OR 2.21, 95% CI 1.07 – 4.56, $p < 0.05$), ASA > 2 (OR 6.83, 95% CI 2.10 – 22.22, $p < 0.01$), and CT-Sarcopenia Score (OR 1.88, 95% CI 1.09 – 3.24, $p < 0.01$) were associated with CFS > 4. mGPS (OR 1.35, 95% CI 0.89 – 2.03, $p = 0.16$) was not independently associated with CFS > 4.

Mean (95% CI) survival in the CFS ≤ 4 vs. CFS > 4 subgroups was 25.8 (23.5 – 28.2) vs. 16.8 (14.2 – 19.5) months ($p < 0.001$, figure 11.2). Mean (95% CI) survival in the high VFI vs. low VFI subgroups was 22.1 (19.6 – 24.7) vs. 19.9 (17.0 – 22.7) months ($p = 0.26$). Mean (95% CI) survival in the high SFI vs. low SFI subgroups was 22.2 (18.6 – 25.8) vs. 20.8 (18.5 – 23.1) months ($p = 0.48$). Mean (95% CI) survival in the CT-Sarcopenia Score 0 vs. CT-Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 subgroups was 25.4 (22.8 – 28.1) vs. 18.4 (15.9 – 20.9) vs. 18.4 (15.9 – 20.9) months ($p < 0.001$, figure 11.3). Mean (95% CI) survival in the mGPS 0 vs. 1 vs. 2 subgroups was 27.2 (24.7 – 29.8) months vs. 24.4 (20.3 – 28.6) months vs. 17.1 (14.5 – 19.8) months ($p < 0.001$, figure 11.4).

The relationship between baseline clinical characteristics, CT-derived body composition parameters, and mortality in the entire patient cohort is shown in table 11.3. On univariate analysis, age > 75 ($p < 0.01$), CFS > 4 ($p < 0.001$), CT-Sarcopenia Score (< 0.001), and

mGPS (<0.001) were associated with increased mortality. On multivariate analysis, CFS > 4 (HR 2.14, 95% CI 1.25 – 3.66, $p < 0.01$), CT-Sarcopenia Score (HR 1.47, 95% CI 1.03 – 2.09, $p < 0.05$), and mGPS (HR 1.54, 95% CI 1.11 – 2.13, $p < 0.01$) were associated with increased mortality.

Table 11.4 displays 1 year survival in patients sub-grouped by CT-Sarcopenia Score, mGPS, and CFS. There were significant trends towards inferior 1 year survival with both increasing CT-SS and mGPS irrespective of frailty. Patients with CT-Sarcopenia Score 0 & CFS ≤ 4 had 90% (SE 5%) 1-year survival, compared with 35% (SE 9%) in patients with CT-Sarcopenia Score 2 & CFS > 4 ($p < 0.001$). Patients with mGPS 0 & CFS ≤ 4 had 94% (SE 4%) 1-year survival compared with 44% (SE 6%) in the mGPS 2 & CFS > 4 subgroup ($p < 0.001$).

144 patients (79%) underwent inpatient revascularisation on the index admission included in the study period. The rate of intervention in patients with CFS ≤ 4 vs. CFS > 4 was 75 (86%) vs. 69 (73%) ($p < 0.05$). The rate of intervention in patients with CT-Sarcopenia Score 0 vs. CT-Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 was 45 (80%) vs. 69 (86%) vs. 26 (62%) ($p < 0.05$). There was no difference in the rate of intervention between mGPS sub-groups ($p = 0.81$).

Sub-group analyses were performed on patients presenting without tissue loss ($n = 33$, 18%). There were 15 deaths during the follow-up period in this sub-group. On univariate analyses CT-Sarcopenia Score (HR 2.99, 95% CI 1.40 – 6.37, $p < 0.01$) and mGPS (HR 2.19, 95% CI 1.10 – 4.35, $p < 0.05$) were associated with increased mortality, whilst CFS > 4 (HR 2.52, 95% CI 0.85 – 7.42, $p = 0.09$) was not. The low number of events in this sub-group precluded meaningful multivariate analyses. There was no difference in CT-Sarcopenia Score ($p = 0.83$) or mGPS ($p = 0.37$) between patients with tissue loss and those without tissue loss.

The overall 1-year major limb amputation rate in the entire study cohort was 28.4% ($n = 54$). The overall 1-year major limb amputation-free survival in the entire study cohort was 53.2% ($n = 100$). The rate of 1-year major limb amputation-free survival in patients with CFS ≤ 4 vs. CFS > 4 was 63.3% vs. 32.0% ($p < 0.001$). The rate of 1-year major limb amputation-free survival in patients with CT-Sarcopenia Score 0 vs. CT-Sarcopenia Score 1 vs. CT-Sarcopenia Score 2 was 69.0% vs. 41.5% vs. 28.9% ($p < 0.001$). The rate of 1-year major limb amputation-free survival in patients with mGPS 0 vs. mGPS 1 vs. mGPS

was 82.0% vs. 64.3% vs. 25.7% ($p < 0.001$). On univariate analysis, tissue loss ($p < 0.05$), CFS > 4 ($p < 0.001$), CT-Sarcopenia Score ($p < 0.001$), and mGPS ($p < 0.001$) were associated with increased odds of limb loss or death at 1 year. On multivariate analysis, CFS > 4 (OR 2.80, 95% CI 1.35 – 5.78, $p < 0.01$) and mGPS (OR 3.36, 95% CI 2.15 – 5.25, $p < 0.001$) were associated with increased odds of limb loss or death at 1 year.

11.4 DISCUSSION

The present study reports for the first time the potential prognostic value of frailty, CT-derived body composition, and systemic inflammation in a real-world cohort of patients presenting with CLTI. Furthermore, we report an association between CFS and CT-Sarcopenia Score. CFS, CT-Sarcopenia Score, and mGPS were associated with poorer overall survival and limb salvage rates in patients presenting as unscheduled admissions with CLTI. Patients with elevated CFS or CT-Sarcopenia Score were less likely to undergo revascularisation. Moreover, these findings appear to be independent of disease severity, measured as presenting with or without tissue loss, an important potentially confounding factor in measuring the systemic inflammatory response. The addition of validated measures of tissue loss severity and presence of infection would improve the validity of the present conclusions and is an important area for further investigation.

Frailty assessment as a prognostic factor as well as the endemic nature of frailty in patients with CLTI has been previously reported^{336,342}. However, the association with body composition, and the factors evaluated in the present study, is a novel finding. The multifactorial aetiology of frailty is incompletely understood, however the association between frailty and activation of the systemic inflammatory response is emerging as an important component^{339,343,344}. The lack of association between mGPS and CFS observed in the present study may reflect an underpowered study, however further investigation is warranted. Whilst CT-Sarcopenia Score and mGPS are more resource demanding to quantify than CFS, the independent association with survival observed suggests a potential role in clinical prognostication as part of multimodal assessment. The manual analysis methods used in the present study are time-intensive limiting their utility; instead automated artificial intelligence-based systems show promise in their application to routine clinical practice³⁴⁵.

Identifying a subset of patients with CLTI who are more likely to experience poor prognosis is a key aspect of the management of CLTI; indeed the recognition of tailored management strategy based on prognosis has been well described for almost 20 years since the landmark BASIL trial²⁹, and subsequently supported by other authors. Moreover, the recent BEST-CLI study highlights inferior outcomes in a sub-group of patients, describing differences based on revascularisation strategy³¹, complementing our hypothesis of patient-specific prognostic factors. Post-hoc analysis of systemic inflammation in the BEST-CLI cohort would be of particular interest and may contribute to our understanding of assessing

prognosis in patients with CLTI. Optimal prognostic assessments are likely to be multimodal, and the results of the present study suggest that CFS, CT-Sarcopenia Score, and mGPS are potentially useful clinical tools.

Whilst there are prior studies reporting inferior survival and limb salvage rates in sarcopenic patients, there was heterogeneity in the assessment of sarcopenia; Matsubara et al¹³¹ reported skeletal muscle area without normalisation, and Taniguchi et al³³² report psoas muscle index (normalised to height²). Normalisation of CT-derived muscle parameters is widely accepted to be the superior technique in patients with cancer, with SMI considered to be the superior parameter for prognostication⁸⁰. The present study attempts to resolve these methodological concerns and provide a uniform framework for the future reporting of body composition related prognostication in this patient group. A benefit to the use of CT-Sarcopenia Score compared with either SMI or SMD in isolation, is the more holistic assessment of sarcopenia, incorporating both muscle mass (SMI) and muscle density (SMD, which has been proposed as a marker of muscle function) as per the EWGSOP2 definition of sarcopenia²⁴⁷. Loss of skeletal muscle is a key feature of sarcopenia, which has a well described association with poor prognosis³⁴⁶. Sarcopenia is predominantly described in patients with cancer, however there is an increasing recognition of the prevalence of sarcopenia in a range of chronic conditions³⁴⁷.

The present study demonstrated that, even in patients without tissue loss, a baseline elevated magnitude of systemic inflammation conferred inferior prognosis, highlighting a potential clinically relevant target for intervention. The CANTOS trial demonstrated a reduction in cardiovascular events following IL-1 β blockade in patients with ischaemic heart disease compared with placebo¹⁷³. IL-1 β blockade in patients with LEAD has been investigated, and an improvement in walking distance reported, however these data are derived from small patient groups and require validation¹⁹². A key limitation of this therapeutic strategy is the increased risk of significant infection, which was noted by the CANTOS authors. Further prospective studies are required, in particular in a patient cohort presenting without tissue loss, to evaluate the effect on long-term prognosis as well as limb salvage rates. Moreover, serial inflammatory profiling in this patient cohort may help to clarify the effect that revascularisation has on systemic inflammation; if systemic inflammation were to persist despite successful revascularisation the rationale for immunomodulation may be strengthened.

Chronic activation of the SIR is associated with sarcopenia, which is also associated with the frailty syndrome³⁴⁸. Furthermore, systemic inflammation is also associated with increasing fatigue, reduced function, and reduced quality of life in older adults³⁴⁹. The majority of studies to date report CRP levels rather than using the parameters in this study which provide a more holistic representation of systemic inflammation²¹⁰. Defining the specific relationship between frailty and SIR and the mechanism therein warrants further study, and may contribute to the development of novel prognostic scoring systems assessing both frailty and systemic inflammation.

In the present study there were a number of limitations. A relatively small sample size was studied and therefore limits the generalisability of our conclusions. The study is also limited by retrospective single centre design. Use of the Society for Vascular Surgery Wound Ischaemia and Foot Infection (WIFI³³¹) Score may have allowed for us to more comprehensively describe the cohort, however WIFI scores were not available for the majority of patients in the present study. Moreover, adjusting for WIFI scores may be useful in reducing the potential bias introduced through the confounding effect of tissue damage or infection on the systemic inflammatory response. Despite this, the primary outcome of the present study was mortality, and whilst the association between WIFI and limb salvage appears to be growing, there remain conflicting reports of the association between WIFI and mortality^{27,350}. The thresholds of CT-derived body composition parameters were derived from the dataset reported in this study, introducing a potential source of bias, and these thresholds require external validation.

Frailty assessed by CFS was independently associated with CT-derived body composition. CFS, CT-Sarcopenia Score, and mGPS were independently associated with poorer survival in patients presenting as unscheduled admissions with CLTI. Therefore, frailty assessment in these patients should include a measure of the systemic inflammatory response and body composition. Multimodal prognostic assessment including CFS, CT-Sarcopenia Score, and mGPS is a potential novel clinical tool.

11.5 TABLES

Table 11.1: Classification of abnormal CT-derived body composition and number in each sub-group in a cohort of patients presenting acutely with chronic limb threatening ischaemia.

Table 11.2: The association between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and CFS in patients presenting acutely with chronic limb threatening ischaemia.

Table 11.3: The relationship between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and mortality in patients presenting acutely with chronic limb threatening ischaemia described by cox proportional hazards models (n=190).

Table 11.4: %1 year survival and standard error in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CT-BC parameters, mGPS, and CFS (n=190).

Table 11.1 Classification of abnormal CT-derived body composition and number in each sub-group in a cohort of patients presenting acutely with chronic limb threatening ischaemia

High visceral fat index (VFI)		N (%)
Males	$>40\text{cm}^2/\text{m}^2$	91 (78%)
Females	$>114\text{cm}^2/\text{m}^2$	8 (12%)
Total		99 (54%)
High subcutaneous fat index (SFI)		
Males	$>80\text{cm}^2/\text{m}^2$	22 (20%)
Females	$>103\text{cm}^2/\text{m}^2$	30 (46%)
Total		52 (30%)
Low skeletal muscle index (SMI)		
Males	$<40\text{cm}^2/\text{m}^2$	26 (22%)
Females	$<41\text{cm}^2/\text{m}^2$	31 (45%)
Total		57 (31%)
Low skeletal muscle density (SMD)		
Males	$<37\text{ HU}$	69 (60%)
Females	$<37\text{ HU}$	46 (67%)
Total		115 (62%)
CT-Sarcopenia Score (CT-SS)		
CT-SS 0	High SMI & High SMD	58 (32%)
CT-SS 1	Low SMI & High SMD OR High SMI & Low SMD	82 (44%)
CT-SS 2	Low SMI & Low SMD	45 (24%)

Table 11.2 The association between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and CFS in patients presenting acutely with chronic limb threatening ischaemia

	CFS ≤4 (n = 90)	CFS >4 (n = 100)		Univariate	Multivariate
	n (%)	n (%)	p	CFS >4	CFS >4
Age ≥75	22 (24%)	56 (56%)	<0.001	3.93 2.11 – 7.33 p<0.001	2.21 1.07 – 4.56 <0.05
Female Sex	26 (29%)	46 (46%)	<0.05	2.10 1.15 – 3.83 <0.05	1.08 0.42 – 2.82 0.88
BMI ≥ 25	58 (64%)	57 (57%)	0.30	0.73 0.41 – 1.31 0.30	-
MUST ≥ 2	4 (5%)	15 (15%)	<0.05	3.80 1.12 – 11.91 <0.05	2.25 0.51 – 9.92 0.28
ASA > 2	64 (74%)	93 (95%)	<0.001	6.39 2.30 – 17.76 <0.001	6.83 2.10 – 22.22 <0.01
Tissue Loss	72 (81%)	83 (84%)	0.30	1.23 0.57 – 2.60 0.60	-
High VFI	58 (65%)	41 (42%)	<0.01	0.40 0.22 – 0.72 <0.01	0.47 0.19 – 1.19 0.11
High SFI	24 (28%)	28 (31%)	0.71	1.13 0.59 – 2.16 0.71	-
CT-SS					
0	41 (46%)	17 (18%)	<0.001	2.38	1.88
1	34 (38%)	48 (50%)		1.55 – 3.64	1.09 – 3.24
2	14 (16%)	31 (32%)		<0.001	<0.05
mGPS					
0	31 (35%)	19 (19%)	<0.01	1.68	1.35
1	16 (18%)	12 (12%)		1.19 – 2.36	0.89 – 2.03
2	41 (47%)	68 (69%)		<0.01	0.16
For covariates with >2 subgroups, the first category was considered as the reference category.					

Table 11.3 The relationship between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and mortality in patients presenting acutely with chronic limb threatening ischaemia described by cox proportional hazards models (n=190)

		Univariate			Multivariate		
	n	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age (≤ 75 / > 75)	112 (59%) / 78 (41%)	1.87	1.20 – 2.92	<0.01	1.25	0.78 – 2.03	0.36
Clinical Frailty Score > 4	100 (53%)	3.12	1.89 – 5.15	<0.001	2.14	1.25 – 3.66	<0.01
Female Sex	72 (38%)	1.11	0.71 – 1.75	0.65	-	-	-
BMI (< 25 / ≥ 25 kg/m²)	75 (40%) / 115 (60%)	0.82	0.53 – 1.29	0.39	-	-	-
MUST (< 2 / ≥ 2)	169 (90%) / 19 (10%)	2.38	0.51 – 11.0	0.27	-	-	-
ASA (≤ 2 / > 2)	27 (15%) / 157 (85%)	1.83	0.84 – 3.98	0.13	-	-	-
Tissue Loss on presentation	155 (82%)	0.96	0.54 – 1.71	0.88	-	-	-
High VFI	99 (54%)	0.77	0.49 – 1.21	0.25	-	-	-
High SFI	52 (30%)	0.83	0.49 – 1.40	0.49	-	-	-

Table 11.4 %1 year survival and standard error in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CT-BC parameters, mGPS, and CFS (n =190)

		CFS $\leq$ 4			CFS > 4		
	n	1yr OS (%SE)		n	1yr OS (%SE)		
CT-SS 0	41	90% (SE 5%)		17	82% (SE 9%)		$p = 0.08$
CT-SS 1	34	79% (SE 7%)		48	56% (SE 7%)		$p < 0.05$
CT-SS 2	14	71% (SE 12%)		31	35% (SE 9%)		$p = 0.09$
		$p < 0.05$			$p < 0.05$		
mGPS 0	31	94% (SE 4%)		19	84% (SE 8%)		$p < 0.05$
mGPS 1	16	94% (SE 6%)		12	67% (SE 14%)		$p < 0.05$
mGPS 2	41	71% (SE 7%)		68	44% (SE 6%)		$p < 0.05$
		$p < 0.05$			$p < 0.01$		

11.6 FIGURES

Figure 11.1: Scatter plots of a). SFI (cm²/m²) vs. VFI (cm²/m²) and b). SMI (cm²/m²) vs. SMD (HU) in patients presenting acutely with chronic limb threatening ischaemia, sub-grouped by CFS. $p < 0.001$ for all correlations.

Figure 11.2: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CFS, $p < 0.001$ (log-rank method).

Figure 11.3: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CT-SS, $p < 0.001$ (log-rank method).

Figure 11.4: Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by mGPS, $p < 0.001$ (log-rank method).

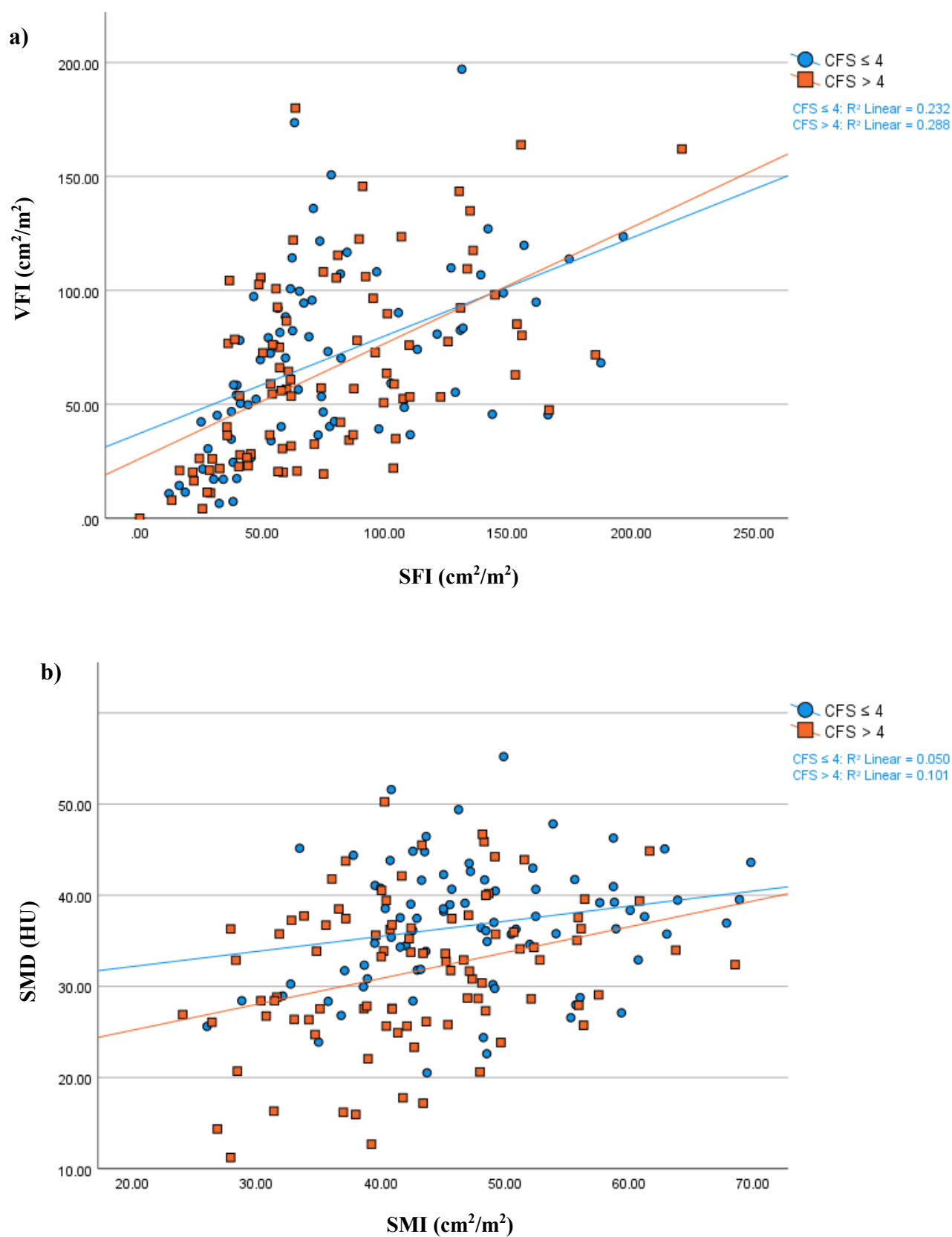
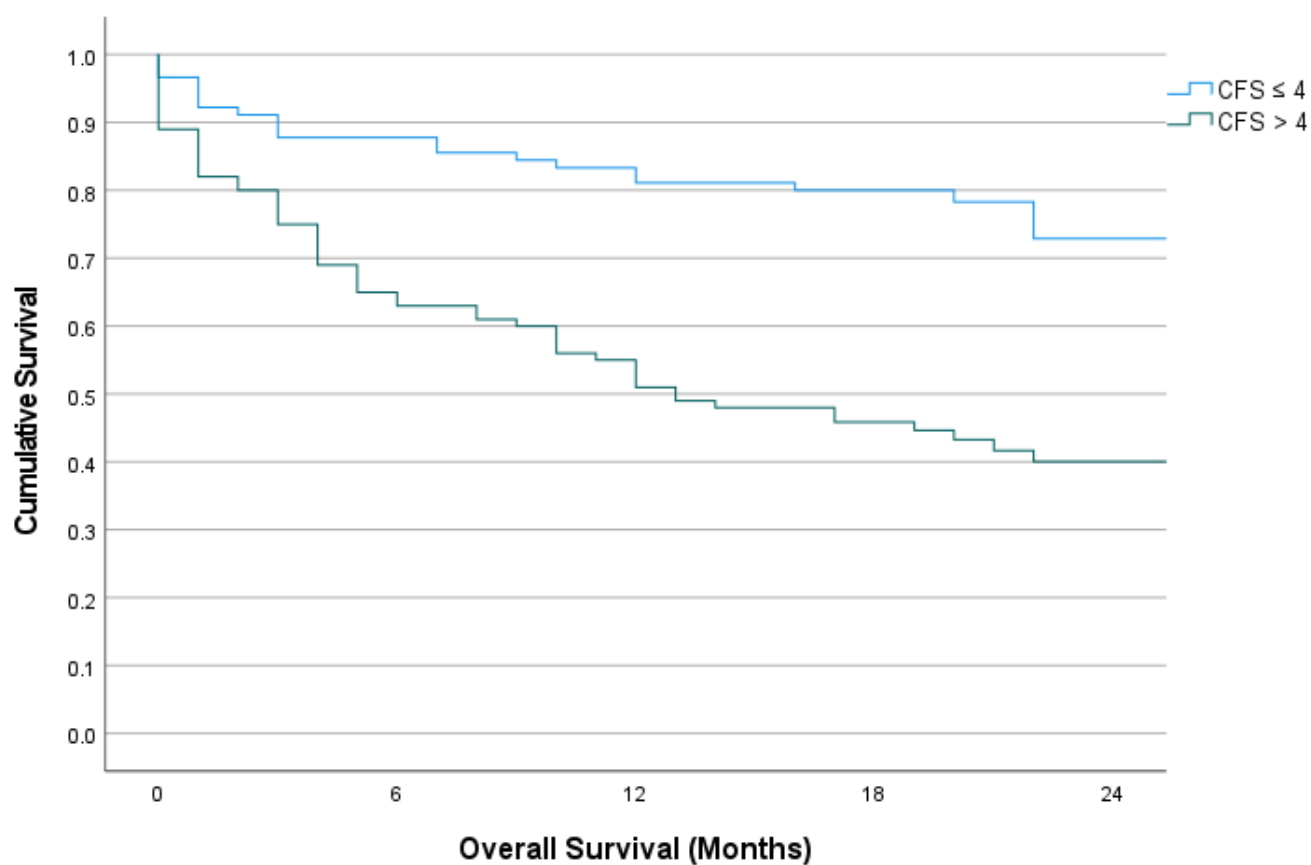
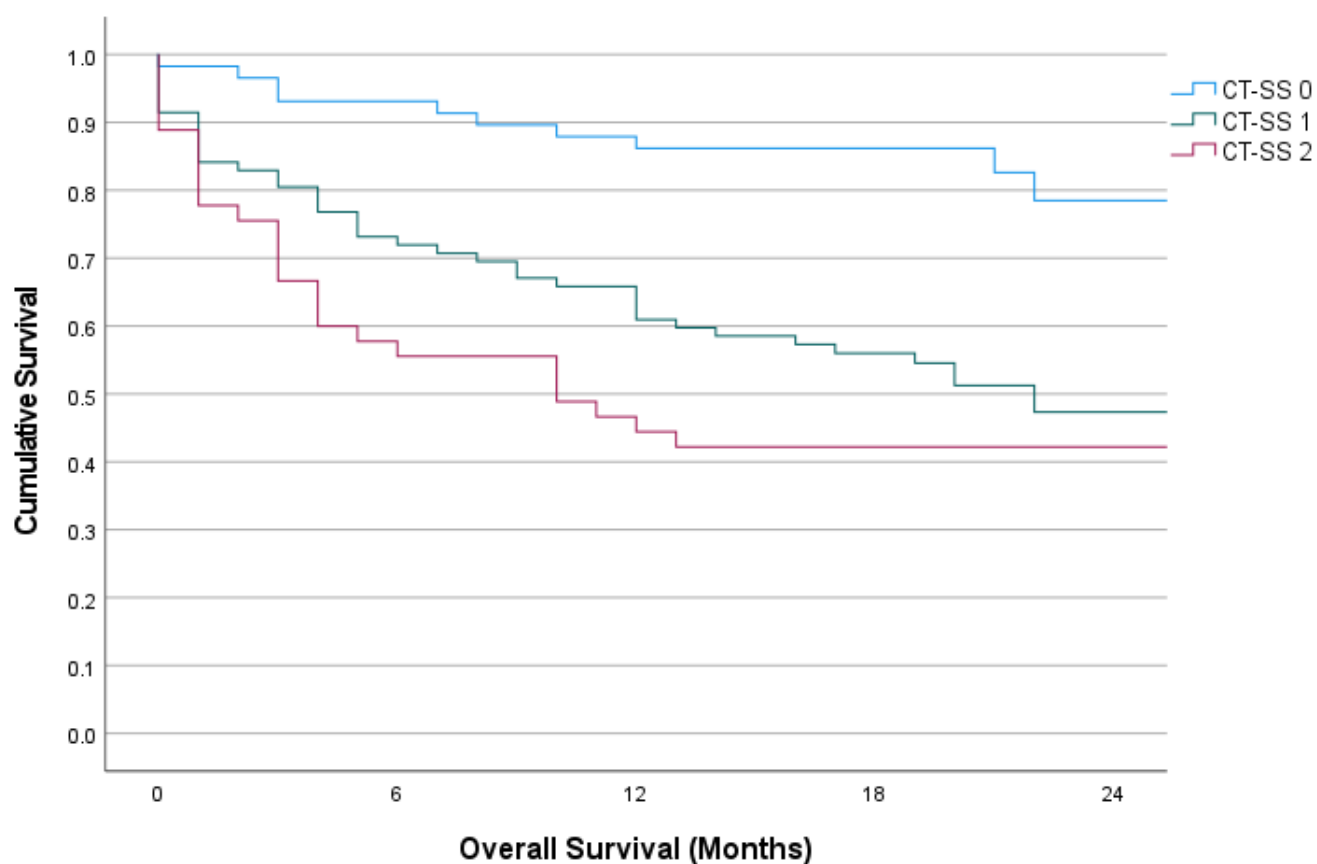


Figure 11.1 Scatter plots of a). SFI (cm²/m²) vs. VFI (cm²/m²) and b). SMI (cm²/m²) vs. SMD (HU) in patients presenting acutely with chronic limb threatening ischaemia, sub-grouped by CFS. $p < 0.001$ for all correlations.



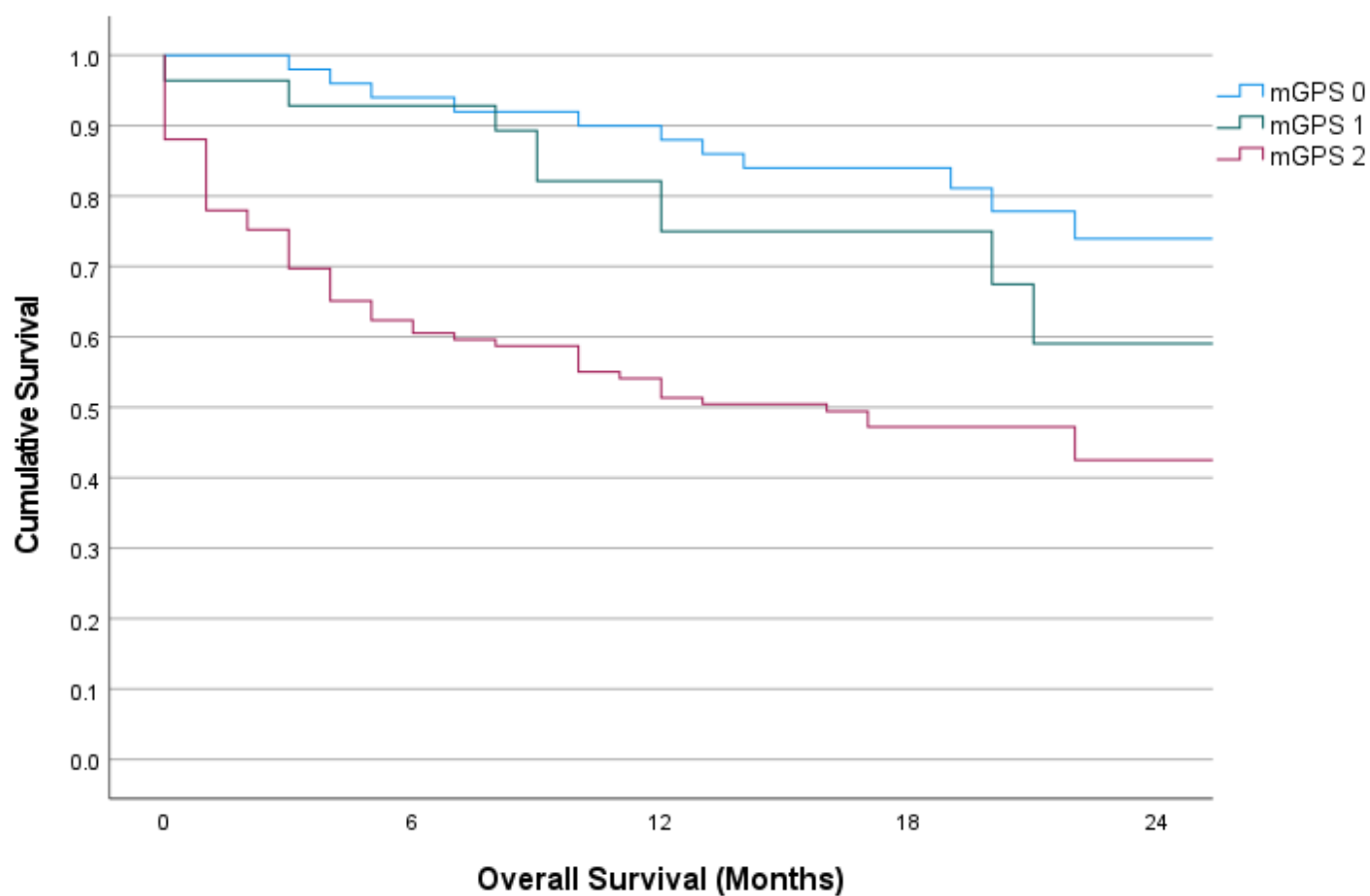
		Interval (Months)				
		0	6	12	18	24
Number at Risk	CFS ≤ 4	90	79	75	60	18
	CFS > 4	100	65	55	41	19

Figure 11.2 Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CFS, $p < 0.001$ (log-rank method)



		Interval (Months)				
		0	6	12	18	24
Number at Risk	CT-SS 0	58	54	51	45	15
	CT-SS 1	82	60	54	40	16
	CT-SS 2	45	26	21	15	6

Figure 11.3 Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by CT-SS, $p < 0.001$ (log-rank method)



		Interval (Months)				
		0	6	12	18	24
Number at Risk	mGPS 0	50	47	45	29	11
	mGPS 1	28	26	23	13	5
	mGPS 2	109	68	59	31	8

Figure 11.4 Kaplan-Meier survival plots and life table in patients presenting acutely with chronic limb threatening ischaemia when sub-grouped by mGPS, $p < 0.001$ (log-rank method)

12 THE RELATIONSHIP BETWEEN CT-DERIVED CERVICAL MUSCLE MASS AND QUALITY, SYSTEMIC INFLAMMATION, AND SURVIVAL IN SYMPTOMATIC PATIENTS UNDERGOING CAROTID ENDARTERECTOMY

12.1 INTRODUCTION

As described in section 1.1.2.3, atherosclerotic disease affecting the cerebral circulation is termed cerebrovascular disease, and the clinical manifestation of TIA/CVA may lead to patients undergoing surgical revascularisation of their ICA in the form of CEA. Patient selection is of paramount importance in the pre-operative assessment of patients who may be suitable for CEA, therefore identification of optimal prognostic factors is of particular interest.

Historically, CT-BC has been most commonly performed on abdominal imaging typically at the L3 vertebral level. More recently, cervical muscle mass and quality at the C3 vertebral level have been quantified via CT and appear to influence prognosis in patients with head and neck cancer³⁵¹. The association between sarcopenia and outcomes has been explored in patients undergoing carotid endarterectomy, however to date C3 skeletal muscle area (C3 SMA) has not been reported, with masseter area the most commonly reported measure to date^{352,353}. Similarly, the prognostic value of SIR in carotid surgery has been explored, with several authors reporting inferior outcomes in patients with an elevated NLR^{354,355}. Alternative measures of the SIR, and the interaction between muscle mass and inflammation, remain unreported in this patient cohort. There are a paucity of data documenting these relationships in patients with cardiovascular disease, particularly cerebrovascular disease.

The present study examines the association between CT-derived cervical muscle mass and quality, systemic inflammation, and survival in patients undergoing carotid endarterectomy.

12.2 MATERIALS & METHODS

12.2.1 PATIENT SELECTION

The recruitment of the carotid endarterectomy cohort is described in section 1.7.2.3. In order to perform CT-BC, a pre-operative planning CT angiogram at the C3 level was required; the choice of whether this was required or whether case planning was based on duplex ultrasonography was at the discretion of the operative team.

12.2.2 BASELINE DATA COLLECTION

Data collection is described in section 1.5.2. Comorbidity was assessed using ASA (≤ 2 / > 2), which along with age (< 75 , ≥ 75) and BMI ($< 25\text{kg/m}^2$, $\geq 25\text{kg/m}^2$) were considered as categorical variables. Patients with missing baseline data were selectively excluded from relevant analyses.

12.2.3 OUTCOMES OF INTEREST

The primary outcome was overall mortality during the follow-up period. The secondary outcome was 5-year survival, chosen as this reflected a clinically relevant outcome in this patient group. Sources of outcome data are described in section 1.5.2.

12.2.4 CT-BC ANALYSIS

Body composition analysis was performed on arterial-phase CTs performed as part of surgical planning at the C3 vertebral level. Using methodology previously described in cohorts of patients with head and neck cancer³⁵⁶, sternocleidomastoid and paravertebral muscle groups were manually measured using ImageJ v1.53 with the same technical steps as in abdominal CT analysis (section 1.7.3). Again, muscle tissue thresholds of -29 to +150 HU were used. This generated the C3 SMA which was normalised to height² to generate the C3 skeletal muscle index (C3 SMI). The C3 skeletal muscle density (C3 SMD) was also recorded, which, as per established practice, was not normalised⁸⁰. Additionally, using the formula proposed by Swartz *et al*³⁵⁷, the L3 derived skeletal muscle index (L3 dSMI) was calculated from C3 SMA. To determine optimal thresholds of continuous variables for dichotomisation of body composition parameters into “Normal” and “Low”, the “surv_cutpoint” function of the “survminer” R package was used, using the maximally selected rank statistic technique. In keeping with prior reports⁸⁴, preliminary analyses showed a difference in median C3 SMI and L3 dSMI between sex ($p < 0.001$) and

BMI ($p < 0.001$) sub-groups, and in C3 SMD between sex ($p < 0.05$) sub-groups.

Therefore, sex- (C3 SMI, L3 dSMI, C3 SMD) and BMI- (C3 SMI, L3 dSMI) specific thresholds were derived to account for these differences, in keeping with established methodology from abdominal CTs in patients with cancer⁸⁴. Outcomes were compared between sub-groups of CT-BC parameter.

12.2.5 INFLAMMATORY PROFILING

Institutional policy during the study period was to admit patients to hospital on the evening prior to surgery, where pre-operative blood work was routinely performed as part of existing patient care. SIG was used to assess the pre-operative SIR, calculated as described in chapter 5, and outcomes compared between groups of SIG 0 (considered “non-inflamed”) vs. SIG 1 (considered “mildly inflamed”) vs. $SIG \geq 2$ (considered “inflamed”).

12.2.6 STATISTICAL ANALYSIS

General statistical analyses are described in section 1.7.4. To avoid confounding due to multicollinearity, C3 SMI and L3 dSMI were modelled in separate multivariate models, with the values for C3 SMI preferentially reported due to cervical CT-BC being the main covariate of interest. % 5-year survival and % standard error (SE) were calculated using censored survival data for each sub-group of CT-BC parameter and SIG, and absolute differences between sub-groups were compared. p values < 0.05 were considered statistically significant. To account for potential selection bias, patients excluded due to missing CT or SIG were compared with the final study cohort..

12.3 RESULTS

There were 970 patients screened for eligibility; following exclusions based on missing CT or SIG, 618 patients were included in the final analysis. Median (IQR) follow-up was 69 (52) months. There were 178 deaths during the follow-up period, mean (95% CI) survival in the entire cohort was 101.4 (96.3 – 106.5) months, and 5-year survival was 77% (SE 2%).

188 (30%) patients were aged ≥ 75 , 436 (71%) were male, 426 (70%) had a BMI ≥ 25 , 397 (68%) had ASA > 2 , and 312 (50%) and 306 (50%) of cases were performed for TIA and CVA respectively. Thresholds of cervical CT-BC parameters associated with inferior prognosis are shown in table 12.1. There were 328 (54%) patients with low C3 SMI, 270 (44%) patients with a low L3 dSMI, and 189 (31%) patients with low C3 SMD. There were 325 (53%) patients with SIG 0, 197 (32%) patients with SIG 1, and 94 (15%) patients with SIG ≥ 2 . The association between cervical CT-BC parameters and baseline clinical characteristics is shown in table 12.2.

Mean (95% CI) survival in the normal C3 SMI vs. low C3 SMI subgroups was 110.3 (103.3 – 117.4) vs. 93.5 (86.6 – 100.3) months ($p < 0.01$, Figure 12.1). Mean (95% CI) survival in the normal C3 SMD vs. low C3 SMD subgroups was 109.8 (103.7 – 116.0) vs. 84.2 (76.2 – 92.1) months ($p < 0.001$, Figure 12.2). Mean (95% CI) survival in the SIG 0 vs. SIG 1 vs. SIG ≥ 2 subgroups was 110.5 (104.1 – 117.0) vs. 97.3 (88.1 – 106.5) vs. 74.9 (62.7 – 87.1) months ($p < 0.001$, Figure 12.3). Patients with normal C3 SMI & SIG 0 had a mean (95% CI) survival of 116.3 (107.9 – 124.7) months, compared with 67.8 (52.4 – 82.9) months in patients with low C3 SMI & SIG ≥ 2 ($p < 0.001$, figure 12.4). Patients with normal C3 SMD & SIG 0 had a mean (95% CI) survival of 113.9 (106.3 – 121.5) months, compared with 40.5 (31.2 – 49.8) months in patients with low C3 SMD & SIG ≥ 2 ($p < 0.001$, figure 12.5). Mean (95% CI) survival in the normal L3 dSMI vs. low L3 dSMI subgroups was 114.6 (108.1 – 121.0) vs. 85.3 (77.9 – 106.9) months ($p < 0.001$, Figure 12.6).

The association between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and survival is shown in Table 12.3. On multivariate analysis, age ≥ 75 (HR 2.17, 95% CI 1.58 – 2.97, $p < 0.001$), ASA > 2 (HR 2.06, 95% CI 1.35 – 3.12, < 0.001), Low C3 SMD (HR 1.84, 95% CI 1.33 – 2.54, < 0.001), and SIG (HR 1.63, 95% CI 1.33 – 1.99, < 0.001) were independently associated with increased mortality, whilst BMI $\geq$

25kg/m² was independently associated with decreased mortality (HR 0.64, 95% CI 0.47 – 0.89, $p < 0.01$).

Patients with Normal C3 SMI & SIG 0 had 89% (SE 3%) %5-year survival, compared with 43% (SE 7%) in patients with Low C3 SMI & SIG ≥ 2 ($p < 0.001$). Patients with Normal C3 SMD & SIG 0 had 87% (SE 2%) %5-year survival, compared with 26% (SE 8%) in patients with Low C3 SMD & SIG ≥ 2 ($p < 0.001$). Patients with Normal L3 dSMI & SIG 0 had 89% (SE 2%) %5-year survival, compared with 40% (SE 7%) in patients with Low L3 dSMI & SIG ≥ 2 ($p < 0.001$).

In order to account potential selection bias, patients who were excluded due to missing CT-BC parameter or SIG ($n = 352$) were compared with the final study cohort (table 12.4).

There was a greater proportion of excluded patients with ASA > 2 (87% vs. 68%, $p < 0.001$), however other parameters were similar between sub-groups.

12.4 DISCUSSION

The results of the present study describe a potential prognostic role for both CT-derived cervical muscle analysis and assessment of the systemic inflammatory response in patients undergoing carotid endarterectomy for symptomatic carotid artery disease. These novel observations in this patient cohort add to the growing body of evidence supporting the potential clinical role for CT-derived muscle analysis and assessment of the systemic inflammatory response in risk stratification and patient selection for major surgical intervention. It was of interest that several of the standard clinical variables (Age, ASA) had larger hazard ratios than C3 SMD and SIG. Nevertheless, these hazard ratios were from multivariate analyses and this would indicate that the association with survival of such standard clinical variables may be improved by inclusion of the additional variables. Additionally, by transforming cervical muscle mass to abdominal muscle mass, the present study reproduces the methodology used by Swartz *et al* in a non-cancer population, which may allow for comparison with other populations where L3 CT-BC has been performed³⁵⁷. It is likely that the inferior survival in patients with low cervical muscle mass/quality and activation of the SIR reflects increased cardiovascular morbidity, as an association between chronic inflammation and atherosclerotic disease is well established^{148,324,358}. We propose that presentation with TIA or CVA should be considered as an “end-organ” manifestation of atherosclerosis and reflects a greater systemic burden of atherosclerotic disease. The potential clinical benefit to identifying these patients at risk of inferior cardiovascular outcome is the role of individualised secondary prevention strategies.

Identifying patients with inferior prognosis is essential to patient selection for surgery due to the prophylactic nature of carotid intervention. In order to justify the exposure to peri-procedural risk, a candidate patient must be likely to have sufficient survival irrespective of intervention, in order to derive benefit in CVA risk reduction by surgery. The present study reported a mean survival of 40 months in patients with low C3 SMD and $SIG \geq 2$; in this “high risk” sub-group, the benefit of intervention is mitigated by poor overall long-term survival. Identifying these higher risk patients is likely to be of particular value in the asymptomatic carotid cohort, where the benefit of intervention is thought to be more limited than in those with symptomatic lesions^{38,39}. Reproducing the results of the present study in an asymptomatic carotid cohort would be of particular interest. Furthermore, evaluation of the prognostic value of C3 SMD and SIG in a wider cohort of patients presenting with a cerebrovascular event and a likely symptomatic carotid lesion who do not undergo surgery is an important area for further research. Comparing the prognostic

value of these parameters and conventional clinical assessments of fitness and long-term survival in this patient group would allow for their clinical utility in patient selection to be assessed more accurately.

A potential method of selecting patients at increased risk of future stroke in addition to grade of stenosis is plaque morphology, with a range of methods of radiological assessment on multiple modalities reported³⁵⁹. Higher risk plaque may be ulcerated or haemorrhagic, both of which may be involved in the instigation of an inflammatory response. An association between radiologically high risk plaque and transcriptomic features of inflammation has been described, however studies reporting the association of these factors with routinely available markers of systemic inflammation are lacking. Histopathological or molecular analyses of plaque can clearly only be performed following endarterectomy, therefore the use of these analyses in patient selection is limited and a measure available prior to surgery may have better real world clinical utility.

The prognostic value of CT-BC and the SIR in patients with cerebrovascular disease has been previously described; two studies report inferior outcomes relating to sarcopenia as defined by masseter area^{352,353} and two studies report inferior outcomes in patients with elevated pre-operative NLR^{354,355}. The present study is the first to report the combined relationships and association with survival of both of these factors, which has been extensively reported in patients with cancer and is reported in chapters 6 and 11 in vascular surgical conditions. The predominant cervical CT-BC parameter reported in patients with head and neck cancer is the C3 SMI rather than masseter area, and is recommended by the authors of a recent meta-analysis³⁵¹. Normalisation of muscle areas is well established in the measurement of CT-BC parameters, therefore the present study employs more robust methodology than previous studies. Similarly, whilst the use of NLR and mGPS as an assessment of the SIR from myeloid and liver tissue respectively has been widely reported, SIG incorporating both, represents a more comprehensive assessment.

The prevalence, associations, and prognostic value of low skeletal muscle mass have been assessed in a range of disease states. The majority of studies report on patients with cancer, where standardised thresholds of skeletal muscle mass and density at L3 have been proposed and validated⁸⁴. The present study analysed muscle mass and density at C3, as abdominal CTs were not available in patients undergoing assessment for carotid endarterectomy. Nonetheless, sarcopenia is a systemic disease process, which in principle should affect skeletal muscle globally, thereby supporting our rationale for measuring

cervical musculature. Furthermore, multiple studies in patient with head and neck cancer report outcomes based on C3 SMI³⁵¹. We also reported the L3 dSMI using a previously proposed method of derivation³⁵⁷. There appear to be shared risk factors which contribute to similar prevalences of sarcopenia irrespective of disease state, as reported in chapter 8. By reporting and reproducing the derivation of L3 dSMI from C3 SMI, the results of the present study enable the potential comparison of muscle mass between cohorts using different measurement techniques, as well as contributing to the evidence base that sarcopenia can be assessed at a variety of vertebral levels depending on the availability of relevant imaging.

The present study is limited by retrospective design, relatively small sample-size in certain sub-groups, and data-derived thresholds for CT-BC parameters. The use of arterial phase images may limit comparison with external cohorts, due to the potential confounding effect of CT phase on SMD measurement²⁴⁵. Patients with asymptomatic carotid lesions were not included, thereby limiting the application of conclusions to the entire population of patients undergoing carotid endarterectomy, however the cohort reflects contemporary real-world UK practice³⁷. Lack of a “healthy” control group potentially limits the validity of our conclusions, however the exposure to ionising radiation required for CT scanning makes this non-feasible. Data detailing specific cause of death were not available, we therefore inferred that the likely increased mortality is cardiovascular in aetiology based on previous literature, however this is a limitation and potential source of bias. The use of ASA to measure comorbidity is a potential source of bias in a retrospective study due to changing implementation of ASA, which is particularly apparent in the context of recent cerebrovascular event given that fewer patients than expected had ASA > 2.

In conclusion, cervical CT-derived muscle mass and density, and readily available markers of systemic inflammation such as SIG may be used to identify patients with inferior long-term prognosis following carotid endarterectomy. These factors may offer clinical utility in selecting patients likely to benefit from surgery, and in developing novel secondary prevention strategies, though large prospective validation of the present results is required.

12.5 TABLES

Table 12.1: Threshold values of cervical CT-BC parameters associated with inferior survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618).

Table 12.2: The association between baseline clinical characteristics and systemic inflammation, sub-grouped by CT-BC parameters, in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618).

Table 12.3: The relationship between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618).

Table 12.1: Threshold values of cervical CT-BC parameters associated with inferior survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618)	
Low C3 SMI	
Males, BMI < 25.0 kg/m ²	≤ 14.8 cm ² /m ²
Males, BMI ≥ 25.0 kg/m ²	≤ 17.7 cm ² /m ²
Females, BMI < 25.0 kg/m ²	≤ 12.8 cm ² /m ²
Females, BMI ≥ 25.0 kg/m ²	≤ 11.8 cm ² /m ²
Low C3 SMD	
Males	≤ 43.7 HU
Females	≤ 37.4 HU
Low L3 dSMI	
Males, BMI < 25.0 kg/m ²	≤ 50.0 cm ² /m ²
Males, BMI ≥ 25.0 kg/m ²	≤ 50.5 cm ² /m ²
Females, BMI < 25.0 kg/m ²	≤ 32.7 cm ² /m ²
Females, BMI ≥ 25.0 kg/m ²	≤ 37.1 cm ² /m ²

Table 12.2: The association between baseline clinical characteristics and systemic inflammation, sub-grouped by CT-BC parameters, in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618)

	Normal C3 SMI	Low C3 SMI	<i>p</i>	Normal C3 SMD	Low C3 SMD	<i>p</i>
Age ≥ 75	76 (27%)	111 (34%)	0.06	117 (27%)	71 (38%)	<0.05
Female Sex	127 (45%)	53 (16%)	<0.001	154 (36%)	26 (14%)	<0.001
BMI ≥ 25 kg/m²	201 (71%)	225 (69%)	0.61	286 (67%)	140 (75%)	0.06
ASA > 2	180 (68%)	217 (70%)	0.63	262 (65%)	135 (75%)	<0.05
CVA at diagnosis	142 (50%)	160 (50%)	0.91	208 (49%)	98 (53%)	0.41
SIG (≥ 2)	31 (11%)	63 (19%)	<0.05	62 (15%)	33 (18%)	0.09

Table 12.3: The relationship between baseline clinical characteristics, CT-BC parameters, systemic inflammation, and overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis (n = 618)

		Univariate			Multivariate		
Covariate	N (%)	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Age ≥ 75	188 (30%)	2.46	1.83 – 3.31	<0.001	2.17	1.58 – 2.97	<0.001
Female Sex	180 (29%)	1.27	0.93 – 1.73	0.13	-	-	-
BMI ≥ 25 kg/m ²	426 (70%)	0.70	0.51 – 0.95	<0.05	0.64	0.47 – 0.89	<0.01
ASA > 2	397 (68%)	2.36	1.56 – 3.56	<0.001	2.06	1.35 – 3.12	<0.001
CVA at diagnosis	306 (50%)	1.01	0.75 – 1.36	0.95	-	-	-
Low C3 SMI*	328 (54%)	1.62	1.20 – 2.19	<0.01	1.20*	0.86 – 1.67	0.28
Low L3 dSMI*	270 (44%)	2.38	1.75 – 3.22	<0.001	1.40*	0.97 – 2.02	0.07
Low C3 SMD	189 (31%)	2.02	1.50 – 2.71	<0.001	1.84	1.33 – 2.54	<0.001
SIG (≥ 2)	95 (15%)	1.68	1.40 – 2.03	<0.001	1.63	1.33 – 1.99	<0.001

For covariates with >2 subgroups, the first category was considered as the reference category. * - C3 SMI and L3 dSMI modelled separately in multivariate model to avoid multicollinearity, values reported for other covariates in the multivariate model pertain to the model including C3 SMI.

Table 12.4: The comparison between the final study cohort and patients excluded from the study on the basis of missing CT-BC parameters or SIG			
	Excluded Patients (n = 352)	Final Study Cohort (n = 618)	<i>p</i>
Age			
< 75	239 (68%)	430 (70%)	0.68
≥ 75	111 (32%)	188 (30%)	
Sex			
Male	249 (71%)	438 (71%)	0.97
Female	103 (29%)	180 (29%)	
BMI			
< 25 kg/m ²	76 (25%)	187 (31%)	0.07
≥ 25 kg/m ²	231 (75%)	426 (69%)	
ASA			
≤ 2	37 (13%)	184 (32%)	<0.001
> 2	260 (87%)	397 (68%)	
Indication			
CVA	45 (43%)	219 (48%)	0.11
TIA	59 (57%)	238 (52%)	

12.6 FIGURES

Figure 12.1: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle index (C3 SMI), $p < 0.01$.

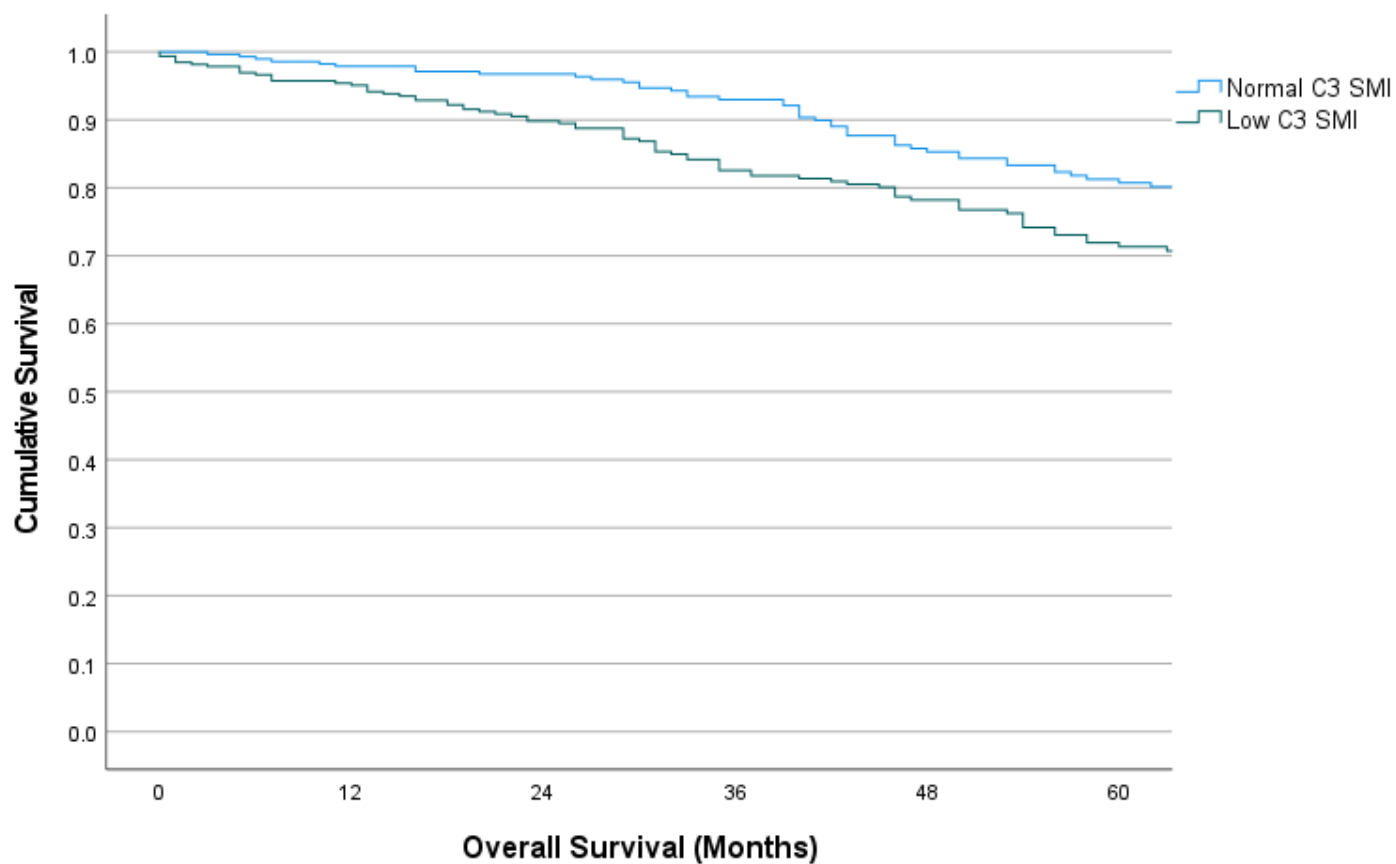
Figure 12.2: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle density (C3 SMD), $p < 0.001$.

Figure 12.3: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by systemic inflammatory grade (SIG), $p < 0.001$.

Figure 12.4: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle index (C3 SMI) & systemic inflammatory grade (SIG), $p < 0.001$.

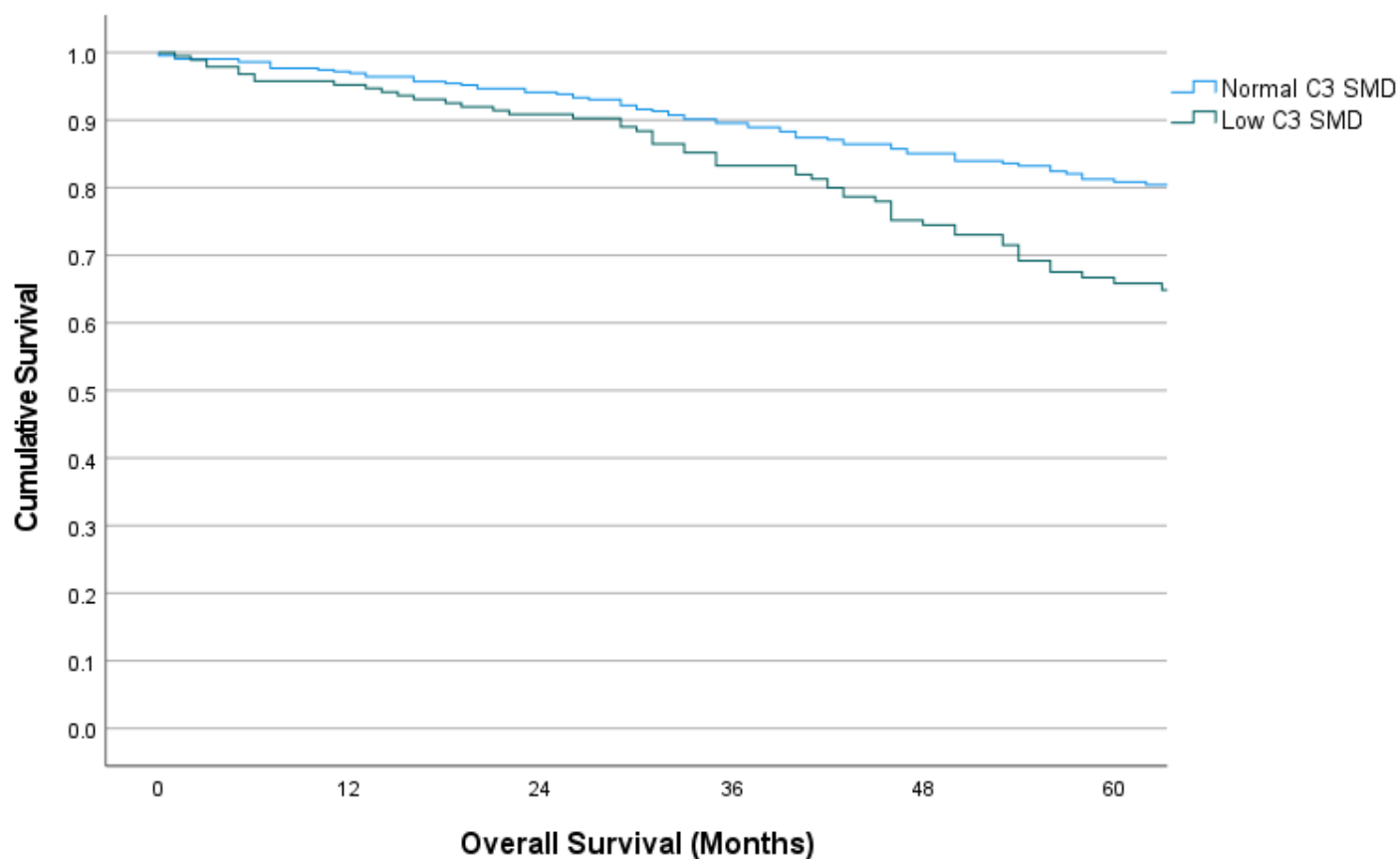
Figure 12.5: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle density (C3 SMD) & systemic inflammatory grade (SIG), $p < 0.001$.

Figure 12.6: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by L3 derived skeletal muscle index (L3 dSMI), $p < 0.001$.



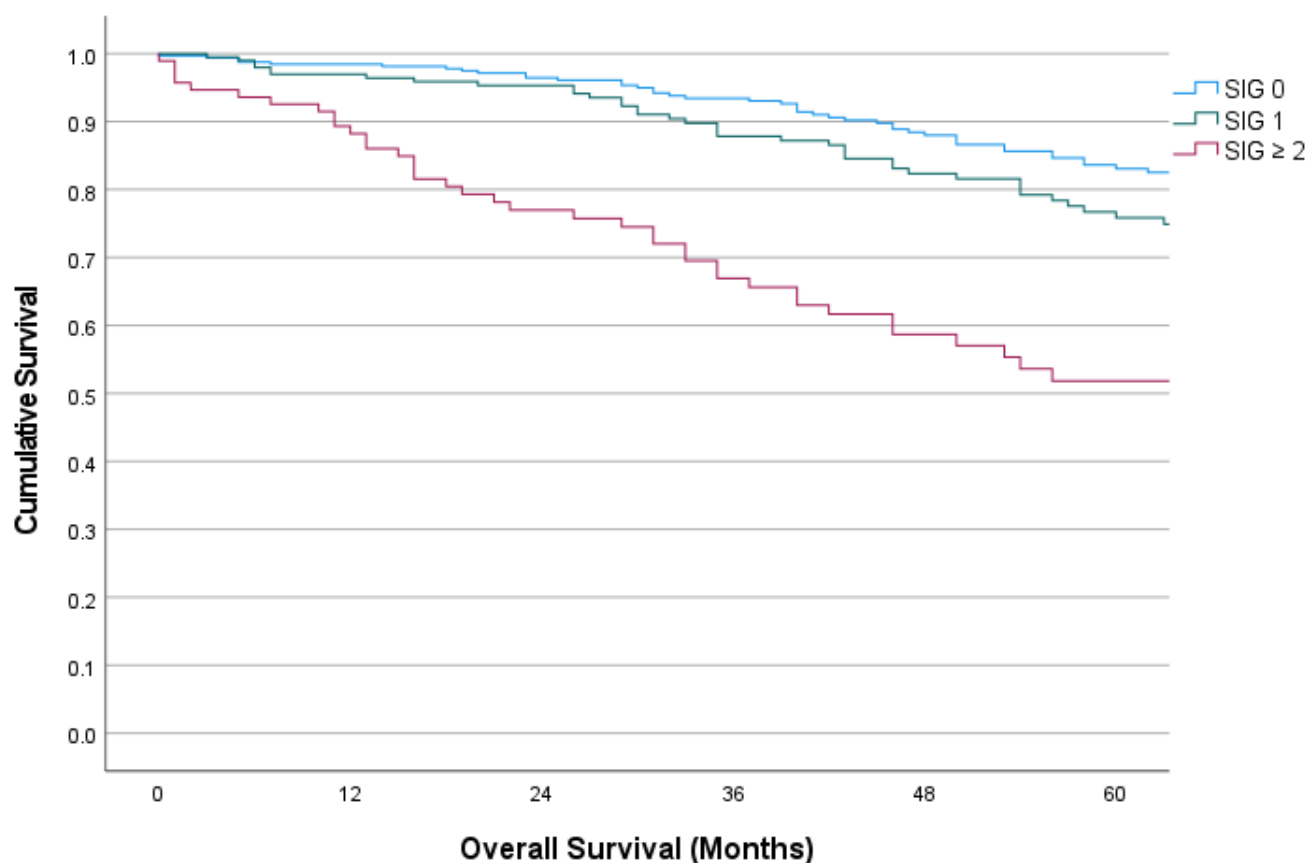
		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	Normal C3 SMI	285	270	246	214	176	150
	Low C3 SMI	328	303	256	205	165	123

Figure 12.1: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle index (C3 SMI), $p < 0.01$.



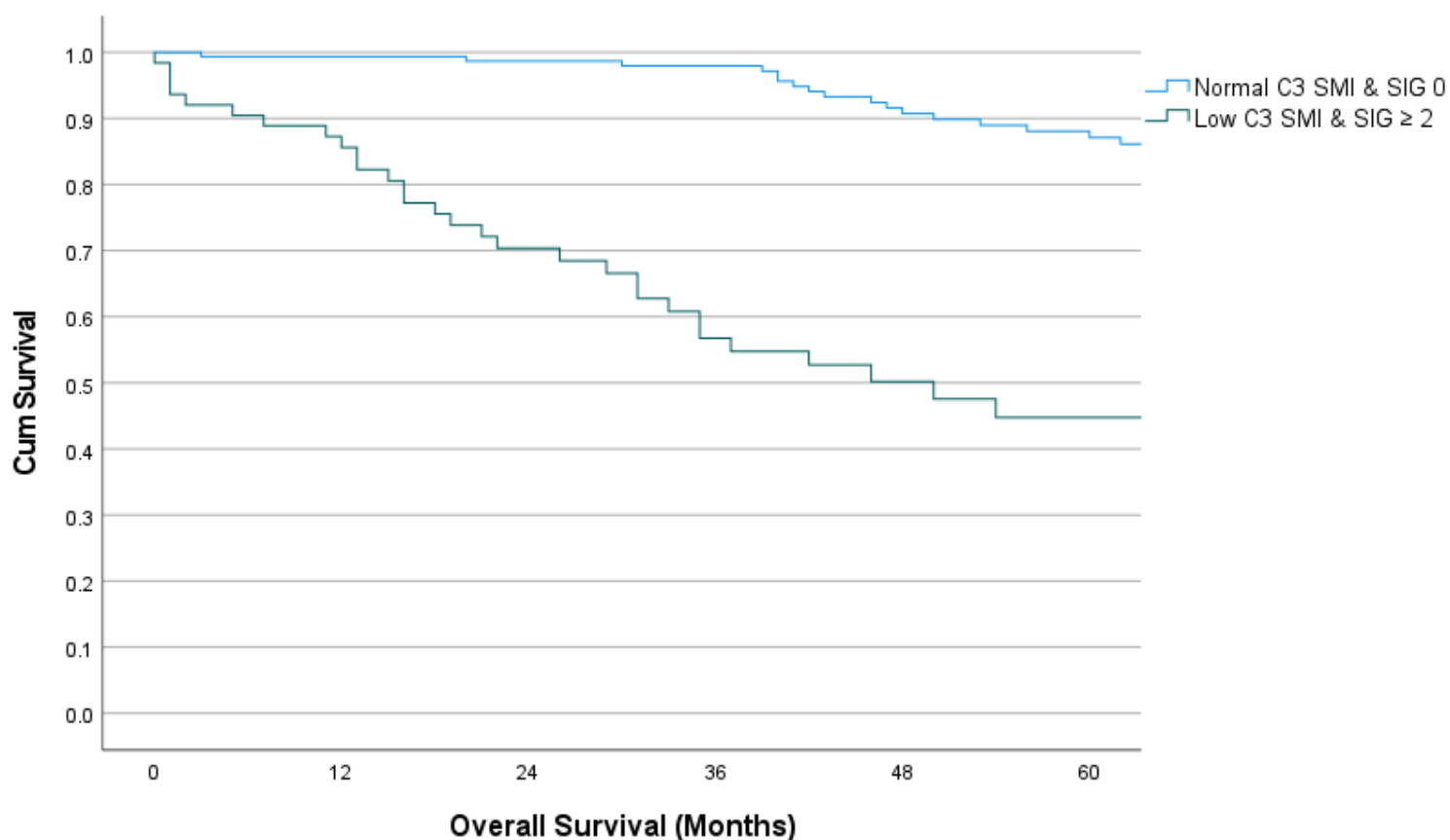
		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	Normal C3 SMD	429	400	348	295	237	198
	Low C3 SMD	189	178	159	129	106	77

Figure 12.2: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle density (C3 SMD), $p < 0.001$.



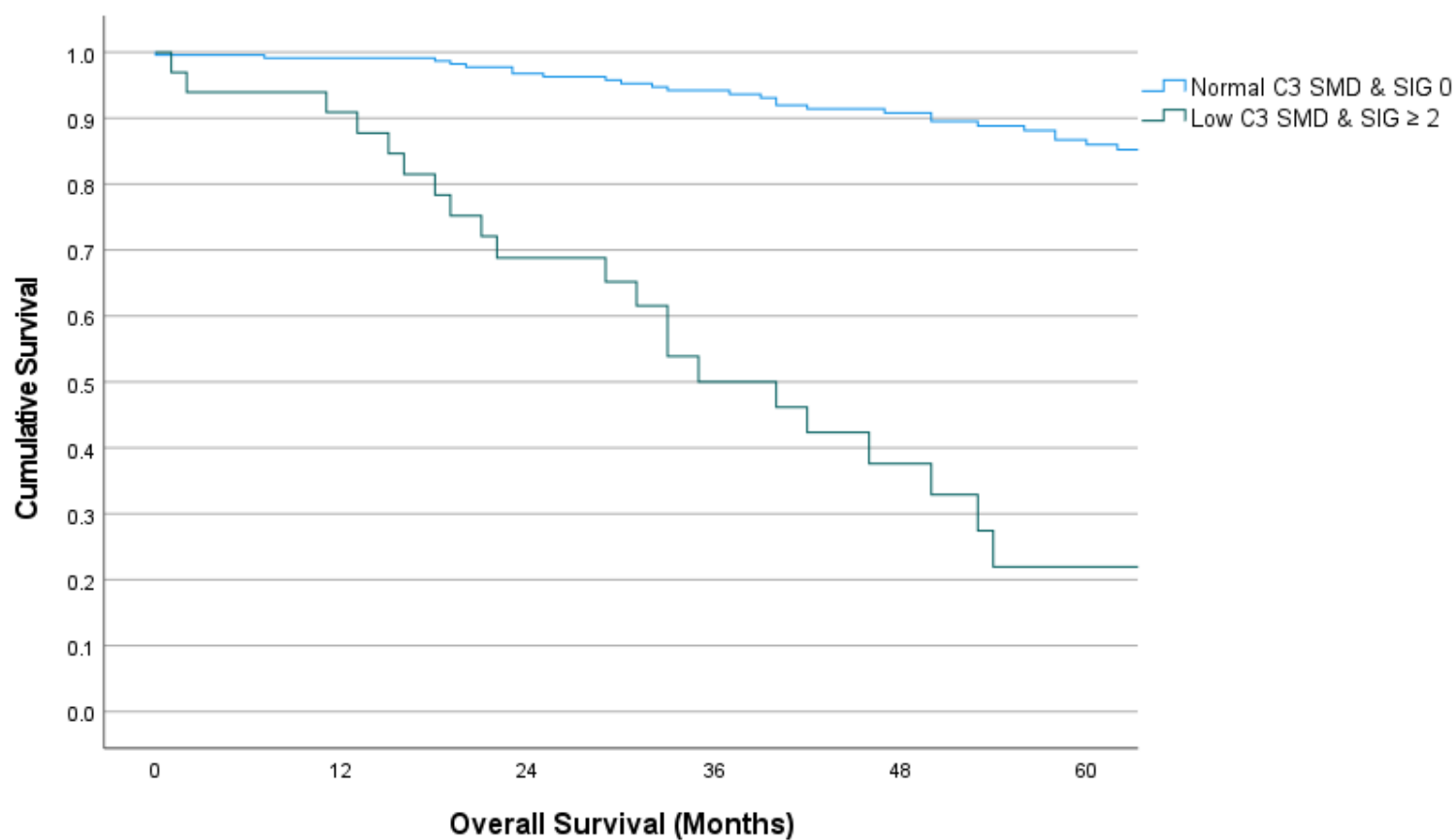
		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	SIG 0	325	308	278	236	194	158
	SIG 1	197	186	161	134	110	89
	SIG ≥ 2	94	82	66	52	37	27

Figure 12.3: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by systemic inflammatory grade (SIG), $p < 0.001$.



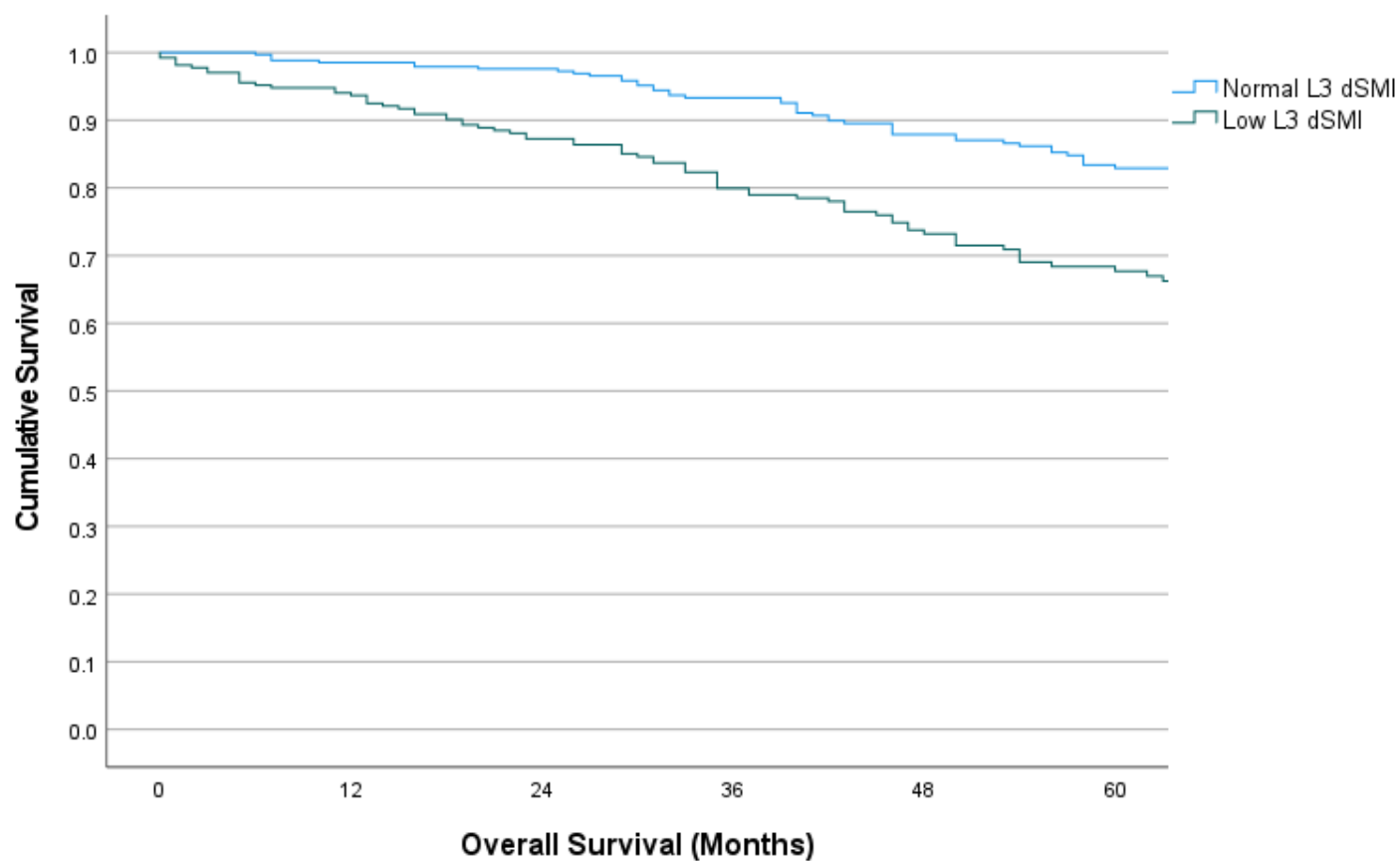
		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	Normal C3 SMI & SIG 0	159	152	141	128	106	93
	Low C3 SMI & SIG ≥ 2	63	53	40	28	20	13

Figure 12.4: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle index (C3 SMI) & systemic inflammatory grade (SIG), $p < 0.001$.



		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	Normal C3 SMD & SIG 0	236	223	200	172	141	119
	Low C3 SMD & SIG ≥ 2	33	29	21	13	8	3

Figure 12.5: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by C3 skeletal muscle density (C3 SMD) & systemic inflammatory grade (SIG), $p < 0.001$.



		Interval (Months)					
		0	12	24	36	48	60
Number at Risk	Normal L3 dSMI	341	327	291	251	206	173
	Low L3 dSMI	270	244	209	166	133	100

Figure 12.6: Overall survival in patients undergoing carotid endarterectomy for symptomatic carotid stenosis when sub-grouped by L3 derived skeletal muscle index (L3 dSMI), $p < 0.001$.

13 LONGITUDINAL ASSOCIATION BETWEEN STATINS AND CHANGES IN CT-BODY COMPOSITION IN PATIENTS WITH ABDOMINAL AORTIC ANEURYSM

13.1 INTRODUCTION

In previous chapters, the potential prognostic value and associations of CT-BC parameters and measures of the SIR both independently (chapters 3 and 5 respectively) and together (chapter 6) in patients with AAA have been discussed. We highlight a clear association between altered CT-BC, systemic inflammation, and outcomes in this patient group.

In the wider literature investigating CT-BC, predictors of low skeletal muscle mass in the pre-operative period have been extensively investigated. However, factors associated with the rate of skeletal muscle loss through longitudinal analyses are less well described. Several studies in patients both with and without cardiovascular disease report longitudinal analyses^{359,360}. It remains uncertain whether either disease-specific or host-specific factors dominate the development and progression of low skeletal muscle mass, with the data presented in chapter 8 suggesting that host factors may play a greater role than previously thought. The current lack of longitudinal CT-BC data limit our understanding of the natural history of skeletal muscle loss even when the disease with which it may be associated is treated, for example repair of AAA or cancer resection.

Statins, HMG-CoA reductase inhibitors, are one of the most commonly prescribed medications in high and middle income countries³⁶¹. Their predominant role is in primary and secondary prevention of cardiovascular disease, largely thought to be due to their lipid-lowering effect. Guidelines recommend prescribing statins in patients with AAA on this basis²². More recently, the effect of statins as anti-inflammatory medications has become more widely reported and the anti-inflammatory effect as a potential therapeutic mechanism explored^{61,362}. The major side-effect of statins, reported in up to 15% of patients, is myalgia, with the underlying myopathic mechanism poorly understood^{363,364}. Somewhat paradoxically, small series of patients with cardiovascular disease have emerged describing an association between statin therapy, increased baseline skeletal muscle mass³⁶⁵, and reduced rate of skeletal muscle loss³⁶⁶. In patients with cardiovascular disease, studies describing longitudinal CT-BC data and those describing the role of statin

therapy are relatively small and in some cases report non-standard measures of CT-BC parameters.

The present study aimed to describe the association between pre-operative and longitudinal CT-BC parameters, statin therapy, systemic inflammation, and survival in a cohort of patients undergoing elective intervention for AAA.

13.2 MATERIALS & METHODS

13.2.1 PATIENT SELECTION

The patient recruitment and data collection for the AAA cohort is discussed in section 1.7.2.1. Age (≤ 75 , > 75) and BMI ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$) were considered as categorical variables. The minimum follow-up interval for survival analysis was two years from the date of surgery.

13.2.2 PRESCRIBING DATA

Data on pre-operative medications were recorded from pre-assessment clinic data, which are routinely performed in all patients prior to major elective intervention. This constitutes a structured assessment which is performed by a specialist nurse practitioner, where accurate current prescribing data is recorded from both primary care records and directly from the patient. Specific choice of statin therapy was at the discretion of the primary care team based on their local policies, and typical practice in patients with AAA is to prescribe the maximum tolerated dose. Patients were sub-grouped by statin use (yes / no) and outcomes compared between sub-groups.

13.2.3 PRE-OPERATIVE CT IMAGES

Contrast-enhanced arterial-phase CTs performed routinely as part of pre-operative workup were accessed, and a slice at the midpoint of the L3 vertebral body (identified by anatomical landmarks) chosen for analysis.

13.2.4 FOLLOW-UP CT IMAGES

Longitudinal analyses of follow-up contrast-enhanced arterial-phase CT images at L3 in patients undergoing EVAR or F/B-EVAR (OSR patients do not typically undergo surveillance) was performed. Surveillance protocols were different between institutions (with some preferring ultrasound surveillance), however typical policy was to perform a follow-up CT at approximately 12 months post-procedure. Medical records of all patients undergoing EVAR or F/B-EVAR were screened, and CTs performed ≥ 11 months post-procedure were included, with no maximal time interval (range 11 – 71 months). Cases were excluded if the CT was performed for non-surveillance indications, if follow-up CT identified an incidental confounding pathology (e.g. new radiological diagnosis of cancer), or if a new confounding pathology was documented in the medical records between index

procedure and follow-up scan. Cases were not excluded on the basis of endoleak as this was thought unlikely to influence CT-BC.

13.2.5 BODY COMPOSITION ANALYSIS

Body composition analysis was performed using the methodology described in section 1.7.3. The thresholds derived in chapter 3 were applied to each parameter to sub-group patients into “normal” and “high/low”. Additionally, for follow-up CTs, the Δ SMI (cm^2/m^2) was calculated as $\text{SMI}_{\text{follow-up}} - \text{SMI}_{\text{pre-op}}$. The % Δ SMI was then calculated as $\Delta\text{SMI} / \text{SMI}_{\text{pre-op}}$, and was normalised to the interval from baseline CT to surveillance CT to generate % Δ SMI/year. This method was repeated for SFI, VFI, and SMD. Patients were also sub-grouped based on SMI or SMD change ($\leq 10\%$ or $> 10\%$ loss in keeping with previous longitudinal CT-BC analyses³⁵⁹) and comparisons between groups made.

13.2.6 INFLAMMATORY PROFILING

SIG was chosen as the inflammation-based prognostic score of interest, calculated as described in chapter 5. Outcomes were compared between groups of SIG 0 (considered “non-inflamed”) vs. SIG 1 (considered “mildly inflamed”) vs. SIG ≥ 2 (considered “inflamed”).

13.2.7 OUTCOMES OF INTEREST

The outcomes of interest were the association between statin therapy and pre-operative CT-BC parameters, the difference between pre-operative and follow-up CT-BC parameters, and the different factors associated with $>10\%$ or $\leq 10\%$ skeletal muscle loss from pre-operative to follow-up CT.

13.2.8 STATISTICAL ANALYSES

General statistical analyses are described in section 1.7.4. Differences between paired continuous data were performed using the Wilcoxon Matched Pairs test, and between paired categorical data using the McNemar test. Missing data were selectively excluded from relevant analyses on a case-by-case basis. Typically, missing CT-BC parameters were due to CT image compromise or missing height, and missing SIG was due to lack of CRP on pre-operative bloodwork. Due to the wide range in follow-up CT interval, a sensitivity analysis only on CTs performed 11 – 18 months following intervention was performed.

All analyses were performed using IBM SPSS 28.0. p values < 0.05 were considered statistically significant.

13.3 RESULTS

756 patients undergoing elective intervention for AAA were eligible for inclusion into the study. There were 154 (20%) patients treated by OSR, 702 (93%) males, and a median (IQR) age of 73.0 (11.0) years. Median (IQR) follow-up was 75 (32) months, and there were 272 (36%) deaths during the follow-up period. Mean (95% CI) survival in the entire study population was 90.0 (84.0 – 96.1) months. Regarding longitudinal analyses, there were 599 patients who underwent EVAR or F/B-EVAR with suitable pre-operative CTs for comparison, of which 273 (46%) had a suitable follow-up CT and were included in longitudinal analyses. Median (IQR) time from procedure to follow-up CT was 15 (9) months. Table 13.1 displays the differences between patients who underwent EVAR or F/B-EVAR with ($n = 273$) and without ($n = 326$) follow-up CTs. Patients with follow-up CTs were typically younger ($p < 0.05$), with lower socio-economic deprivation ($p < 0.05$), and a lower prevalence of pre-operative anaemia ($p < 0.01$).

The characteristics of the entire study cohort when sub-grouped by statin therapy are shown in Table 13.2. There were 582 patients (77%) receiving statin therapy, and 174 patients (23%) not receiving statin therapy, and during follow-up there were 206 (35%) deaths in the statin therapy sub-group and 66 (38%) deaths in the no statin therapy sub-group. Patients receiving statin therapy had a higher ASA ($p < 0.001$), and a higher BMI ($p < 0.05$). Regarding CT-BC, high SFI ($p < 0.05$) and high VFI ($p < 0.01$) were more prevalent in patients receiving statin therapy, whilst low SMI ($p < 0.001$) was less prevalent in patients receiving statin therapy. On univariate analysis of patients taking statins, higher age ($p < 0.001$), high creatinine ($p < 0.05$), low haemoglobin ($p < 0.01$), low pre-operative SMI ($p < 0.001$), and low pre-operative SMD ($p < 0.01$) were associated with inferior survival, whilst high BMI ($p < 0.01$), high pre-operative SFI ($p < 0.01$), and high pre-operative VFI ($p < 0.05$) were associated with superior survival. On multivariate analysis of patients taking statins, higher age (HR 1.72, 95% CI 1.31 – 2.26, $p < 0.001$), high pre-operative SFI (HR 0.59, 95% CI 0.37 – 0.95, $p < 0.05$), and low pre-operative SMD (HR 1.75, 95% CI 1.23 – 2.49, $p < 0.01$) were associated with survival. On univariate analysis of patients not taking statins, higher age ($p < 0.001$), higher AAA diameter ($p < 0.05$), high creatinine ($p < 0.01$), low haemoglobin ($p < 0.001$), low pre-operative SMI ($p < 0.001$), and low pre-operative SMD ($p < 0.05$) were associated with inferior survival, whilst OSR ($p < 0.01$) was associated with superior survival. On multivariate analysis of patients not taking statins, higher age (HR 1.77, 95% CI 1.05 – 3.00, $p < 0.05$) and low pre-operative SMI (HR 2.71, 95% CI 1.44 – 5.10, $p < 0.01$) were associated with survival.

Table 13.3 displays the differences between pre-operative and follow-up categorical CT-BC parameters in the entire longitudinal cohort ($n = 273$) and in patients sub-grouped by statin therapy. In the entire longitudinal cohort, from pre-operative to follow-up CTs the comparative prevalences of high SFI ($p = 0.63$) and high VFI ($p = 0.22$) were similar, and there was an increase in the comparative prevalences of low SMI (43% vs. 50%, $p < 0.01$) and low SMD (64% vs. 88%, $p < 0.001$). These changes are also displayed in waterfall plots in figures 13.1 and 13.2, where $\% \Delta$ SFI/VFI/SMI/SMD per year is displayed. When sub-grouped by statin therapy (statin therapy $n = 218$, no statin therapy $n = 55$), from pre-operative to follow-up CTs there was no change in SFI or VFI in patients both taking and patients not taking statins. In patients taking statins there was an increase in the prevalence of low SMI (38% vs. 45%, $p < 0.05$), and there was an increase in the prevalence of low SMD in both patients taking (64% vs. 89%, $p < 0.001$) and patients not taking (62% vs. 84%, $p < 0.001$) statins.

Table 13.4 displays the sex-specific differences between pre-operative and follow-up median (IQR) CT-BC parameters in the entire longitudinal cohort ($n = 273$) and in patients sub-grouped by statin therapy. Low absolute numbers ($n = 1$) of eligible female patients in the “No Statin Therapy” sub-group precluded meaningful analysis of this sub-group. In the entire longitudinal cohort, from pre-operative to follow-up CTs, there was an increase in median SFI ($p < 0.05$) and VFI ($p < 0.01$) in male patients only, there was a decrease in median SMI ($p < 0.001$ in males, $p < 0.01$ in females) and SMD ($p < 0.001$ in males, $p < 0.01$ in females), In male patients taking statins ($p < 0.05$) and not taking statins ($p < 0.05$) there was an increase in VFI. There was a decrease in median SMI in patients both taking ($p < 0.001$ in males, $p < 0.01$ in females) and not taking ($p < 0.001$) statins, There was a decrease in median SMD in patients both taking ($p < 0.001$ in males, $p < 0.01$ in females) and not taking ($p < 0.001$) statins.

Table 13.5 displays the association between baseline covariates and $>10\%$ loss of SMI or SMD as assessed by a univariate binary logistic regression model. Low pre-operative SMD was associated with reduced odds of $>10\%$ SMD loss (OR 0.59, 95% CI 0.35 – 0.99, $p < 0.05$), whilst other associations were non-significant. The comparison between patients with follow-up CTs based on $\leq 10\%$ loss of SMI ($n = 208$) and $>10\%$ loss of SMI ($n = 65$), and $\leq 10\%$ loss of SMD ($n = 98$) and $>10\%$ loss of SMD ($n = 175$) is shown in table 9.6. Low pre-operative SMD was associated with reduced rate of $>10\%$ loss of SMD (68% vs. 56%, $p < 0.05$), whilst other comparisons were non-significant.

Figure 13.3 displays Kaplan-Meier survival plots in patients sub-grouped by $\leq 10\%$ loss of SMI and $> 10\%$ loss of SMI (figure 13.3a) and by $\leq 10\%$ loss of SMD and $> 10\%$ loss of SMD (figure 13.3b). In patients with $\leq 10\%$ loss of SMI, mean (95% CI) survival was 91.6 (87.2 – 95.9) months vs. 89.3 (80.4 – 98.2) months in patients with $> 10\%$ loss of SMI ($p = 0.58$). In patients with $\leq 10\%$ loss of SMD, mean (95% CI) survival was 89.5 (83.1 – 96.0) months vs. 94.4 (89.3 – 99.5) months in patients with $> 10\%$ loss of SMD ($p = 0.56$).

Scatters plots of change in CT-BC parameters against follow-up interval (months) are shown in figures 13.4 and 13.5. For each CT-BC parameter, the data presented do not show a linear relationship with time. A sensitivity analysis including only patients with a follow-up interval from pre-operative CT to follow-up CT of 11-18 months is shown in table 13.7. In the sensitivity analysis, from pre-operative to follow-up CTs, there was a decrease in median SMI ($p < 0.001$) and SMD ($p < 0.001$), and an increase in the comparative prevalences of low SMI (41% vs. 47%, $p < 0.05$) and low SMD (67% vs. 87%, $p < 0.001$), however there was no significant difference in the change of SFI or VFI.

13.4 DISCUSSION

The present study describes several important observations which contribute to the understanding of the complex interactions between body composition, statins, and systemic inflammation. Skeletal muscle mass and density appear to continue to decline following repair of AAA, with significantly lower values observed at a relatively short interval from surgery. An association between statin therapy and greater pre-operative skeletal muscle mass was observed, however despite this association, statin therapy does not appear to be associated with the rate of loss of skeletal muscle following AAA repair. The typical pattern of change in body composition was a gain in subcutaneous and visceral fat with an associated loss in skeletal muscle mass and quality. This suggests the development of so-called “sarcopenic obesity”, a clinical entity which may confer discrete risk compared to high adiposity or low muscle mass in isolation^{367,368}.

The longitudinal data presented in the present study highlight the progressive nature of skeletal muscle loss, with the marked increase in prevalence of low SMD a particular novel finding of interest. These findings support those observed by Lindström *et al*³⁶⁶, though with the use of more established CT-BC methodology, and assessment of the systemic inflammatory response. Despite the progressive changes in skeletal muscle observed, the present study did not observe a significant difference in mortality when patients were subgrouped based on magnitude of muscle loss, however this may reflect the relatively small sample size and hence power of the study. A difference between the observations of the present study and those of Lindström *et al* is that the former did not observe an association between statin therapy and increased rate of loss of muscle mass. Whilst this may reflect the modest sample size, this in particular highlights the complexity of the relationship between statin therapy and muscle tissue. Systemic inflammation appears to have a detrimental effect on skeletal muscle mass and density; indeed Hacker *et al* propose that low skeletal muscle mass should be considered a symptom of systemic inflammation rather than a discrete prognostic entity²¹¹, and these observations are similar to those observed in chapter 11 of the present thesis. Taken in conjunction with the evidence of statins as anti-inflammatory agents, it is somewhat surprising that those patients taking statins in the present study did not display increased rate of muscle loss. This perhaps highlights the dominant effect of host factors, for example higher age, in determining skeletal muscle loss. Dolan *et al* report that, in a cohort of 783 patients undergoing surgery for colorectal cancer, markers of systemic inflammation (mGPS) were associated with loss of skeletal muscle³⁵⁹. The presence of colorectal cancer may however impact the validity of their

results when discussing a non-cancer cohort; comparative data between patients with CRC and with AAA are discussed in chapter 8. Further analyses of longitudinal CTs in both of these cohorts is required.

The relationship between statin therapy and skeletal muscle has been described in prior studies. Valdivieso *et al* report a series of 136 patients with cardiac failure, where statin therapy was associated with a lower prevalence of clinically assessed sarcopenia³⁶⁵. The present study reports similar observations in a different cohort of patients with cardiovascular disease, with the use of standardised methodology in CT-BC analysis, and the consideration of the SIR, which is an accepted major aetiological factor in the development of low skeletal muscle mass and sarcopenia²⁴⁷. Myopathy as a result of statin therapy is well described, though there remains uncertainty as to the underlying mechanism^{363,364}. This phenomenon makes the finding of higher skeletal muscle mass in the statin cohort somewhat unexpected. Another paradoxical observation is that this preservation of skeletal muscle occurred in the cohort with increased comorbidity and obesity, both of which have been associated with low skeletal muscle mass^{247,371}. Interestingly, the association between low pre-operative SMI and survival was more marked in the cohort of patients who did not receive a statin, in whom SMI itself was typically lower. It may be that as SMI declines, the effect on survival is not manifest until a “tipping point” of muscle mass is reached, and that initially compensation for the loss of muscle mass occurs. Age, an important determinant of muscle mass, was consistently associated with inferior survival, independent of body composition, statin use, or systemic inflammation.

Of particular interest, there was not a reduction in the magnitude of the systemic inflammatory response in patients taking statins. The precise mechanism by which statins exert an anti-inflammatory effect is incompletely understood, with multiple potential pathways suggested³⁷⁰. It may be that SIG, used by the present study, does not capture the pathway involved, such as complement-mediated inflammation, or that the present study was underpowered to observe an effect due to the relatively low prevalence of $SIG \geq 2$ in patients with AAA (as compared to patients with cancer¹⁰⁴). Regardless, the clinical benefit of statins appears to be greatest in patients with activation of the SIR, as observed in the JUPITER trial; Ridker *et al* observed that, in patients with elevated high-sensitivity CRP and low cholesterol, rosuvastatin therapy was associated with a reduced rate of cardiovascular events⁶². Statins are of particular interest as a potential therapeutic agent for given their generally favourable side effect profile, cost, and widespread availability.

Whilst their use may mitigate the effect of systemic inflammation on prognosis, additional immunomodulatory adjuncts may also play a role in improving long term outcomes. A recent meta-analysis reports that, in patients with atherosclerotic disease who are already receiving statin therapy, inflammation is the predominant factor influencing prognosis²⁷⁷. Immunomodulation in atherosclerotic disease has been explored in large trials, with ongoing investigation to identify the agent with optimal efficacy and side effect profile^{173,217}.

The lack of data on drug dose and duration of therapy are potential sources of bias in the present study. It is likely that a proportion of patients in the “statin therapy” sub-group were taking a dose below the maximal target, therefore the population may be somewhat heterogeneous. Despite this, the direct association between statin therapy and maintained skeletal muscle mass was observed, indicating that, should the study be repeated with all patients on maximal dose statin, the “statin effect” would be manifest to a greater extent. This is an important area of further investigation.

The present study is limited by retrospective study design, missing data for some participants, wide range of follow-up intervals, and the use of data-derived thresholds for CT-BC analysis, which are a potential source of bias and require external validation. Despite missing longitudinal data for some patients, a strength of the use of protocolised follow-up CTs is the ability to exclude potentially confounding diagnoses; CTs performed outside of protocol will be subject to potential bias due to the unknown effect on the parameters of interest. An additional weakness of the present study is the wide range of intervals from procedure to follow-up CT (range 12 to 71 months), however normalisation and sensitivity analyses were performed to attempt to mitigate this source of bias. CT surveillance protocols were limited by loss to follow-up, and in some cases access to CT scanning was disrupted due to the Covid-19 pandemic. Low absolute numbers in some sub-groups limit the validity of some conclusions drawn. The conclusions would be strengthened by data on duration and dose of statin therapy, however these data were not available. Additionally, data on the type of statin (e.g. hydrophilic vs. hydrophobic) prescribed were not available, which is another potential source of bias. Specific cause of death may strengthen our assumption regarding increased cardiovascular morbidity and mortality.

We cannot exclude the role of selection bias in our cohort. It may be that the patients who did not take a statin in the present study had previously been intolerant of statin therapy,

indicative of a specific phenotype which is predisposed to statin myopathy. Therefore, this may have resulted in under-representation of patients who did not experience a protective effect of statins on their skeletal muscle mass. Hence, there is the potential to commit a type 1 error in the present study, and hence the results may not be generalisable to a wider unselected population. It would be of interest to investigate a specific cohort of patients who have been intolerant of statin therapy with regards to their skeletal muscle parameters, however this is beyond the scope of the present thesis. Finally, in the present analysis 93% of the patients studied were male and therefore separate analysis of males and females was not carried out given the likely minimal impact of females on the results obtained. It would be of interest to examine the present relationships in a cohort of female patients.

In conclusion, in patients with AAA, skeletal muscle mass and density appear to progressively decline despite treatment of AAA, though specific determinants of this are uncertain, and statin use does not appear to predispose to either muscle loss or preservation. Statin therapy may be associated with a lower rate of pre-operative low skeletal muscle mass, despite greater comorbidity and BMI, however these results must be interpreted with caution given the potential for selection bias in the present cohort of patients. Further investigation of the mechanistic pathways between progressive changes in muscle mass and quality, statin therapy, and systemic inflammation is warranted.

13.5 TABLES

Table 13.1: The difference between baseline clinical characteristics, systemic inflammation, and pre-operative CT-derived body composition parameters between patients with and without per protocol follow-up CTs in a cohort of patients undergoing elective EVAR or F/B-EVAR for AAA (n = 599).

Table 13.2: The difference between demographic and clinicopathological characteristics, CT-BC, systemic inflammation, and the association between demographic and clinicopathological characteristics and survival, in patients undergoing elective EVAR or OSR for AAA sub-grouped by statin therapy (n = 756).

Table 13.3: The comparison of pre-operative and longitudinal CT-derived body composition parameters (categorical) in patients with per protocol follow-up CTs undergoing elective EVAR or F/B-EVAR for AAA, sub-grouped by statin use (n = 273).

Table 13.4: The comparison of pre-operative and longitudinal CT-derived body composition parameters (continuous) in patients with per protocol follow-up CTs undergoing elective EVAR or F/B-EVAR for AAA, sub-grouped by statin use (n = 273).

Table 13.5: The association between demographic and clinicopathological characteristics, CT-BC, systemic inflammation, and magnitude of SMI or SMD loss in patients undergoing elective EVAR or F/B-EVAR for AAA sub-grouped by statin therapy (n = 273).

Table 13.6: The comparison of demographic and clinicopathological characteristics, CT-BC, and systemic inflammation between patients with $>10\%$ and $\leq 10\%$ loss of SMI or SMD on follow-up CT in a cohort of patients undergoing elective EVAR or F/B-EVAR for AAA (n = 273).

Table 13.7: The comparison of pre-operative and longitudinal CT-derived body composition parameters in patients with per protocol follow-up CTs undergoing elective EVAR or F/B-EVAR for AAA, sensitivity analysis with follow-up interval ≥ 11 and ≤ 18 months (n = 180).

Table 13.1: The difference between baseline clinical characteristics, systemic inflammation, and pre-operative CT-derived body composition parameters between patients with and without per protocol follow-up CTs in a cohort of patients undergoing elective EVAR or F/B-EVAR for AAA (n = 599)

	Follow-up CT (n = 273)	No Follow-up CT (n = 326)	p
Age < 65 65 - 75 > 75	16 (6%) 151 (55%) 105 (39%)	15 (5%) 157 (48%) 154 (47%)	< 0.05
Sex Male Female	254 (93%) 19 (7%)	297 (91%) 29 (9%)	0.39
ASA ≤ 2 > 2	154 (57%) 118 (43%)	191 (59%) 134 (41%)	0.60
BMI < 25 kg/m ² ≥ 25 kg/m ²	53 (19%) 220 (81%)	67 (21%) 258 (79%)	0.72
SIMD More Deprived Less Deprived	118 (43%) 154 (57%)	170 (52%) 156 (48%)	< 0.05
Repair Strategy F/B-EVAR EVAR	53 (19%) 220 (81%)	76 (23%) 250 (77%)	0.25
Baseline AAA Diameter <65mm ≥ 65mm	196 (73%) 74 (27%)	233 (72%) 90 (28%)	0.90
Statin Use Yes No	218 (80%) 55 (20%)	251 (77%) 75 (23%)	0.40

Baseline Creatinine Normal High	208 (77%) 62 (23%)	236 (73%) 89 (27%)	0.22
Baseline Haemoglobin Normal Low	227 (84%) 43 (16%)	239 (74%) 86 (26%)	<0.01
SIG 0 1 ≥ 2	134 (56%) 72 (30%) 33 (14%)	137 (52%) 83 (32%) 43 (16%)	0.32
Pre-operative SFI Normal High	31 (12%) 224 (88%)	38 (12%) 265 (88%)	0.81
Pre-operative VFI Normal High	67 (25%) 106 (75%)	79 (25%) 241 (75%)	0.97
Pre-operative SMI Normal Low	156 (57%) 117 (43%)	167 (54%) 142 (46%)	0.45
Pre-operative SMD Normal Low	98 (36%) 175 (64%)	97 (31%) 218 (69%)	0.19

Table 13.2: The difference between demographic and clinicopathological characteristics, CT-BC, systemic inflammation, and the association between demographic and clinicopathological characteristics and survival, in patients undergoing elective EVAR or OSR for AAA sub-grouped by statin therapy (n = 756)

	Statin Therapy (n=582)	No Statin Therapy (n=174)	<i>p</i> *	Statin Therapy (n=582)		No Statin Therapy (n=174)	
				Univariate‡	Multivariate‡	Univariate‡	Multivariate‡
Age < 65 65 - 75 > 75†	42 (7%) 313 (54%) 227 (39%)	10 (6%) 93 (53%) 71 (41%)	0.53	2.03 1.59 – 2.60 <0.001	1.72 1.31 – 2.26 <0.001	2.70 1.72 – 4.25 <0.001	1.77 1.05 – 3.00 <0.05
Sex Male Female†	538 (92%) 44 (8%)	162 (93%) 12 (7%)	0.77	1.19 0.73 – 1.93 0.48	-	0.71 0.22 – 2.28 0.57	-
ASA ≤ 2 > 2†	298 (51%) 281 (49%)	117 (68%) 56 (32%)	<0.001	1.10 0.84 – 1.45 0.49	-	1.57 0.95 - 2.59 0.08	-
BMI < 25 kg/m ² ≥ 25 kg/m ² †	109 (19%) 470 (81%)	47 (27%) 126 (73%)	<0.05	0.63 0.45 – 0.86 <0.01	1.08 0.68 – 1.70 0.76	1.11 0.64 – 1.94 0.71	-
SIMD More Deprived† Less Deprived	279 (48%) 300 (52%)	71 (41%) 103 (59%)	0.09	0.85 0.65 – 1.13 0.26	-	0.87 0.53 – 1.45 0.60	-
Repair Strategy EVAR or F/B- EVAR OSR†	473 (81%) 109 (19%)	131 (75%) 43 (25%)	0.08	0.84 0.58 – 1.23 0.37	-	0.33 0.15 – 0.73 <0.01	0.50 0.21 – 1.15 0.10
AAA Diameter < 65mm ≥ 65mm†	419 (73%) 159 (27%)	123 (72%) 49 (28%)	0.80	1.19 0.89 – 1.59 0.25	-	1.85 1.12 – 3.06 <0.05	1.34 0.76 – 2.37 0.32
Baseline Creatinine	447 (77%) 131 (23%)	129 (75%) 43 (25%)	0.52	1.48 1.10 – 2.00	1.18 0.85 – 1.65	2.20 1.31 – 3.69	1.54 0.86 – 2.77

Table 13.3: The comparison of pre-operative and longitudinal CT-derived body composition parameters (categorical) in patients with per protocol follow-up CTs undergoing elective EVAR or F/B-EVAR for AAA, sub-grouped by statin use (n = 273)

	Entire Longitudinal Cohort (n = 273)			Statin Therapy (n = 218)			No Statin Therapy (n = 55)		
	Pre-operative CT	Follow-up CT	<i>p</i>	Pre-operative CT	Follow-up CT	<i>p</i>	Pre-operative CT	Follow-up CT	<i>p</i>
SFI									
Normal SFI	31 (12%)	22 (13%)		19 (9%)	21 (10%)		12 (24%)	12 (22%)	
High SFI	224 (88%)	230 (87%)	0.63	186 (91%)	188 (90%)	0.58	38 (76%)	42 (78%)	1.00
VFI									
Normal VFI	67 (25%)	59 (22%)		49 (23%)	44 (20%)		18 (33%)	15 (27%)	
High VFI	206 (75%)	214 (78%)	0.22	169 (77%)	174 (80%)	0.46	37 (67%)	40 (73%)	0.25
SMI									
Normal SMI	156 (57%)	137 (50%)		134 (62%)	119 (55%)		22 (40%)	18 (33%)	
Low SMI	117 (43%)	135 (50%)	<0.01	84 (38%)	99 (45%)	<0.05	33 (60%)	36 (67%)	0.25
SMD									
Normal SMD	98 (36%)	33 (12%)		77 (36%)	24 (11%)		21 (38%)	9 (16%)	
Low SMD	175 (64%)	240 (88%)	<0.01	141 (64%)	194 (89%)	<0.001	34 (62%)	46 (84%)	<0.001

Table 13.5: The association between demographic and clinicopathological characteristics, CT-BC, systemic inflammation, and magnitude of SMI or SMD loss in patients undergoing elective EVAR or F/B-EVAR for AAA sub-grouped by statin therapy (n = 273)

	SMI Loss > 10% (n = 65)	SMD Loss > 10% (n =175)
Age > 75	0.92 0.61 – 1.38 $p = 0.69$	1.36 0.95 – 1.95 $p = 0.10$
Female Sex	0.84 0.27 – 2.64 $p = 0.77$	1.23 0.45 – 3.35 $p = 0.69$
ASA > 2	1.07 0.61 – 1.87 $p = 0.82$	0.88 0.54 – 1.46 $p = 0.62$
BMI ≥ 25 kg/m²	0.59 0.31 – 1.14 $p = 0.12$	0.99 0.53 – 1.86 $p = 0.99$
SIMD (More Deprived)	1.02 0.58 – 1.78 $p = 0.96$	1.18 0.71 – 1.93 $p = 0.53$
AAA Diameter ≥ 65mm	0.83 0.44 – 1.57 $p = 0.56$	1.05 0.60 – 1.83 $p = 0.87$
Statin Use	0.71 0.36 – 1.37 $p = 0.31$	0.76 0.40 – 1.43 $p = 0.39$
High Baseline Creatinine	0.98 0.50 – 1.92 $p = 0.94$	1.14 0.62 – 2.10 $p = 0.67$
Low Baseline Hb	1.46 0.71 – 3.00 $p = 0.31$	0.66 0.34 – 1.28 $p = 0.22$
SIG ≥ 2	0.99 0.65 – 1.51 $p = 0.97$	0.93 0.65 – 1.34 $p = 0.71$
High Pre-operative SFI	0.89 0.38 – 2.11 $p = 0.79$	2.00 0.94 – 4.25 $p = 0.07$
High Pre-operative VFI	0.81 0.43 – 1.51 $p = 0.50$	1.00 0.56 – 1.77 $p = 0.99$
Low Pre-operative SMI	0.86 0.49 – 1.51 $p = 0.59$	1.22 0.74 – 2.01 $p = 0.45$
Low Pre-operative SMD	1.16 0.65 – 2.06 $p = 0.62$	0.59 0.35 – 0.99 $p < 0.05$

Table 13.6: The comparison of demographic and clinicopathological characteristics, CT-BC, and systemic inflammation between patients with >10% and ≤10% loss of SMI or SMD on follow-up CT in a cohort of patients undergoing elective EVAR or F/B-EVAR for AAA (n = 273)

	>10% Loss of SMI (n = 65)	≤10% Loss of SMI (n = 208)	<i>p</i>	>10% Loss of SMD (n = 175)	≤10% Loss of SMD (n = 98)	<i>p</i>
Age < 65 65 - 75 > 75	3 (5%) 37 (57%) 25 (38%)	13 (6%) 114 (55%) 81 (39%)	0.88	18 (10%) 71 (41%) 86 (49%)	15 (15%) 44 (45%) 39 (40%)	0.10
Sex Male Female	61 (94%) 4 (6%)	193 (93%) 15 (7%)	0.77	162 (93%) 13 (7%)	92 (94%) 6 (6%)	0.69
ASA ≤ 2 > 2	36 (55%) 29 (45%)	118 (57%) 89 (43%)	0.82	101 (58%) 74 (42%)	53 (55) 44 (45%)	0.63
BMI < 25 kg/m ² ≥ 25 kg/m ²	17 (26%) 48 (74%)	36 (17%) 172 (83%)	0.12	34 (19%) 141 (81%)	19 (19%) 79 (81%)	0.99
SIMD More Deprived Less Deprived	28 (43%) 37 (57%)	90 (44%) 117 (56%)	0.96	73 (42%) 101 (58%)	45 (46%) 53 (54%)	0.53
Baseline AAA Diameter <65mm ≥ 65mm	49 (75%) 16 (25%)	147 (72%) 58 (28%)	0.56	125 (72%) 48 (28%)	71 (73%) 26 (27%)	0.87
Statin Use Yes No	49 (75%) 16 (25%)	169 (81%) 39 (19%)	0.30	137 (78%) 28 (22%)	81 (83%) 17 (17%)	0.39
Baseline Creatinine Normal High	51 (79%) 14 (21%)	157 (77%) 48 (23%)	0.75	133 (77%) 39 (23%)	78 (80%) 20 (20%)	0.76

Baseline Haemoglobin Normal Low	52 (80%) 13 (20%)	175 (85%) 30 (15%)	0.30	149 (86%) 24 (14%)	78 (80%) 19 (20%)	0.22
SIG 0 1 ≥ 2	31 (57%) 15 (28%) 8 (15%)	103 (56%) 57 (31%) 25 (13%)	0.97	85 (57%) 44 (30%) 20 (13%)	49 (54%) 28 (31%) 13 (15%)	0.71
Pre-operative SFI Normal High	8 (13%) 53 (87%)	23 (12%) 171 (88%)	0.79	15 (9%) 146 (91%)	16 (17%) 78 (83%)	0.07
Pre-operative VFI Normal High	18 (28%) 47 (72%)	49 (24%) 159 (76%)	0.50	43 (25%) 132 (75%)	24 (25%) 74 (75%)	0.99
Pre-operative SMI Normal Low	39 (60%) 26 (40%)	117 (56%) 91 (44%)	0.60	97 (55%) 78 (45%)	59 (60%) 39 (40%)	0.45
Pre-operative SMD Normal Low	22 (34%) 43 (66%)	76 (37%) 132 (63%)	0.69	77 (44%) 98 (56%)	31 (32%) 67 (68%)	<0.05

Table 13.7: The comparison of pre-operative and longitudinal CT-derived body composition parameters in patients with per protocol follow-up CTs undergoing elective EVAR or F/B-EVAR for AAA, sensitivity analysis with follow-up interval ≥ 11 and ≤ 18 months (n = 180)

	Pre-operative CT (n = 180)	Follow-up CT (n = 180)	<i>p</i>
SFI Median (IQR)	65.5 (40.2) cm ² /m ²	67.1 (38.1) cm ² /m ²	0.89
Normal SFI High SFI	20 (12%) 146 (88%)	25 (15%) 147 (85%)	0.11
VFI Median (IQR)	88.8 (60.1) cm ² /m ²	89.9 (57.4) cm ² /m ²	0.28
Normal VFI High VFI	41 (23%) 139 (77%)	38 (21%) 142 (79%)	0.66
SMI Median (IQR)	51.0 (12.4) cm ² /m ²	48.6 (12.9) cm ² /m ²	<0.001
Normal SMI Low SMI	107 (59%) 73 (41%)	95 (53%) 84 (47%)	<0.05
SMD Median (IQR)	37.1 (9.7) HU	32.1 (11.3) HU	<0.001
Normal SMD Low SMD	60 (33%) 120 (67%)	23 (13%) 157 (87%)	<0.001

13.6 FIGURES

Figure 13.1: Percentage change in A) Subcutaneous Fat Index (Δ SFI) and B) Visceral Fat Index (Δ VFI) per year between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm AAA ($n = 273$). X axis is a plot of individual cases.

Figure 13.2: Percentage change in A) Skeletal Muscle Index (Δ SMI) and B) Skeletal Muscle Density (Δ SMD) per year between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$). X axis is a plot of individual cases.

Figure 13.3: Kaplan-Meier survival plots and life table for loss ($\leq 10\%$ / $> 10\%$) of a) skeletal muscle index (SMI, $p = 0.58$) and b) skeletal muscle density (SMD, $p = 0.56$) between pre-operative and follow-up CT subgroups in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$).

Figure 13.4 Scatter plots of total percentage change of A) Subcutaneous fat index (Δ SFI), $R^2 = 0.160$, $p = 0.012$ B) Visceral fat index (Δ VFI), $R^2 = 0.193$, $p = 0.001$ against number of months between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$).

Figure 13.5 Scatter plots of total percentage change of A) Skeletal Muscle Index (Δ SMI), $R^2 = -0.132$, $p = 0.030$. B) Skeletal Muscle Density (Δ SMD), $R^2 = -0.100$, $p = 0.098$ against number of months between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$).

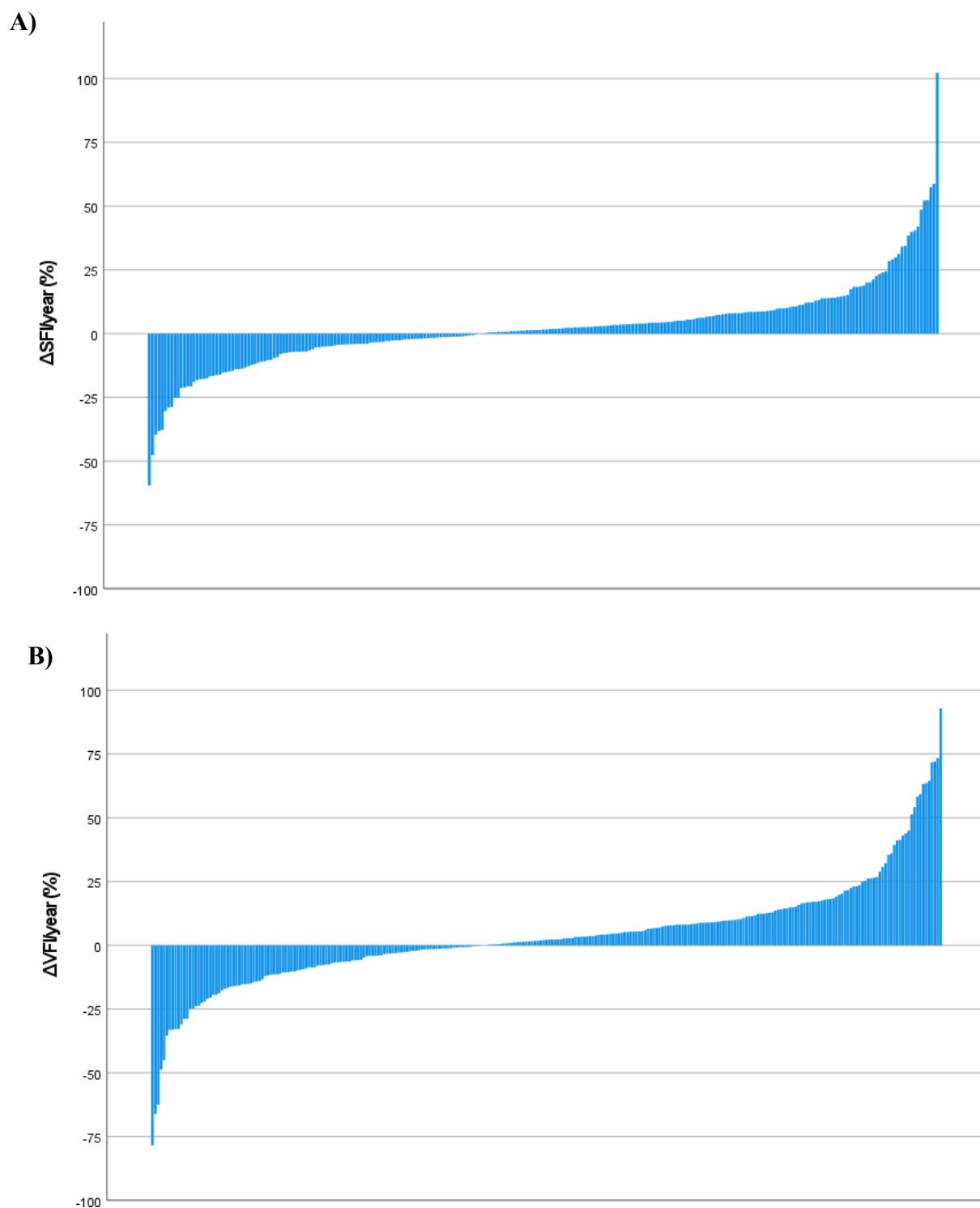


Figure 13.1 Percentage change in A) Subcutaneous fat index (ΔSFI) and B) Visceral fat index (ΔVFI) per year between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm AAA ($n = 273$). Each X axis plot represents an individual case.

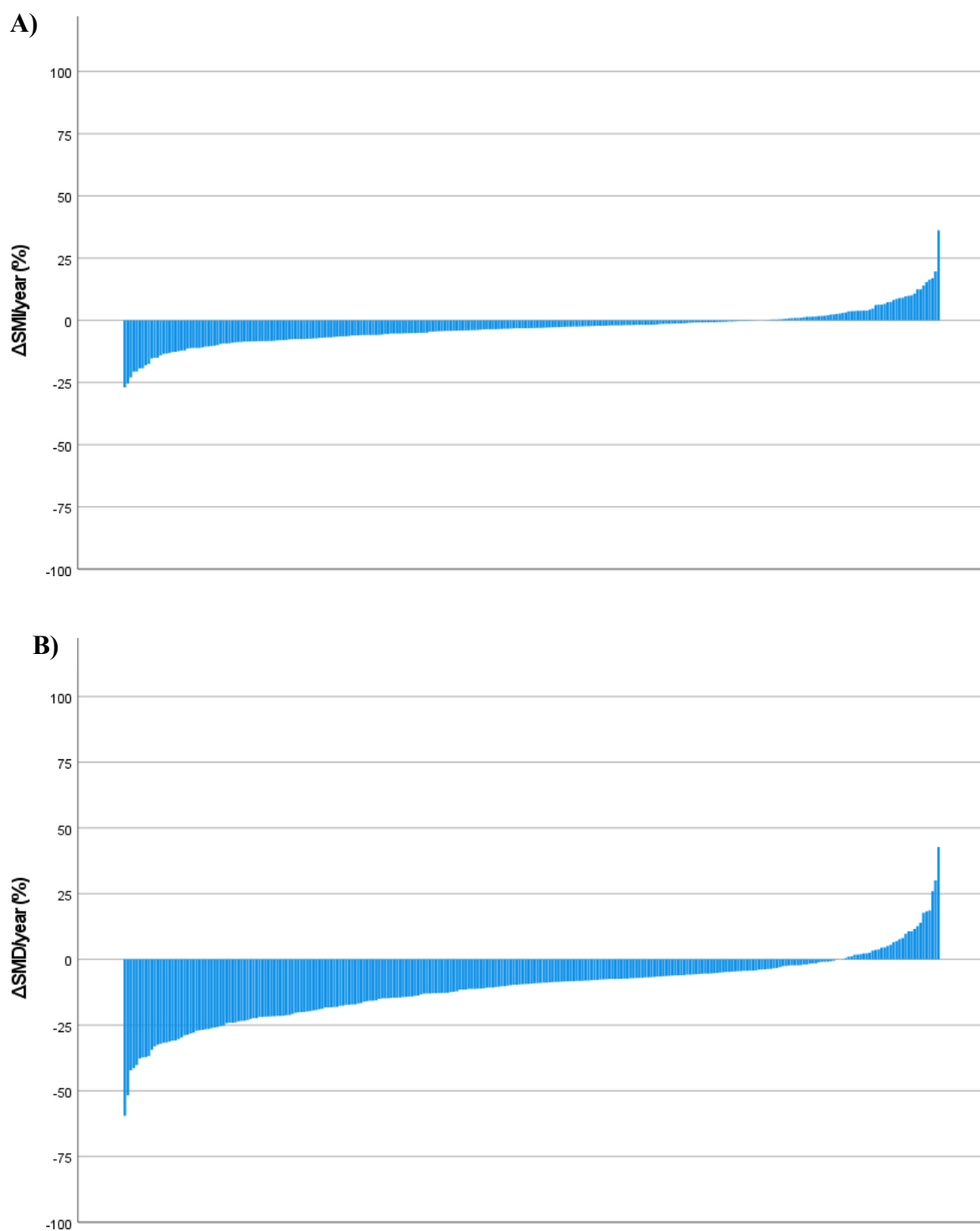
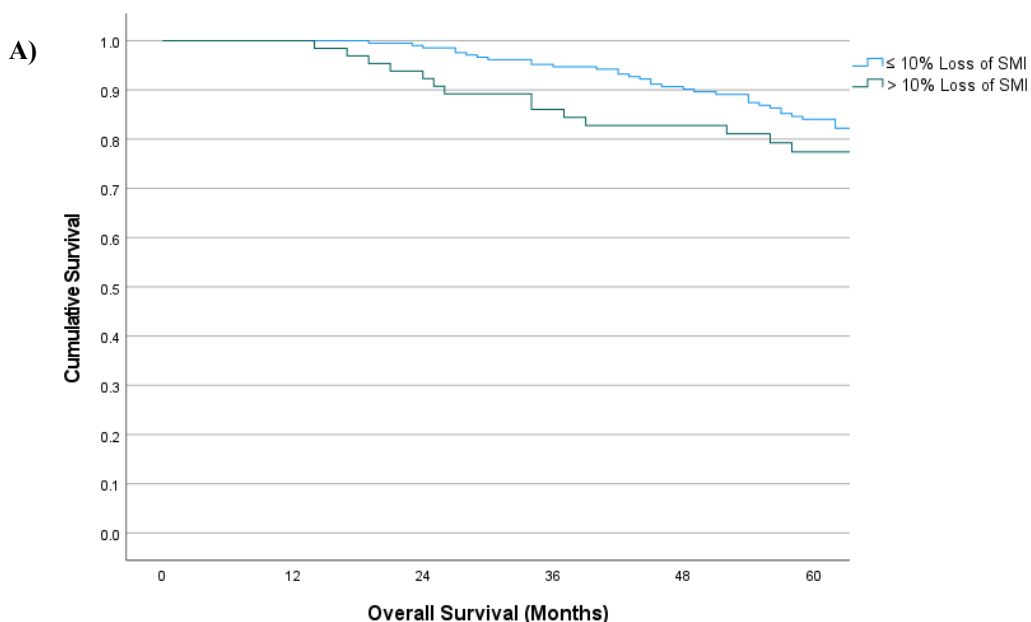
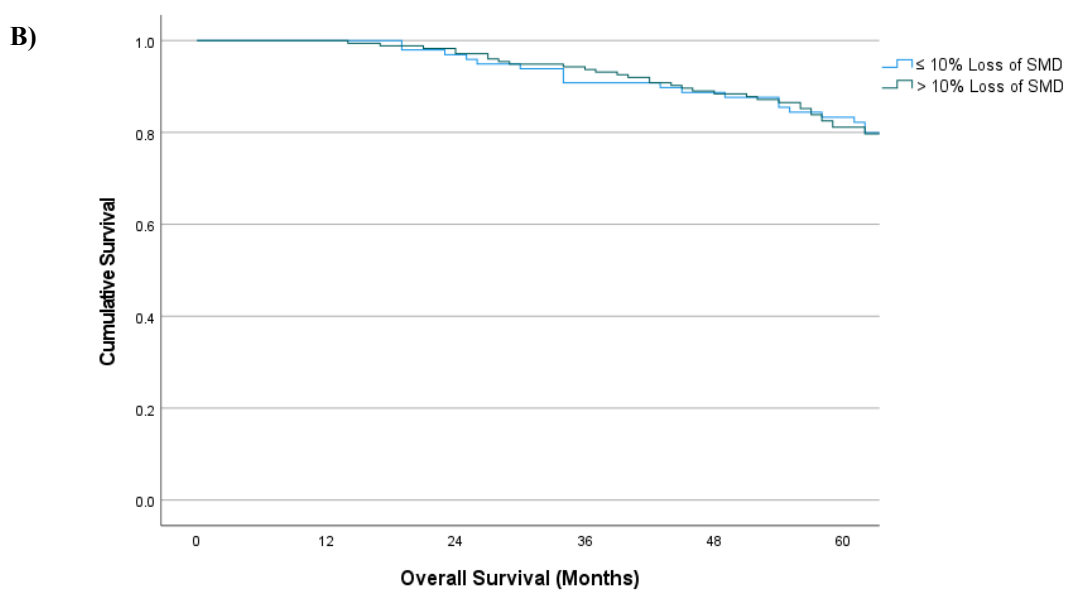


Figure 13.2 Percentage change in A) Skeletal Muscle Index (ΔSMI) and B) Skeletal Muscle Density (ΔSMD) per year between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$). Each X axis plot represents an individual case.



	Number at Risk					
Months	0	12	24	36	48	60
$\leq 10\%$ Loss of SMI	208	208	206	196	174	141
$> 10\%$ Loss of SMI	65	65	61	53	49	39



	Number at Risk					
Months	0	12	24	36	48	60
$\leq 10\%$ Loss of SMD	98	97	95	89	84	76
$> 10\%$ Loss of SMD	175	174	172	165	146	117

Figure 13.3 Kaplan-Meier survival plots and life table for loss ($\leq 10\%$ / $> 10\%$) of A) skeletal muscle index (SMI, $p = 0.58$) and B) skeletal muscle density (SMD, $p = 0.56$) between pre-operative and follow-up CT subgroups in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$)

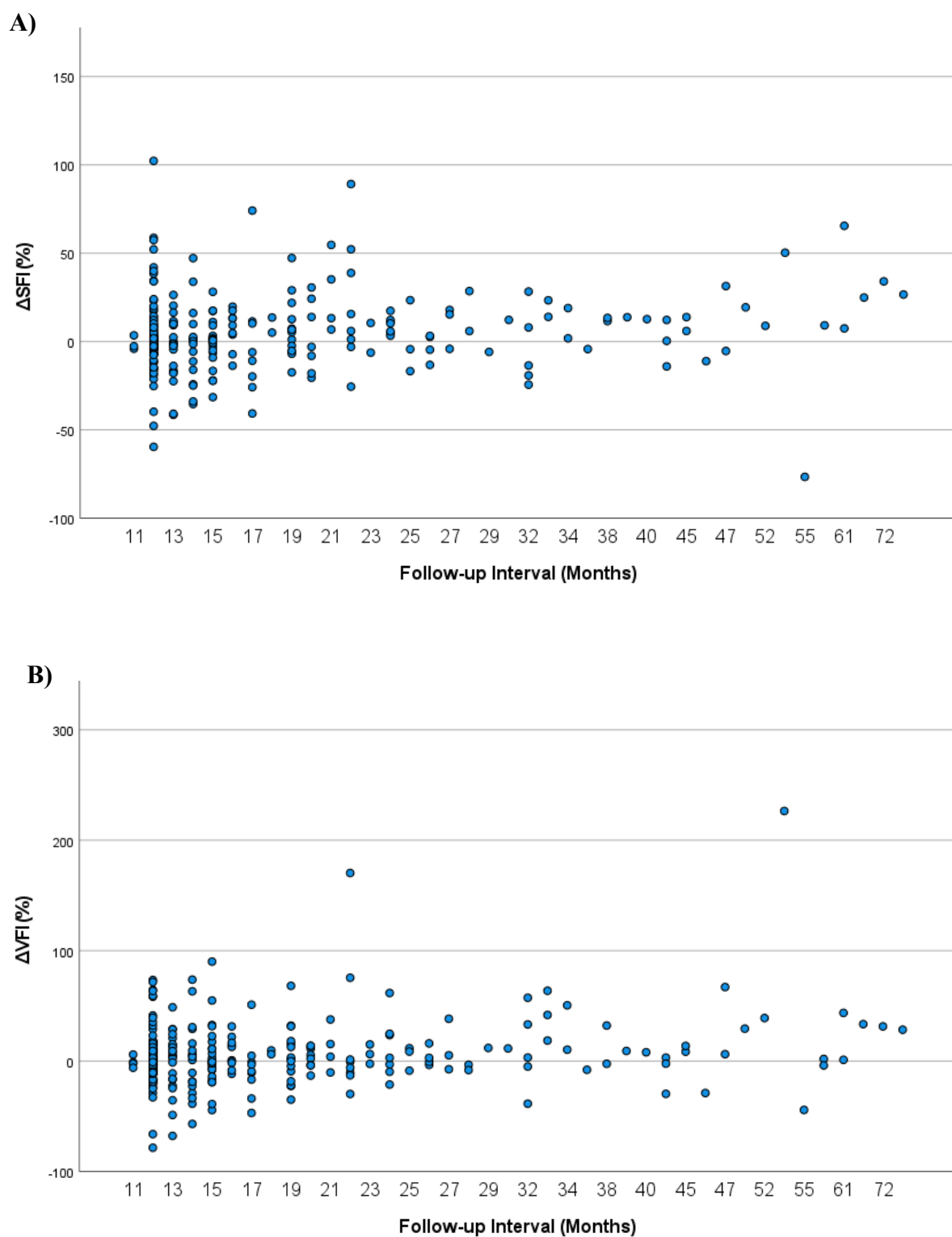


Figure 13.4 Scatter plots of total percentage change of **A)** Subcutaneous fat index (ΔSFI), $R^2 = 0.160$, $p = 0.012$ **B)** Visceral fat index (ΔVFI), $R^2 = 0.193$, $p = 0.001$ against number of months between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$)

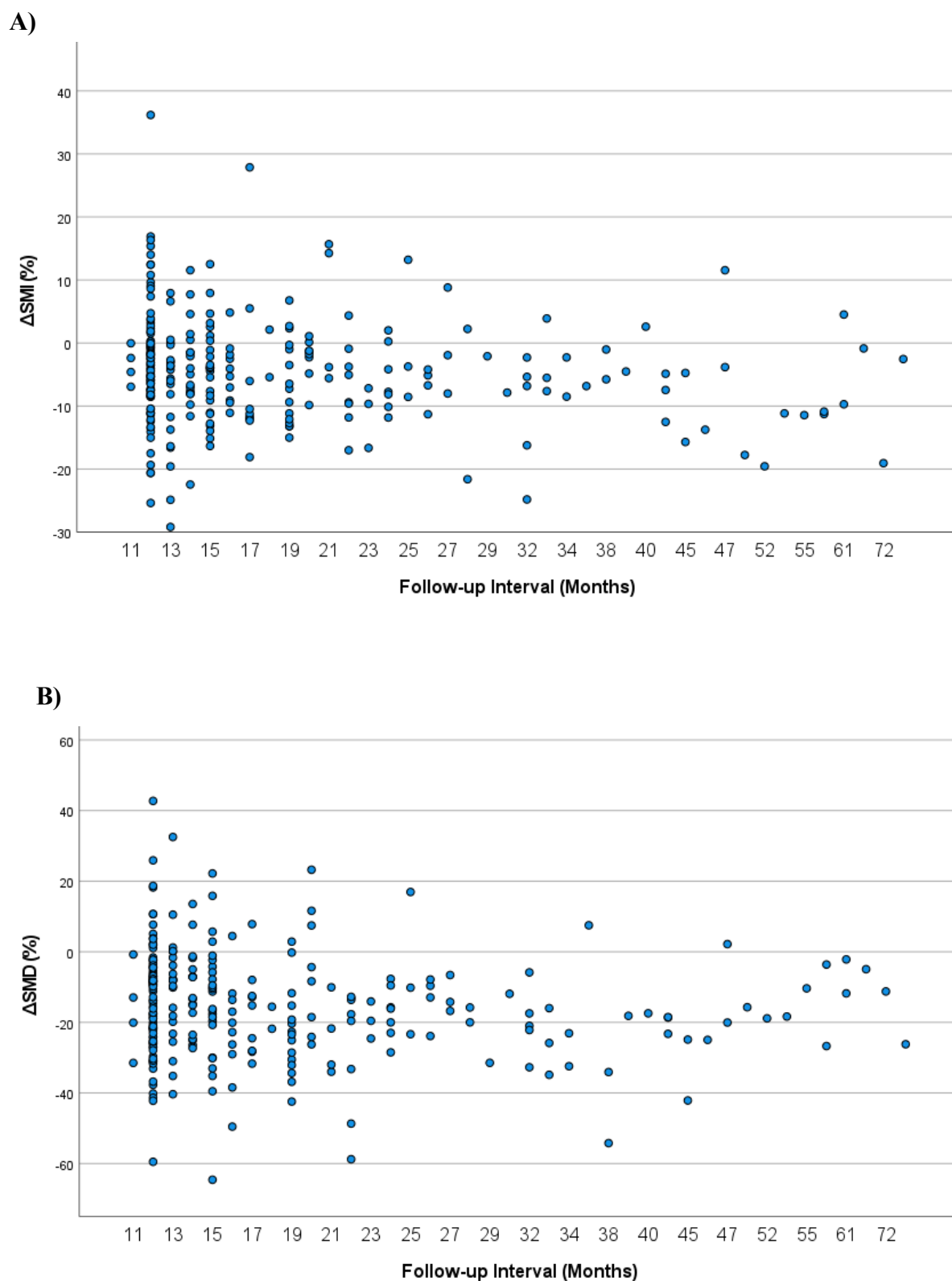


Figure 13.5 Scatter plots of total percentage change of A) Skeletal Muscle Index (ΔSMI), $R^2 = -0.132$, $p = 0.030$. B) Skeletal Muscle Density (ΔSMD), $R^2 = -0.100$, $p = 0.098$ against number of months between pre-operative and follow-up CTs in patients undergoing elective endovascular repair of abdominal aortic aneurysm ($n = 273$)

14 LONGITUDINAL ANALYSES OF CT-DERIVED LIVER & MUSCLE PARAMETERS, CLINICOPATHOLOGICAL CHARACTERISTICS, AND SURVIVAL IN PATIENTS UNDERGOING ELECTIVE ENDOVASCULAR ANEURYSM REPAIR

14.1 INTRODUCTION

In the previous chapter, the longitudinal changes in CT-BC parameters (SMI, SMD, VFI, SFI) were described in patients with AAA. Additionally, the role of statin therapy as a potentially protective factor in preserving muscle mass was identified, with patients taking statins having a lower rate of low pre-operative SMI. In addition to these “conventional” CT-BC parameters, there is a growing interest in analysis of alternative organ or tissue types, particularly with the emerging development of automated and volumetric CT analysis tools³⁷¹.

Liver volume has been investigated as a potentially key component of sarcopenia and development of the cachexia syndrome. Reports to date are in their infancy and unsurprisingly are somewhat conflicting, with some authors reporting an increase in liver volume associated with cancer-related cachexia³⁷², however some authors reporting no association^{373,374}. Determinants of liver mass are poorly understood, though appear to include age, sex, and BMI^{375,376}. The interactions between CT-derived liver and muscle parameters are poorly understood, and in particular analysis of the liver in patients with AAA has not been previously reported. Moreover, there is a paucity of evidence describing the longitudinal changes in these parameters in the setting of protocolised surveillance imaging. The present study therefore aimed to describe the interactions between CT-derived liver and skeletal muscle parameters, and their longitudinal changes following repair of AAA.

14.2 MATERIALS & METHODS

14.2.1 PATIENT ELIGIBILITY

The recruitment of the AAA cohort is described in section 1.7.2.1.

14.2.2 DATA COLLECTION

Clinical and demographic data were collected as described in section 1.5.2. Age (<75 , ≥ 75 years), comorbidity (ASA, ≤ 2 , > 2), and BMI ($< 25 \text{ kg/m}^2$, $\geq 25 \text{ kg/m}^2$) were considered as categorical variables. Pre-operative systemic inflammation was assessed using the SIG, calculated as described in chapter 5.

14.2.3 CT-BC ANALYSIS

CT-BC analysis was performed on arterial phase pre-operative planning CTs and on follow-up CTs performed as part of existing surveillance protocols, with the measurement technique performed as described in section 1.7.3. Regarding muscle and fat analyses, SMI, SFI (both normalised to height²) and SMD, VFA (no normalisation) were reported. Previously reported and validated thresholds from patients with CRC associated with inferior survival for each of these parameters were applied to the cohort to allow for sub-grouping for comparison^{78,79,84}.

To record liver parameters, the technique described by McGovern et al was performed³⁷⁸. To provide validation of the methodology, liver measurements were performed on a wider cohort of patients (which included cases present in the final study cohort) undergoing elective intervention (both open and EVAR) for AAA ($n = 872$). All scans were analysed by one researcher (Nicholas Andrew Bradley), however a random subset ($n = 487$, 56%) were also independently analysed by a second researcher (Hannah Sleight), with an intraclass correlation of 0.974 obtained between researchers, indicating excellent reproducibility of the technique. Scans were assessed in axial slices within Carestream Vue Picture Archiving and Communicating System (PACS) v12.2, and the maximal cross sectional liver area was determined visually by the researcher. The freehand measurement tool already present within this software was then used to manually segment liver tissue, excluding the inferior vena cava and gallbladder, whilst including intrahepatic vascular and biliary structures. Liver cross sectional area (cm^2) and density (HU) were recorded from each scan.

Validated thresholds of continuous liver parameters are unreported, necessitating the derivation of novel thresholds associated with inferior survival in this cohort. First, liver area and density were analysed as continuous variables in univariate cox proportional hazards models, confirming association with survival ($p < 0.05$ for both). Next, differences in median liver area and density between subgroups of sex and BMI were observed using Mann-Whitney tests ($p < 0.05$ for all comparisons). Therefore, sex and BMI category specific thresholds were derived. The “surv_cutpoint” package of R was used to determine optimal cutoff using the maximally selected log rank statistic. Thresholds of CT-derived liver parameters are displayed in table 14.1. Patients who had undergone liver resection, or those with significant cystic liver disease precluding measurement, were excluded. These novel thresholds were first derived from the wider cohort of patients ($n = 872$) and thereafter applied to the cohort included in the analyses of the present study.

14.2.4 STATISTICAL ANALYSES

General statistical analyses are described in section 1.7.4. Liver area (cm^2) and density (HU) were examined as factors of interest. Additionally, the relationship between liver/muscle area/density was examined through calculation of ratios; liver area:skeletal muscle area and liver density:SMD. The association between continuous variables was assessed using linear regression, with the R^2 value reported; skeletal muscle area was used rather than SMI to avoid confounding when compared to liver area. Whilst typical practice was to perform surveillance CT at 12 months following initial procedure, there were differences in the follow-up interval between pre-operative and follow-up CTs, largely due to variation between centres and disruption to services caused by the Covid-19 pandemic, therefore longitudinal analyses were normalised to follow-up interval (years) to adjust for this; values were therefore reported as % change per year. Analyses were performed using IBM SPSS version 28.0 (IBM, NY, USA) and RStudio 2022.02.01 (Posit PBC, MA, USA). p values < 0.05 were considered statistically significant.

14.3 RESULTS

Following exclusions there were 266 patients with liver parameters available who were included in the final study cohort. Median (IQR) follow-up was 80.5 (24) months and there were 85 deaths during the follow-up period. Following application of thresholds of liver parameters to the final cohort, there were 154 (58%) patients with low pre-operative liver area, and 69 (26%) of patients with low pre-operative liver density.

Scatter plots of pre-operative vs. follow-up CT-BC parameters and linear regression results are shown in figure 14.1. Pre-operative liver area and follow-up liver area were strongly correlated ($R^2 = 0.715$, $p < 0.001$, figure 14.1a). Pre-operative liver density and follow-up liver density were weakly correlated ($R^2 = 0.229$, $p < 0.001$, figure 14.1b). Pre-operative skeletal muscle area and follow-up skeletal muscle area were strongly correlated ($R^2 = 0.803$, $p < 0.001$, figure 14.1c). Pre-operative SMD and follow-up SMD were moderately correlated ($R^2 = 0.502$, $p < 0.001$, figure 14.1d).

Table 14.2 shows the associations between pre-operative clinicopathological factors, pre-operative CT-BC parameters, and overall survival. On univariate analysis, age >75 ($p < 0.001$), low SMI ($p < 0.05$), and low SMD ($p < 0.001$) were associated with inferior survival. On multivariate analysis, age >75 (HR 2.11, 95% CI 1.35 – 3.29, $p < 0.001$) and low SMD (HR 1.69, 95% CI 1.09 – 2.62, $p < 0.05$) were independently associated with inferior survival.

A comparison of CT-BC parameters from pre-operative to follow-up CT is shown in table 14.3. Between timepoints, there was an increase in the prevalence of low SMI ($p < 0.001$), low SMD ($p < 0.001$), and low liver area ($p < 0.001$). Median VFA ($p < 0.01$) and SFI ($p < 0.05$) increased, however this did not result in a significant change in the proportion of patients with high VFA or SFI. Liver density did not significantly change between timepoints.

Figure 14.2 shows waterfall plots of longitudinal change (%/year) in the ratio of liver area:skeletal muscle area (figure 14.2a) and liver density:skeletal muscle density (figure 14.2b). Liver area:skeletal muscle area increased in 164 (62%) of patients, and liver density:skeletal muscle density increased in 206 (77%) of patients. The median (IQR) increase in liver area:skeletal muscle area was 1.5 (11.0) %/year, compared with 10.5 (23.6) %/year increase in liver density:skeletal muscle density ($p < 0.001$). On visual

inspection, there is a striking increase in liver density:skeletal muscle density in the majority of patients.

Table 14.4 shows the differences in % change of liver area:skeletal muscle area and liver density:skeletal muscle density in relation to baseline clinicopathological factors. Patients with low pre-operative liver area had a higher % change of liver area:skeletal muscle area per year than those with normal pre-operative liver area (1.79% vs. 0.48%, $p < 0.05$).

Patients with low pre-operative liver density had a higher % change of liver density:skeletal muscle density per year than those with normal pre-operative liver density (13.54% vs. 8.22%, $p < 0.001$). There was no difference in survival outcomes in the sub-groups of patients based on change in either ratio ($p > 0.05$ for both analyses).

14.4 DISCUSSION

The results of the present study, using the novel CT based method of McGovern *et al*³⁷⁸, showed for the first time how the relationship between liver and muscle mass and density changed per year. This showed clearly that, relative to liver mass and density, skeletal muscle mass and especially density were lost at a greater rate in patients undergoing elective endovascular repair.

The basis of this differential loss of protein liver and muscle is not clear. The role of the liver in the development and progression of sarcopenia has long been recognised, with associations between altered hepatic protein regulation and skeletal muscle breakdown described in patients with and without cirrhosis^{379–382}. It has been observed that during a catabolic state (e.g. major injury) the liver typically increases the rate of protein synthesis, in particular the acute phase response proteins³⁸³ by the liberation of amino acids from muscle tissue as an attempt to increase amino acid availability. However, given the present results and the relatively lower levels of systemic inflammation in patients with AAA compared with colorectal cancer (described in chapter 8) systemic inflammation may not be the main driving mechanism. Therefore, in keeping with prior descriptions of sarcopenia in cardiovascular cohorts³⁸⁴, the present results may reflect muscle deconditioning which develops in the context of chronic exposure to multiple cardiovascular disease risk factors (such as chronic hypertensive disease^{383,384}, cigarette smoking^{387–389}), as well as increasing age⁶⁷. Comparative evaluation of these relationships in cardiovascular cohorts with a greater magnitude of systemic inflammation, such as those with chronic limb threatening ischaemia (described in chapters 10 and 11), would be of particular interest.

The results of the present study also validate the methodology developed in patients with colorectal cancer³⁷⁸. There are several methodological differences between prior studies reporting CT-derived liver parameters. For example, McGovern *et al* measured maximal cross sectional liver area, and in a sub-group analysis found this to be well correlated with total volume³⁷⁸. Additionally, McGovern *et al* normalised liver area to height to create the liver mass index (LMI). Other authors have used different measurement techniques and did not perform normalisation^{377,390}. The present authors employed the same measurement technique as McGovern *et al*, however chose not to normalise values to patient height, as there is a lack of evidence describing height as a confounding variable in liver mass or density. Furthermore, the thresholds used to sub-group patients accounted for variation

based on BMI. Whilst we did not assess the correlation between maximal cross-sectional liver area and liver volume, the present study confirms that the technique employed is highly reproducible between observers. Our observations regarding liver density may be challenging to reproduce in a non-cardiovascular cohort, as the effect of the phase of CT scan on liver density is unknown, and the majority of the literature report findings based on portal venous phase CTs. Phase of scan may also influence skeletal muscle measurement, though this is disputed^{245,389}.

The results of the present study show that the principle factors associated with change in liver area:skeletal muscle area and liver density:skeletal muscle density are pre-operative liver area and density respectively would indicate that liver mass and density are relatively preserved whereas muscle mass and density are lost. It would be of considerable interest to carry out a similar longitudinal study in patients with a higher systemic inflammatory burden to examine how the liver/ muscle relationship was altered.

Compared with the literature describing CT-derived muscle and fat parameters, CT-derived liver parameters are relatively underreported. Moreover, data describing longitudinal changes in all CT-BC parameters are lacking; Dolan *et al* report that low skeletal muscle mass and density are largely maintained following resection for colorectal cancer³⁶¹. As described in chapter 8, patients undergoing EVAR for AAA are likely to be older than those undergoing colorectal cancer resection, which may in part explain the differences observed in SMD in the present study. Several studies have reported factors associated with liver mass, however liver density is unreported^{375–378,390}. Associations between skeletal muscle mass and liver mass have been described by Dello *et al*³⁷⁶ in patients undergoing liver resection for cancer. Interestingly, these observations contradict those described by Lodewick *et al*, which were also in a liver resection cohort³⁷⁵.

The ratios of liver area and density to skeletal muscle area and density highlight the effect of age on SMD in particular. Increasing age is known to be a strong determinant of muscle mass, and in chapter 8 we report a striking association between age and loss of SMD irrespective of disease state. Given that liver density was preserved between timepoints, the increase in the ratio of liver density:skeletal muscle density likely reflects an exaggerated loss of SMD in patients. In the absence of confounding variables (excluded in the present study), these observations may suggest that increasing age is an important determinant of muscle density. Whilst low muscle mass is also associated with increasing age, it appears that the loss of liver occurs at a similar trajectory. These relationships are poorly

understood, and the nature of liver density and muscle density, and their prognostic value, remains uncertain.

Whilst mass of tissues (e.g. fat measurements, skeletal muscle) has historically been the predominant factor of interest, more recently the density, in particular SMD, has been afforded greater attention. Indeed, SMD rather than SMI was found to be the predominant factor associated with cancer diagnosis and cancer-mediated inflammation in chapter 8. Moreover, SMD may be associated with inferior physiological fitness in patients undergoing major cancer resection⁸³. The relatively minimal longitudinal change observed in liver mass compared to liver density are also observed in skeletal muscle, highlighting similarities in the progressive changes between these two tissues. The underlying aetiology, and the relative contributions of tissue mass and density to prognosis remain poorly understood, and further evaluation is required to define their interactions. Examination of the prognosis and associations seen in patients who have preserved liver or muscle mass, yet abnormal liver or muscle density, and the reciprocal distribution, is of particular interest.

The present study is limited by several factors. The effect of the phase of CT scan on CT-derived liver measurement is uncertain, however all patients were analysed using the same phase. The retrospective nature of the study, low absolute numbers in certain sub-groups, and missing data for some participants limits certain analyses. The longitudinal analyses were performed on CTs with a wide range of follow-up intervals, however steps were taken to adjust for this. The thresholds used to sub-group patients based on liver parameters are derived from the present cohort, therefore are subject to bias. Additionally, they lack external validation and in particular the threshold for liver density in males with BMI ≥ 25 was markedly different to the other thresholds. Finally, the methodology for quantifying liver tissue, whilst described previously³⁷⁸, is not widely reported and therefore further validation is required.

In conclusion, the results of the present study describe the longitudinal changes in CT-derived liver and skeletal muscle parameters in a cohort of patients undergoing elective intervention for AAA. Strikingly, the ratio of liver density:skeletal muscle density markedly increased between timepoints. These novel observations contribute to our understanding of body composition in cardiovascular disease.

14.5 TABLES

Table 14.1: Thresholds of CT-derived liver parameters associated with inferior survival in patients undergoing elective intervention for AAA (n = 872).

Table 14.2: The associations between clinicopathological factors, pre-operative CT-derived body composition parameters, and overall survival in patients undergoing elective EVAR for AAA (n = 266).

Table 14.3: The associations between pre-operative and follow-up CT-derived body composition parameters in patients undergoing elective EVAR for AAA (n = 266).

Table 14.4: The associations between clinicopathological factors and change in CT-derived liver ratios in patients undergoing elective EVAR for AAA (n = 266).

Table 14.1: Thresholds of CT-derived liver parameters associated with inferior survival in patients undergoing elective intervention for AAA (n = 872)

Parameter	Threshold
Liver Area	
Males, BMI <25	186.7 cm ²
Males, BMI ≥25	226.6 cm ²
Females, BMI <25	157.4 cm ²
Females, BMI ≥25	219.7 cm ²
Liver Density	
Males, BMI <25	68.1 HU
Males, BMI ≥25	40.0 HU
Females, BMI <25	68.9 HU
Females, BMI ≥25	63.0 HU

Table 14.2: The associations between clinicopathological factors, pre-operative CT-derived body composition parameters, and overall survival in patients undergoing elective EVAR for AAA (n = 266)

		Univariate		Multivariate	
	N (%)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Age ≤75 >75*	160 (60%) 106 (40%)	2.48 (1.61 – 3.82)	<0.001	2.11 (1.35 – 3.29)	<0.001
Sex Male Female*	247 (93%) 19 (19%)	1.15 (0.53 – 2.50)	0.72	-	-
ASA ≤2 >2*	150 (57%) 115 (43%)	1.28 (0.84 – 1.96)	0.26	-	-
Statin Use No Yes*	53 (20%) 213 (80%)	1.02 (0.60 – 1.73)	0.95	-	-
SIG 0 1 ≥2*	130 (56%) 70 (30%) 32 (14%)	0.90 (0.65 – 1.24)	0.51	-	-
BMI <25 ≥25*	53 (20%) 213 (80%)	1.35 (0.75 – 2.44)	0.32	-	-
SMI (Martin)† Normal Low*	136 (51%) 130 (49%)	1.77 (0.14 – 2.73)	<0.05	1.45 (0.93 – 2.26)	0.10
SMD (Martin)† Normal Low*	171 (64%) 95 (36%)	2.06 (1.34 – 3.15)	<0.001	1.69 (1.09 – 2.62)	<0.05
VFA (Doyle)† Normal High*	54 (20%) 212 (80%)	1.32 (0.76 – 2.31)	0.33	-	-
SFI (Ebadi)† Normal High*	68 (27%) 182 (73%)	0.91 (0.56 – 1.46)	0.69	-	-
Liver Area† Normal Low*	112 (42%)	1.41 (0.90 – 2.22)	0.13	-	-

	154 (58%)				
Liver Density† Normal Low*	197 (74%) 69 (26%)	0.57 (0.32 – 1.01)	0.06	-	-
HR pertain to the category marked with * compared to the reference category. †: pre-operative values.					

Table 14.3: The associations between pre-operative and follow-up CT-derived body composition parameters in patients undergoing elective EVAR for AAA (n = 266)

	Initial CT	Follow-up CT	<i>p</i>
Low SMI (Martin)	130 (49%)	168 (63%)	<0.001
Median (IQR) SMI (cm²/m²)	49.8 (12.7)	47.4 (12.7)	<0.001
Low SMD (Martin)	95 (36%)	182 (68%)	<0.001
Median (IQR) SMD (HU)	37.3 (10.0)	31.0 (10.4)	<0.001
High VFA (Doyle)	212 (80%)	218 (82%)	0.35
Median (IQR) VFA (cm²)	252.0 (163.3)	263.4 (159.8)	<0.01
High SFI (Ebadi)	182 (73%)	194 (76%)	0.38
Median (IQR) SFI (cm²/m²)	63.0 (38.1)	67.4 (39.5)	<0.05
Low Liver Area	154 (58%)	189 (71%)	<0.001
Median (IQR) Liver Area (cm²)	200.7 (53.1)	199.1 (51.3)	<0.001
Low Liver Density	69 (26%)	81 (31%)	0.11
Median (IQR) Liver Density (HU)	58.0 (15.0)	58.0 (14.0)	0.13
P values generated through paired Wilcoxon tests (continuous data), and paired McNemar's Test (categorical data). Data displayed as n (%) unless stated.			

Table 14.4: The associations between clinicopathological factors and change in CT-derived liver ratios in patients undergoing elective EVAR for AAA (n = 266)

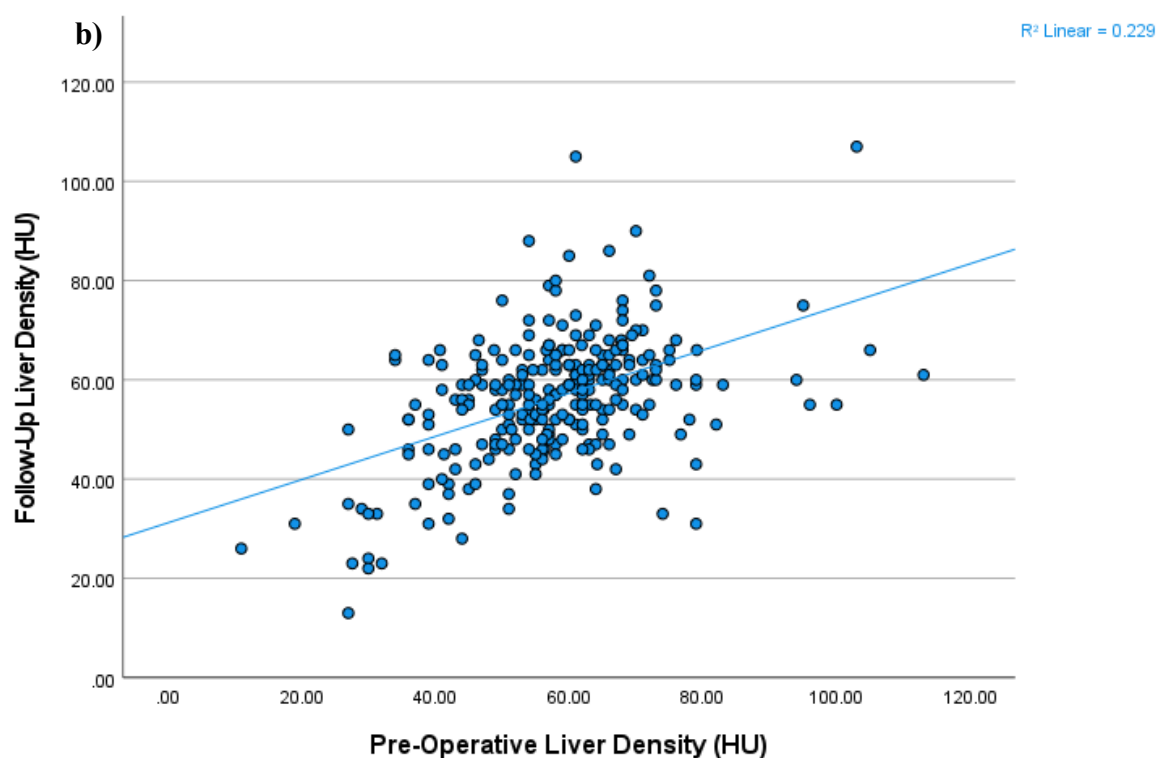
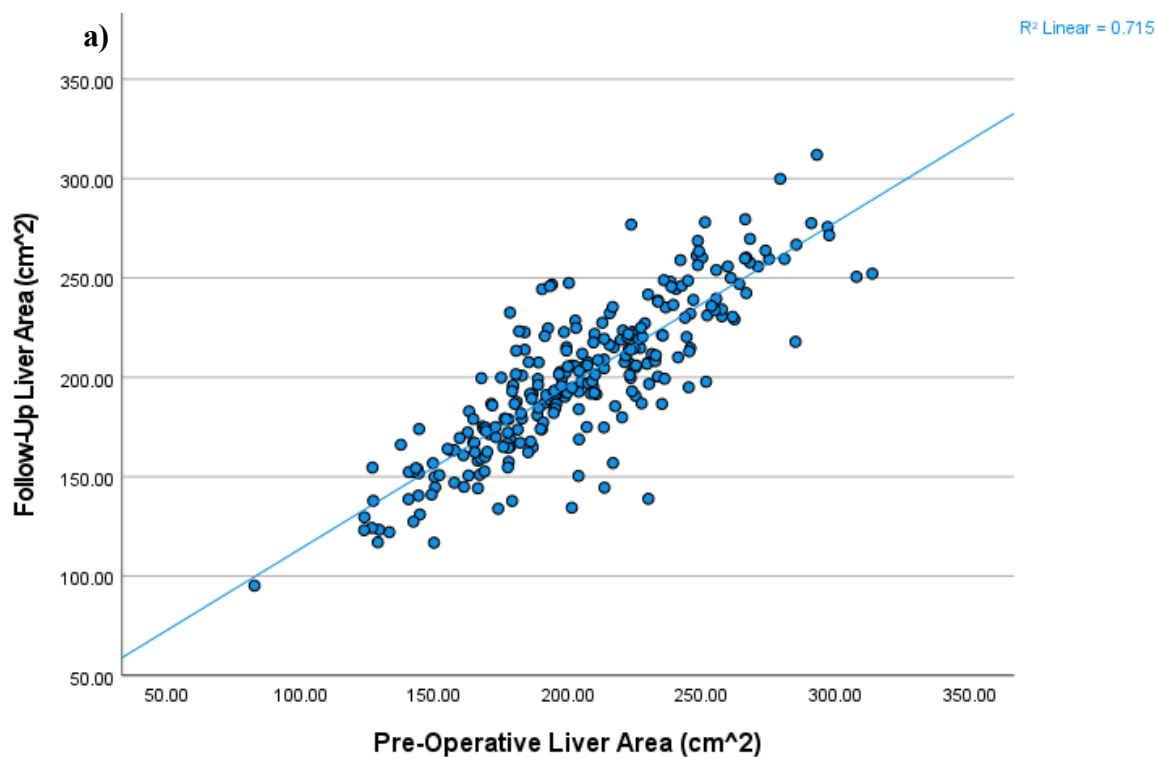
	% change in liver area:skeletal muscle area per year (median, IQR)	<i>p</i>	% change in liver density:skeletal muscle density per year (median, IQR)	<i>p</i>
Age ≤75 >75	0.88 (10.85) 2.10 (11.40)	0.78	8.73 (23.46) 12.66 (22.20)	0.33
Sex Male Female	1.28 (11.67) 0.76 (7.46)	0.53	9.52 (23.71) 17.56 (35.39)	0.09
ASA ≤2 >2	0.09 (11.96) 2.25 (10.31)	0.32	10.20 (24.43) 9.84 (25.43)	0.45
Statin Use Yes No	1.11 (12.01) 1.50 (11.11)	0.96	10.29 (22.18) 6.47 (30.21)	0.45
SIG 0 1 ≥2*	1.91 (11.23) 1.03 (10.94) 1.23 (13.71)	0.94	10.89 (25.78) 9.28 (23.17) 9.79 (24.62)	0.88
BMI <25 ≥25	2.24 (9.78) 0.94 (11.77)	0.82	12.39 (18.59) 9.21 (25.32)	0.59
SMI (Martin)† Normal Low	1.50 (11.24) 0.31 (11.40)	0.30	9.65 (23.52) 10.49 (24.36)	0.86
SMD (Martin)† Normal Low	1.28 (10.53) 1.05 (14.55)	0.35	9.84 (24.80) 10.42 (21.81)	0.51
VFA (Doyle)† Normal High	1.50 (11.26) 1.10 (12.01)	0.92	10.49 (20.35) 10.03 (25.47)	0.92
SFI (Ebadi)† Normal High	0.94 (9.13) 1.29 (12.30)	0.39	8.52 (21.60) 10.33 (24.19)	0.35
Liver Area† Normal Low	0.48 (12.14) 1.79 (11.55)	<0.05	8.83 (22.01) 10.95 (24.61)	0.40
Liver Density† Normal Low	1.10 (11.08) 1.50 (11.88)	0.55	8.22 (22.77) 13.54 (25.92)	<0.001
Overall Survival (HR, 95% CI)	0.99 (0.98 – 1.02)	0.74	1.01 (0.99 – 1.02)	0.07

p values generated through Mann-Whitney or Kruskal-Wallis tests comparing median values. Survival analyses performed using univariate cox proportional hazards models †: pre-operative values.

14.6 FIGURES

Figure 14.1: Scatter plots of pre-operative vs. follow-up a) liver area b) liver density c) skeletal muscle area d) skeletal muscle density in patients undergoing elective EVAR for AAA (n = 266). R^2 values generated through linear regression. $p < 0.001$ for all analyses.

Figure 14.2: Waterfall-plots of percentage change from pre-operative to follow-up CT in a) liver area:skeletal muscle area, b) liver density: skeletal muscle density in patients undergoing elective EVAR for AAA, normalised to follow-up interval (years) (n = 266). X axis is a plot of individual cases.



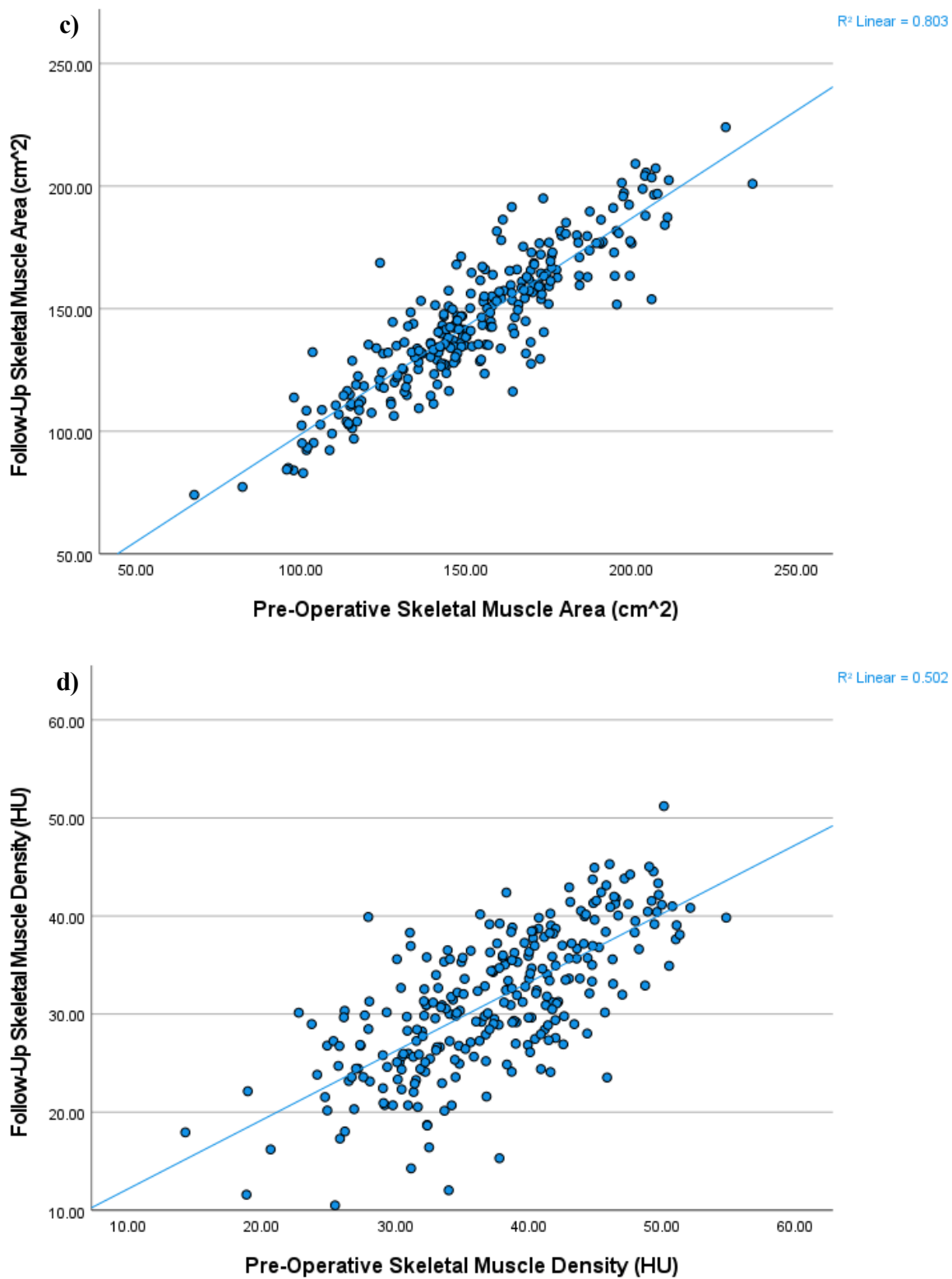


Figure 14.1: Scatter plots of pre-operative vs. follow-up a) liver area b) liver density c) skeletal muscle area d) skeletal muscle density in patients undergoing elective EVAR for AAA (n = 266). R^2 values generated through linear regression. $p < 0.001$ for all analyses

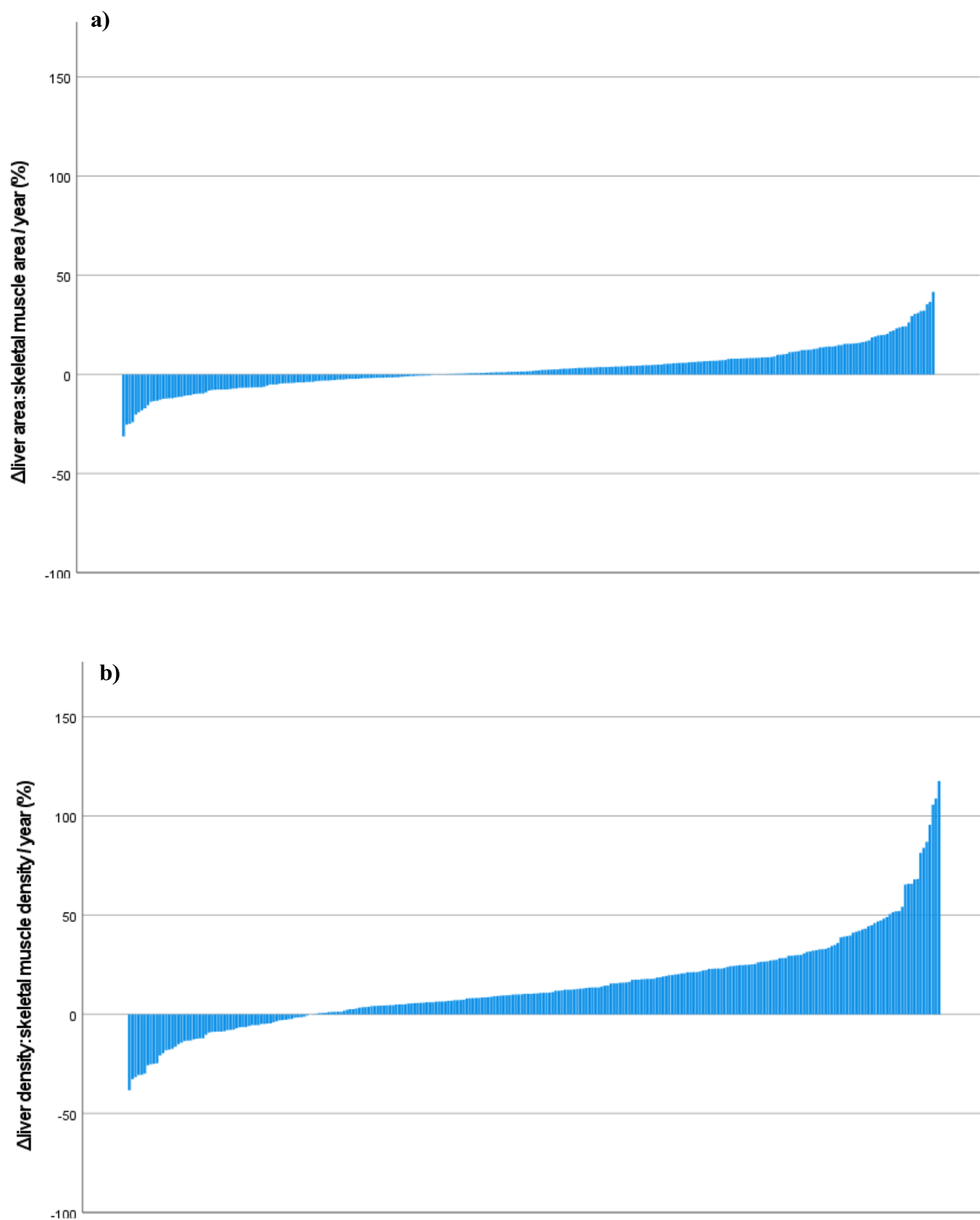


Figure 14.2: Waterfall-plots of percentage change from pre-operative to follow-up CT in a) liver area:skeletal muscle area, b) liver density: skeletal muscle density in patients undergoing elective EVAR for AAA, normalised to follow-up interval (years) (n = 266). Each X axis plot represents an individual case.

15 CONCLUSIONS

15.1 OVERVIEW OF THESIS

The data presented in this thesis predominantly describe the associations and potential prognostic effect of both CT-BC parameters and markers of the SIR in three common vascular surgical conditions which encompass over 90% of contemporary UK vascular surgical practice³⁷. The prevalence of clinicopathological factors, CT-BC parameters, and markers of the SIR in each cohort is summarised in table 15.1. Using validated thresholds derived from patients with cancer (Martin *et al*⁸⁴) to avoid disease-specific bias, low SMI is found in over 50% of patients in each of the studied disease states, with CLTI having the highest prevalence. SMD analyses were only available for AAA and CLTI cohorts, with low SMD clearly more prevalent in patients with CLTI. Similarly, the magnitude of systemic inflammation is clearly greater in patients with CLTI, which is a predictable phenomenon based on potential tissue loss/infection and an expected greater burden of systemic atherosclerosis compared to AAA or carotid endarterectomy cohorts. Of particular interest, across all of the studied cohorts, there was a clear association between one-year survival outcomes and each of these factors of interest (SMI, SMD, and SIG).

15.1.1 CHAPTER-BY-CHAPTER SUMMARY

In chapter 2 the literature predating the present thesis which describes the potential prognostic role of CT-derived skeletal muscle parameters in patients undergoing elective endovascular repair of aortic aneurysm was reviewed. Obvious methodological heterogeneity was observed, with limitations as compared to standardised methodology used in patients with cancer. Despite this, on meta-analysis a clear association between low skeletal muscle mass and inferior survival outcomes was observed.

Chapter 3 attempted to resolve the methodological issues in the wider literature which had been highlighted in chapter 2, and added the novel descriptions of prognostication using SMD and fat indices in this patient group. The independent association of SMI with survival in a large multicentre cohort of patients undergoing EVAR or F/B-EVAR for AAA was observed. This was performed using novel thresholds derived from the dataset presented in the study, which require external validation.

Table 15.1: A comparison of clinical characteristics, CT-derived body composition, systemic inflammation, and survival in a vascular surgical cohort of patients (n = 1681).				
	Elective AAA (n = 875)	Unscheduled CLTI (n = 190)	Carotid Endarterectomy (n = 616)	p
Age				
<75	529 (61%)	112 (59%)	429 (70%)	<0.001
≥75	346 (39%)	78 (41%)	187 (30%)	
Sex				
Male	800 (91%)	118 (62%)	436 (71%)	<0.001
Female	75 (9%)	72 (38%)	180 (29%)	
ASA				
≤2	429 (49%)	27 (15%)	184 (32%)	0.86
>2	442 (51%)	157 (85%)	395 (68%)	
BMI				
<25kg/m ²	194 (22%)	75 (40%)	187 (31%)	0.82
≥25kg/m ²	676 (78%)	115 (60%)	424 (69%)	
VFA (Doyle)				
Normal	177 (21%)	51 (28%)	-	<0.01
High	688 (79%)	134 (72%)	-	
SFI (Ebadi)				
Normal	218 (27%)	50 (28%)	-	<0.001
High	599 (73%)	126 (72%)	-	
SMI (Martin)				
Normal	398 (47%)	77 (42%)	302 (49%)	<0.05
Low	451 (53%)	108 (58%)	309 (51%)	
SMD (Martin)				
Normal	572 (67%)	79 (43%)	-	<0.01
Low	282 (33%)	106 (57%)	-	
SIG				
0	388 (53%)	29 (16%)	325 (53%)	<0.001
1	236 (33%)	20 (11%)	197 (32%)	
≥2	103 (14%)	137 (74%)	94 (15%)	
One-Year Survival†				
Normal SMI	96% (1%)	78% (5%)	98% (1%)	-
Low SMI	92% (1%)	61% (5%)	95% (1%)	
	p <0.05	p <0.01	p <0.01	
One-Year Survival†				
Normal SMD	95% (1%)	78% (5%)	-	-
Low SMD	93% (1%)	60% (5%)	-	
	p <0.001	p <0.01	-	
One-Year Survival†				
SIG 0	96% (1%)	90% (6%)	98% (1%)	-
SIG 1	92% (2%)	90% (7%)	97% (1%)	
SIG ≥2	86% (3%)	60 (4%)	89% (3%)	
	p <0.05	p <0.001	p <0.001	
Data presented as N (%) unless otherwise specified. † Data presented as % survival (% standard error). p values generated through linear-by-linear Chi-Squared analyses and log-rank method (survival data). Missing data were selectively excluded from relevant analyses.				

A systematic review of the literature describing prognosis in relation to NLR and PLR following repair of AAA was presented in chapter 4. Only nine eligible studies were identified, reporting outcome on 4571 patients, 4356 (95%) of whom underwent an

elective procedure. In the studies predicting long-term outcomes, elevated NLR and PLR were generally associated with inferior long-term survival, however heterogeneity in methodology was noted. Measures of the acute phase response were not represented by the current literature and were identified as an area for further investigation.

In chapter 5 the recently described SIG, which allows for composite assessment of the acute-phase and differential white cell inflammatory responses, was investigated as a possible prognostic factor in patients with AAA. The novel observation of independent inferior survival outcomes with increasing magnitude of SIG was described.

Combining the factors of interest from chapters 3 and 5 in chapter 6 allowed for a description of the combined potential prognostic value of both CT-derived sarcopenia (as measured through CT-SS, a novel observation in this patient group) and the SIR (as measured through SIG). There was a marked observation of significantly inferior survival in patients with both low skeletal muscle mass/density and elevated SIG.

The effect of low skeletal muscle mass and quality on objective measures of physiological fitness as measured by CPEX was explored in chapter 7. The hypothesis that low SMI and/or SMD are associated with inferior performance at CPEX was not supported by these data; the findings were inconsistent and whilst trends were observed between CT-SS and CPEX parameters, these did not reach statistical significance. The complexity of the relationship between muscle parameters and physical function is highlighted by these results, in particular the role of SMD as possible a marker of muscle function. However, the limitations of each method of assessment (i.e. both CT-BC and CPEX) are important in analysing these results. Particularly striking was the observation that CT-SS outperformed each CPEX parameter in terms of association with survival following aneurysm repair.

In chapter 8 a direct comparison between two large cohorts of patients with different disease states (AAA and CRC) was performed. At the time of writing, similar comparisons between non-malignant and malignant disease have not previously been reported. The conventional dogma, that sarcopenia is predominantly an entity associated with cancer, was challenged through the observation of similar rates of low SMI in both AAA and CRC cohorts. There was a markedly greater prevalence of both activation of the SIR and low SMD in the CRC cohort, supporting a hypothesis that the predominant effect of the tumour as an inflammatory locus which has a detrimental effect on muscle content rather than global muscle architecture. A particular association between increasing age and fall in

SMI, and to a greater extent SMD, was observed in both cohorts. The results supported the hypothesis that shared risk factors, particularly increasing age, are the principal determinants of muscle mass, rather than disease-specific factors.

Whilst the predominant assessment of the systemic inflammatory response has been based on pre-operative blood results, in chapter 9 both pre- and post-operative markers of systemic inflammation were investigated in both elective and emergency repair of AAA. An association between post-operative day 3 CRP >300mg/L and inferior 30-day survival was observed in the emergency cohort, however interestingly this association was not retained on multivariate analysis; indeed the pre-operative inflammatory response as assessed by the mGPS dominated prognostication in this setting. In contrast, day 3 CRP >300mg/L was independently associated with inferior twelve-month survival in the elective OSR sub-group. Despite these associations, determinants of greater magnitude of the post-operative SIR were not identified, highlighting the need for further investigation with a view to optimising peri-operative management and risk stratification.

Chapter 10 reviewed the literature describing the association between markers of the SIR and disease severity, clinical outcomes, and technical success of revascularisation strategies in patients with LEAD. Whilst significant heterogeneity precluded meaningful quantitative meta-analysis, on qualitative review of 34 studies reporting on 19870 patients the majority of studies supported an association between elevated NLR (and to a lesser extent, PLR) and each of the outcome measures. However, the evidence base was limited by heterogenous methodology (including timing of sampling, thresholds used to sub-group patients, and patient selection) which somewhat limits the validity of the conclusions in terms of contemporary UK practice.

In chapter 11 the clinical entity of frailty as measured by a validated scoring system (CFS) was investigated in a cohort of patients with CLTI. The relationship between CT-BC parameters, the SIR, and CFS was explored, as well as the associations of each of these factors. There was an independent association between CT-SS and CFS, and each of CT-SS, mGPS, and CFS provided independent value in terms of predicting inferior survival outcomes. These data suggest that whilst sarcopenia and frailty are clearly related, there is potential clinical utility in using both measures together for potential prognostication in patients with CLTI.

Low skeletal muscle mass and density are, both in the present thesis and wider literature, predominantly described based on analyses of abdominal muscle at the L3 vertebral level. In chapter 12 analyses of cervical muscle at the C3 vertebral level were performed in a cohort of patients undergoing carotid endarterectomy for symptomatic carotid lesions, drawing on methodology described in cohorts of patients with head and neck cancer. Additionally, these measurements were transformed using a previously reported formula to provide a value comparable with L3 SMI. Finally, systemic inflammation as measured by SIG was also reported in this patient group. The SMD at C3 was shown to offer independent association with survival along with SIG, highlighting the systemic nature of loss of skeletal muscle mass and density in cardiovascular disease. A potential role for these parameters in patient selection for surgery was described.

The progressive nature of changes in body composition was investigated with longitudinal data in chapter 13. A particular strength to these data was the nature of the surveillance imaging, which was performed in the context of protocolised follow-up, minimising the risk of incident co-pathologies with a potentially confounding effect on body composition. Additionally, the effect of medical therapy known to interact with both muscle tissue and systemic inflammation, statins, was investigated. A progressive decline in both SMI and SMD was observed following repair of AAA, with a particularly striking change in the proportion of patients with low SMD (88% at follow-up imaging). Statin therapy did not appear to influence the changes in muscle mass, however somewhat paradoxically there was a potential benefit associated with statin use; a higher proportion of patients taking statins had a normal pre-operative SMI compared with those not taking statins. The results in this chapter provide novel observations regarding the natural history of skeletal muscle loss and contribute to the evidence for the beneficial effect of statin therapy.

In chapter 14 a less well-described assessment of body composition, liver mass and density, was reported in a cohort of patients with AAA. The relationship between CT-derived liver parameters, skeletal muscle parameters, and with survival outcome was described. From pre-operative CT to follow-up CT, there was a decline in liver area, but a relative preservation of liver density. Similarly to chapter 13, skeletal muscle parameters (SMI and SMD) both decreased during the follow-up period. Skeletal muscle density also dominated on multivariate analyses of potential prognostic factors. These results describe a preferential loss of muscle protein stores rather than hepatic protein stores as part of the development of sarcopenia, and highlight the complex systemic nature of this clinical phenomenon.

15.1.2 GENERAL DISCUSSION

Compared to IHD, AAA, CLTI, and CVD represent far less of a proportion of the global disease burden, yet they remain important health conditions. In particular, the mid- and long-term survival outcomes following diagnosis of CLTI are poor, comparable to, and in fact worse than, many cancer diagnoses³⁹². Strategies to improve outcome in cardiovascular disease are clearly warranted and on a global scale potentially represent the most meaningful strategy to improve health outcomes.

Optimising outcomes in cardiovascular disease can be performed by targeting one of three potential timepoints in the disease trajectory. The first is improved management on detection of occult disease (i.e. prior to a clinical manifestation) through screening and implementing medical prevention strategies, or through primary prevention in high-risk individuals. The second timepoint constitutes improving medical and procedural management of individuals who are diagnosed on the basis of an “end-organ” clinical presentation (i.e. angina pectoris, myocardial infarction, intermittent claudication, CLTI, TIA/CVA) through reduced time-to-treatment and novel management strategies. Thirdly, following management of an “end-organ” manifestation, optimal secondary prevention strategies to reduce the future risk of further cardiovascular event are an important area of cardiovascular disease management. Finally, across each of the timepoints, targeted strategies to improve patient fitness and physiological reserve, whilst simultaneously potentially reducing the burden of comorbidity, may allow for improved outcomes should an individual progress to procedural/surgical intervention. The data presented in this thesis predominantly contribute to our understanding of the latter two of these factors, as well as offering insight into the mechanistic pathways by which certain patients experience inferior outcomes. Additionally, potential novel markers of poor prognosis are explored, which may allow for more robust patient selection for major intervention and guide clinical decision making where equipoise exists between multiple different management strategies.

The data presented in the present thesis reflect typical contemporary vascular surgical practice in Scotland, however due to variable demographic factors may not be generalisable to a wider population. Data on ethnicity and socioeconomic deprivation are not presented, however there is likely to be regional variation within the UK, and certainly variation from international cohorts. The majority (91%) of patients in the AAA cohort were male. The natural history of AAA, as well as the prognosis and complexity in repair, appears to be different in men and women, and the currently recruiting Women’s

Aneurysm Research: Repair Immediately Or Routine Surveillance (WARRIORS) trial may shed some light on these differences³⁹³. Despite the use of sex-specific thresholds for CT-BC parameters throughout the present thesis, the low number of female patients means that caution must be applied when interpreting the results.

15.2 FUTURE WORK

As well as contributing to the existing evidence base, the results presented in this thesis highlight several important areas for future research in this field, with some specific research questions generated.

15.2.1 THE FRAILTY EPIDEMIC

Frailty is increasingly recognised as a major determinant of outcomes across the entire spectrum of worldwide healthcare^{392,393}. Moreover, the increasing burden of frailty on a population level is presenting significant challenges for health and social care and necessitates structural reform of healthcare systems and processes to combat the frailty epidemic. In chapter 11 we highlight an association between both altered body composition and systemic inflammation and frailty in patients with CLTI. Assessing frailty in the clinical setting may present challenges; a range of scoring systems are available^{340,394} however each rely on subjective assessment of patients and patient-reported factors, which may be subject to bias. The use of objective measures of frailty, such as CT-BC parameters or measures of the SIR, would potentially allow for a more robust system of identification of frail patients in the clinical setting, and therefore may optimise the allocation of resources towards those individuals. As discussed in section 1.2.4, these factors should not be used in isolation and should be considered as part of a multimodal assessment of patients. Further validation of the observations in the present thesis is required before this can be considered clinically useful.

15.2.2 OPTIMISATION OF SKELETAL MUSCLE AND “PREHABILITATION”

The observation that low skeletal mass and density are associated with inferior post-operative survival leads naturally to the hypothesis that improving these skeletal muscle parameters may allow for improved survival outcomes. This has been investigated previously in the form of “prehabilitation”, where patients typically enrol in structured exercise programmes prior to undergoing major surgery³⁹⁵. To date, it appears that there may be a benefit in reducing length of stay, post-operative complications, and improving

functional measures (such as the six minute walk test), however results have not been universally reproduced^{396–398}. The complex multifactorial aetiology of sarcopenia necessitates a multimodal approach, and it is therefore likely that a multimodal approach is needed. Given that inflammation is established as a key aetiological factor for sarcopenia, modulation of the SIR is a potentially attractive target in terms of improving skeletal muscle parameters (discussed further in section 15.2.7).

Elective intervention for AAA is potentially a particularly fruitful field for pre-operative improvement in skeletal muscle as the optimal time required to intervene following diagnosis is typically longer than in patients with cancer (other than in very large AAA) due to the relatively insidious onset of aneurysmal disease. Given that sarcopenia as an entity progresses over months to years, it is counterintuitive to assume that meaningful improvement can be made in the relatively short time period that patients await cancer resection.

It remains uncertain whether sarcopenia predisposes to an increased risk of early (i.e. 30-day) post-operative mortality or complications; the low absolute rate in the cohorts presented in the present thesis precluded meaningful analyses. Further investigation in large prospective cohorts is therefore required.

15.2.3 PATIENT SELECTION FOR MAJOR INTERVENTION

In two of the cohorts presented in the present thesis (AAA and carotid endarterectomy) the procedures performed are largely (with the exception of ruptured AAA) prophylactic. Indeed, in patients with symptomatic carotid lesions, a proportion of patients will opt for medical therapy rather than surgical intervention. When considering these interventions, patient selection is of paramount importance. We have presented data which highlight a subset of patients (i.e. those with low skeletal muscle mass and density, and with elevated magnitude of the SIR) who are at risk of inferior survival outcomes. Due to the nature of these procedures, in order to benefit from them there must be a requisite expectation of a minimum survival post-procedure. If this is not the case, then the exposure to peri-procedural risk is of questionable benefit. Our results suggest that the use of CT-BC parameters and inflammation based-scoring systems may offer potential clinical utility in this regard. Prospective analyses of large cohorts directly comparing these factors against existing patient selection strategies, and in particular studies investigating the feasibility of implementing these novel strategies, are required.

Whilst intervention for CLTI is not prophylactic by nature, there are settings where multiple approaches are feasible. In particular, there are patterns of disease where equipoise exists regarding the choice of the more invasive open surgical revascularisation, compared with the less invasive endovascular / hybrid approach. Using CT-BC analyses or measures of the SIR to influence patient selection in this setting is beyond the scope of the data presented in this thesis, however this is an important area for further investigation.

15.2.4 QUALITY OF LIFE OUTCOMES IN CLTI

Historically, studies investigating CLTI have focussed on technical success of revascularisation. This has been criticised, and contemporary studies are instead primarily investigating clinically meaningful outcomes such as limb salvage rates. In addition to this, more attention has been paid to functional quality of life (QoL) measures, often using validated scoring systems, as a meaningful outcome of intervention, particularly in the era of “realistic medicine”³⁹⁹. Both sarcopenia^{400–402} and inflammation^{349,403,404} have been associated with inferior QoL outcomes; further analyses in this patient cohort are required.

15.2.5 DEVELOPING ADVANCED CT-DERIVED SKELETAL MUSCLE ANALYSES AND RADIOMICS

CT-BC analysis is largely considered the “gold standard” method for quantifying skeletal muscle mass and density, with the accepted limitations of invasiveness and requirement for exposure to ionising radiation. Within CT-BC, SMI has largely been the predominant factor of interest reported in the wider literature. The data in the present thesis support a potential greater role for SMD in prognostication, likely taken in conjunction with SMI and a measure of the SIR. However, the recent rapid development in the field of automation, machine learning, and bioinformatics has led to the emergence of radiomics. Radiomics refers to the automated or semi-automated analysis of medical imaging and extraction of mineable features, which undergo post-extraction multivariate regression analyses and validation to determine their association with an outcome variable⁴⁰⁵. These factors are typically not discernible to the human eye, therefore require advanced machine learning capabilities to extract and analyse. Radiomics has predominantly been applied to tumour imaging, however more recently muscle analyses have been reported, and, when used in combination with SMI, the association with gastrointestinal toxicity from chemotherapy appears to be augmented in patients with CRC⁴⁰⁶. These techniques show promise in both identifying optimal potential prognostic factors and in increasing the feasibility of

implementation into clinical practice through automation and require further investigation in cardiovascular disease.

15.2.6 CHARACTERISING THE INFLAMMATORY RESPONSE IN CARDIOVASCULAR DISEASE

The data presented in this thesis describe the SIR as measured by validated scoring systems based on clinically relevant, widely used blood results. However, the complexity of the inflammatory response has been highlighted throughout the present thesis. More accurately defining the precise immunological pathways by which the SIR confers inferior outcome and interacts with the inflammatory environment in atherosclerotic plaque is required with a particular focus on the identification of novel therapeutic targets for potential modulation. Cytokine analyses at baseline and at follow-up have been performed in patients with CLTI, however the presence of tissue loss in these cohorts may confound results somewhat^{407–409}. Additionally, an interaction between elevated cytokine response and low muscle mass in patients with CLTI is described³³³. A further potential parameter of interest is lactate dehydrogenase (LDH), an enzyme found ubiquitously in human cells involved in the lactate-pyruvate metabolic pathway. An association between elevated LDH and inferior outcome is recognised in patients with cancer, and there may be an association between LDH, cachexia, and systemic inflammation⁴¹⁰. Outside of its historic role as a marker of acute myocardial infarction, there is a paucity of evidence describing the associations between LDH and outcomes in cardiovascular cohorts, however LDH may confer inferior prognosis in patients undergoing cardiac surgery⁴¹¹. Defining the inflammatory mechanisms observed in patients with cardiovascular disease may offer novel insights into the nature of these poor prognosis conditions.

15.2.7 INFLAMMATORY MODULATION IN CARDIOVASCULAR DISEASE

The growing body of evidence supporting inflammation as a key driver of cardiovascular disease has led to an interest in modulating the systemic inflammatory response with a view to improving cardiovascular outcomes. The majority of studies have described outcomes in patients with coronary artery disease. High dose rosuvastatin has been associated with improved cardiovascular outcome in patients with activation of the systemic inflammatory response and normal lipid levels⁶². Canakinumab, a monoclonal antibody causing IL-1 β blockade, was associated with improved cardiovascular outcome in the CANTOS trial, however there was an increased risk of infection in the treatment

group¹⁷³. Ziltivekimab is an alternative monoclonal antibody directed against the IL-6 ligand which is being developed specifically for atherosclerotic disease, which appears to lower clinically measured (C-reactive protein) markers of inflammation and is currently being investigated with a view to cardiovascular outcomes^{217,412}. Low dose methotrexate has been investigated however does not appear to confer a benefit in atherosclerotic disease⁴¹³. A further potential avenue for investigation is the effect that modulation of the SIR has not only on clinical outcomes, but also on skeletal muscle mass and density, which may yield clinical benefits as discussed in section 15.2.1.

15.2.8 COLCHICINE IN CARDIOVASCULAR DISEASE

Colchicine is a widely used anti-inflammatory medication derived from the Autumn Crocus which has been reported to have been used to treat inflammatory conditions for over 3000 years⁴¹⁴. The mechanism of action appears to be via multiple pathways; disruption of microtubules and inhibition of chemotaxis, downregulation of E-selectin and L-selection preventing neutrophil attachment, and inhibition of IL-1 β production through disruption of the NLRP3 inflammasome⁴¹⁴. Currently colchicine has FDA approval and is used to treat inflammatory conditions such as gout, Behçets disease, and pericarditis. The major route of administration is oral, either as a tablet or capsule. Colchicine is primarily metabolised by the hepatic CYP3A4 enzymes and excreted via the urine⁴¹⁵. Dose adjustments are therefore required in renal impairment, and colchicine should be avoided in patients with hepatic failure. The most common side effects are gastrointestinal; diarrhoea is reported in up to 23% of patients, with nausea and vomiting less frequently reported⁴¹⁵.

Colchicine has been considered as a potential therapeutic agent to improve cardiovascular outcomes in patients with coronary artery disease for several years, including several large randomised controlled trials. A recent meta-analysis of patients with coronary artery disease reported that, compared with placebo, colchicine was associated with reduced risk of myocardial infarction (OR 0.64; 95% CI, 0.46–0.90, $p=0.01$) and stroke/transient ischemic attack (OR 0.50; 95% CI, 0.31–0.81, $p=0.005$), however at the expense of an increase in gastrointestinal side effects⁴¹⁶. A subset of these studies which report the rate of a composite primary outcome (major adverse cardiovascular event; MACE, a composite of myocardial infarction, ischaemic stroke, and cardiovascular death) are summarised in table 15.2. When weighting for study size, the overall absolute risk reduction as compared to placebo is 2.7%.

Table 15.2: Trials investigating the effect of colchicine on a composite primary outcome (MACE) in patients with atherosclerotic coronary artery disease

Study	Population	Results (primary outcome)	Absolute risk reduction
LoDoCo (2013) ⁴¹⁷	Stable coronary artery disease (n = 532)	5.3% treatment vs. 16.0% placebo ($p < 0.001$)	10.7%
COLCOT (2019) ⁴¹⁸	Recent (30-days) myocardial infarction (n = 4745)	5.5% treatment vs. 7.1% placebo ($p = 0.02$)	1.6%
COPS (2020) ⁴¹⁹	Presentation with acute coronary syndrome (n = 795)	6.1% treatment vs. 9.5% placebo ($p = 0.09$)	3.4%
LoDoCo2 (2020) ⁴²⁰	Stable coronary artery disease (n = 5522)	6.8% treatment vs. 9.6% placebo ($p < 0.001$)	2.8%
		Overall absolute risk reduction (weighted for n)	8.9% – 6.2% = <u>2.7%</u>

The potential benefit of colchicine in patients with LEAD is less well reported. Heindel et al report a retrospective population of patients with LEAD obtained from Medicare records, in which patients were already taking either colchicine (n = 968) or an NSAID (n = 698) for pre-existing gout⁴²¹. Their results did not demonstrate any benefit in MACE or major adverse limb event (MALE) in patients taking colchicine. An important limitation of their study is the patient population; just 1.1% and 12.5% of patients had rest pain and tissue loss respectively. By including patients with less severe symptoms, it is likely that those with a high systemic atherosclerotic burden are under-represented, therefore the potentially highest risk individuals are not included in this study. Moreover, the authors do not report outcomes in relation to intervention for LEAD. This may in part explain the lack of association observed in this study. At the time of writing, there are no randomised trials investigating the potential benefit of colchicine in patients undergoing treatment for CLTI. Of particular interest, the predominant factor in long-term failure of revascularisation is the development of neointimal hyperplasia, which appears to be driven by a local inflammatory cascade⁴²². Therefore, in patients who have undergone revascularisation, there may be a benefit to immunomodulation in terms of patency rates and ultimately limb salvage.

15.2.9 PROPOSED FUTURE STUDY

15.2.9.1 AIMS AND OBJECTIVES

The Adjunctive Colchicine Therapy in CLTI (ACT-CLTI) study aims to investigate the association between adjunctive colchicine therapy and outcomes following revascularisation for chronic limb threatening ischaemia.

15.2.9.2 PRIMARY OUTCOME

The primary outcome is the rate of major adverse cardiovascular and limb event (MACLE), a composite of myocardial infarction, cerebrovascular attack or transient ischaemic attack, cardiac death, and limb loss.

15.2.9.3 SECONDARY OUTCOMES

Secondary outcomes include: overall survival, patency of revascularisation (primary, primary assisted, secondary, and rate of graft failure), limb salvage rates, myocardial infarction, cerebrovascular attack or transient ischaemic attack, cardiac death, dropout rate due to side effect profile of colchicine, change in inflammatory parameters (CRP, albumin, mGPS, NLR, SIG), change in grip strength.

15.2.9.4 DESIGN

The study design is of a multicentre, double blind, placebo controlled randomised trial. Participants will be allocated to groups using permuted block randomisation to ensure matched cohorts for important baseline covariates.

15.2.9.5 SAMPLE SIZE

Based on an adjusted absolute risk reduction of MACE (from previous literature, table 15.2) of 2.7%, the sample size required is 3152 (1576:1576, alpha 0.05, power 0.80). Data will be analysed as both intention-to-treat and per protocol, with intention-to-treat the preferred reporting method.

15.2.9.6 INCLUSION CRITERIA

Inclusion criteria are: adult patient (age ≥ 18 years), undergoing open or endovascular revascularisation procedure performed for CLTI, diagnosed by 2019 GVG guidelines and corroborated by diagnostic imaging modality at the discretion of the clinician.

15.2.9.7 EXCLUSION CRITERIA

Exclusion criteria are: active malignancy, known autoinflammatory comorbidity, hepatic failure, renal impairment precluding colchicine use, patients presenting with acute limb ischaemia, current use of other immunomodulatory medications, patients undergoing

primary major limb amputation, pre-existing colchicine prescription, abandoned attempted revascularisation, immediate technical failure (failure of revascularisation within 7 days of procedure).

15.2.9.8 INTERVENTION

The intervention in the treatment arm will be Colchicine 0.5mg OD (dosing as per LoDoCo2 trial⁴²⁰) vs. placebo in the control arm. Other secondary prevention strategies (statin, antiplatelet, anticoagulant) will be left at the discretion of the clinician

15.2.9.9 FOLLOW-UP

There will be a minimum follow-up of 12 months, and a maximum follow-up of 36 months. Follow-up intervals will be at 3, 12, 24, and 36 months.

15.2.9.10 DATA POINTS (BASELINE)

Data points to be collected at baseline assessment include: demographic and comorbidity data, medications on admission, Clinical Frailty Scale (CFS)³⁴⁰, SVS Wifl Score³³¹, routine admission bloods (Hb, neutrophil count, lymphocyte count, CRP, albumin, creatinine), pattern of disease on imaging (TASC-II), revascularisation strategy (open vs. endovascular vs. hybrid, aortoiliac vs. femoropopliteal vs. crural), grip strength, CT-BC parameters.

15.2.9.11 DATA POINTS (FOLLOW-UP)

Data points to be collected at follow-up include: routine bloods (Hb, neutrophil count, lymphocyte count, CRP, albumin, creatinine), patency confirmation via duplex ultrasonography, reintervention rate, rate of primary outcome and secondary survival outcome, grip strength, CT-BC parameters (if longitudinal CT available as part of existing patient care).

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