Tampere University

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Sarcopenia as a Predictor of Survival in Vascular Patients

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ACADEMIC DISSERTATION
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the Faculty of Medicine and Health Technology of Tampere University,
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To my parents,
And my closest friends,
Without whom none of my success would be possible.

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Iisa Lindström

ABSTRACT

Sarcopenia refers to the reduction of skeletal muscle mass and strength, resulting in an impairment of muscle function and, subsequently, a deterioration in daily activities in aging people. It is an independent clinical condition, and the detection of sarcopenia may be useful in identifying optimal patients who benefit from surgical or other high-risk interventions, therefore optimizing the risk-benefit-ratio and effective allocation of limited resources in health care. Historically, the estimation of physiological reserves with different scoring methods has been utilized in the optimization of patient selection, especially in the case of surgery for elderly patients, but sarcopenia has not been included in these predictive models. The identification of sarcopenia is complicated by a lack of feasible, cost-effective, accurate, and reproducible diagnostic tools to be used in clinical work. Currently, it is evaluated using questionnaires and functional tests. Early recognition of sarcopenia may also enable preoperative interventions, such as physical exercise, to improve the condition of the patient and thereby also the results of surgery. Open and endovascular procedures to treat AAA and acute stroke patients are high-risk interventions, and these patients could benefit from the assessment of muscle parameters as markers of sarcopenia.

The present thesis studied the reliability and suitability of muscle parameters measured from pre- and postoperative computed tomography images, in addition to examining the independent predictive impact of muscle size and density on mortality after open vascular surgical and endovascular interventions. The included patients were treated at the Centre for Vascular Surgery and Interventional Radiology at Tampere University Hospital between 2001 and 2018. The data was collected retrospectively from the Tampere University Hospital vascular register and patient record database, and from the Fimlab Laboratoriot Oy Ltd database. A total of 301 patients undergoing surgery for an abdominal aortic aneurysm and 242 for an internal carotid stenosis, as well as 312 patients who had suffered a sudden cerebral infarction caused by a blockage of the anterior circulation and were treated with mechanical blood clot removal, i.e. mechanical thrombectomy, were included.

The present thesis aimed to identify muscle parameters that independently predict mortality after the vascular or endovascular intervention from pre-procedural

and control computed tomography studies. In four studies, the association of muscle area, density and lean area with short- and long-term survival was studied. The end point was long-term mortality in the abdominal aortic aneurysm and endarterectomy studies, and 3-month postinterventional mortality in the anterior ischaemic stroke study. In addition, changes in the psoas muscle area and density during follow-up were studied in endovascularly treated abdominal aortic aneurysm patients.

Psoas and masseter muscle measurements from computed tomography studies proved to be reliable and repeatable between clinicians. In study I, the density of the psoas muscles, as well as their lean area, at the L2–L3-level axial slices were found to be independent predictors of mortality in patients treated for an abdominal aortic aneurysm. In study II, the relative psoas muscle area change during follow-up was found to be a stronger independent risk factor for mortality than the follow-up psoas muscle area in patients treated by means of endovascular aneurysm repair. In study III, the masseter muscle area was a significant long-term prognostic factor for carotid stenosis patients subjected to endarterectomy. Furthermore, in study IV, in patients with an acute proximal anterior occlusion, the size and density of the masseter muscle were independently associated with the three-month survival after anterior mechanical thrombectomy.

The results of the present thesis, therefore, suggest that muscle parameters may reflect sarcopenia and that they can be used in the prediction of survival in vascular patients. Muscle parameters are reliable, feasible and readily available for clinical work.

TIIVISTELMÄ

Sarkopenialla tarkoitetaan lihaskudoksen vähentymistä ja siitä aiheutuvaa lihasten toiminnan heikentymistä ihmisen ikääntyessä. Sarkopenia on tunnettu, itsenäinen kliininen tila, ja sen arviointia voidaan hyödyntää niiden potilaiden tunnistamisessa, jotka todennäköisesti hyötyvät kirurgisista tai muista korkean riskin toimenpinteistä. Tämä mahdollistaa riski-hyötysuhteen optimionnin ja rajallisten resurssien tehokkaan hyödyntämisen terveydenhuollossa. Perinteisesti fysiologisten reservien arviointia erilaisilla pisteytysmenetelmillä on käytetty potilasvalinnan optimoinnissa erityisesti silloin, kun suunnitellaan korkean riskin leikkaustoimenpidettä iäkkäille potilaille. Aiemmin sarkopeniaa ei ole sisällytetty näihin ennakoiviin malleihin. Sarkopenian tunnistaminen on haastavaa, koska kliinisessä työssä ei ole käytettävissä tarkkaa, kustannustehokasta ja toistettavaa diagnostista menetelmää. Tällä hetkellä sarkopeniaa arvioidaan kyselylomakkeiden ja toiminnallisten testien avulla. Sarkopenian varhainen tunnistaminen saattaa mahdollistaa leikkausta edeltävät toimenpiteet potilaan tilan kohentamiseksi, esimerkiksi liikuntaharjoittelulla, ja sitä kautta myös kirurgisten tulosten optimoimisen.

Väitöskirjassa tutkittiin toimenpidettä edeltävistä ja seurantatietokonetomografiatutkimuksista mitattujen lihasparametrien toistettavuutta sekä lihaksen koon ja tiheyden itsenäistä ennusteellista vaikutusta kuolleisuuteen verisuonikirurgisten ja endovaskulaaristen toimenpiteiden jälkeen. Tutkimukset kohdistuivat Tampereen yliopistollisen sairaalan verisuonikirurgian sekä toimenpideradiologian yksikössä vuosina 2001–2018 hoidettuihin potilaisiin. Tutkimusaineisto kerättiin retrospektiivisesti Tampereen yliopistollisen sairaalan verisuonikirurgian rekisteristä ja potilastietokannasta sekä Fimlab Laboratoriot Oy:n tietokannasta. Tutkimuksiin sisällytettiin 301 vatsa-aortan aneurysman ja 242 sisemmän kaulavaltimoahtauman vuoksi leikattua potilasta sekä 312 potilasta, jotka olivat sairastaneet äkillisen, etukierron valtimon tukkeutumisesta aiheutuneen aivoinfarktin ja jotka hoidettiin mekaanisella verihyytymän poistolla.

Tutkimuksen tavoitteena oli tunnistaa toimenpiteitä edeltävistä ja seurantatietokonetomografiatutkimuksista lihasparametrit, jotka ennustavat itsenäisesti potilaan kuolleisuutta toimenpiteen jälkeen. Neljässä julkaisussa tutkittiin lihaksen koon, tiheyden ja näiden yhteisarvon vaikutusta potilaiden lyhyt- ja

pitkäaikaisennusteeseen. Päävastemuuttuja oli pitkäaikaiskuolleisuus vatsa-aortan aneurysmaa ja kaulavaltimon endarterektomiaa koskeneissa tutkimuksissa sekä kolmen kuukauden kuolleisuus toimenpiteen jälkeen iskeemistä etukierron aivoinfarktia koskevassa tutkimuksessa. Lisäksi tutkittiin lannelihaksen koon ja tiheyden muutosta seurannan aikana kajoavasti hoidetuilla vatsa-aortan aneurysmapotilailla.

Lannelihaksen ja ulomman puremalihaksen mittaukset tietokonetomografiatutkimuksista osoittautuivat luotettaviksi ja toistettaviksi kliinikoiden välillä. Ensimmäisessä osatyössä havaittiin L2–L3-tason aksiaalileikkeistä mitattujen lannelihaksen tiheyden sekä lean-arvon olevan vatsa-aortan aneurysman leikkauksen jälkeiseen ennusteeseen itsenäisesti vaikuttavia ennustetekijöitä. Toisessa osatyössä havaittiin suonensisäisesti hoidettujen vatsa-aortan aneurysmapotilaiden seurannassa lannelihaksen koon suhteellisen muutoksen olevan seurannan aikana voimakkaampi kuolleisuuden ennustetekijä kuin seurantatietokonetomografiatutkimuksesta mitattu lannelihaksen koko. Kolmannessa osatyössä osoitettiin ulomman purentalihaksen koon olevan merkittävä pitkän ajan ennusteeseen vaikuttava tekijä sisemmän kaulavaltimon ahtauman vuoksi leikatuilla potilailla. Lisäksi akuutin proksimaalisen etukierron aivoinfarkin sairastaneilla potilailla ulomman purentalihaksen koko ja tiheys olivat neljännessä osatyössä itsenäisesti yhteydessä potilaan kolmen kuukauden ennusteeseen aivoinfarktin mekaanisen verihyytymän poiston jälkeen.

Väitöskirjan tulosten perusteella näyttää siltä, että lihasparametrit saattavat heijastaa sarkopeniaa ja että niitä voidaan käyttää verisuonikirurgisten potilaiden eloonjäämisen ennustamiseen. Lihasparametrit ovat kliiniseen työhön soveltuvia, luotettavia ja helposti saatavilla olevia muuttujia.

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ABBREVIATIONS

AAA	Abdominal aortic aneurysm
AIS	Acute ischaemic stroke
ALM	Appendicular lean mass
ASA	American Stroke Association
ASPECT	Alberta Stroke Program Early CT Score
ASM	Appendicular skeletal muscle mass
AWGS	Asian Working Group for Sarcopenia
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BSA	Body surface area
CAD	Coronary artery disease
CEA	Carotid endarterectomy
CI	Confidence interval
CT	Computed tomography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
DM	Diabetes
DEXA	Dual-energy X-ray absorptiometry
EVAR	Endovascular aneurysm repair
EWGSOP	European Working Group on Sarcopenia in Older People
FNIH	Foundation for the National Institutes of Health
HTA	Arterial hypertension
HR	Hazard ratio
HU	Hounsfield unit
IANA	International Academy on Nutrition and Aging
ICC	Intraclass correlation coefficient
ICA	Internal carotid artery
IQR	Interquartile range
L1	First lumbar vertebra level
L2	Second lumbar vertebra level

L3	Third lumbar vertebra level
L4	Fourth lumbar vertebra level
L5	Fifth lumbar vertebra level
LMMA	Left multifidus muscle area
LMMD	Left multifidus muscle density
LPMA	Lean psoas muscle area
ΔLPMA	Absolute LPMA change
ΔLPMA/BL	Relative LPMA change (Absolute LPMA change/Baseline LPMA)
MA	Masseter area
MAavg	Average masseter area
MCA	Middle cerebral artery
MD	Masseter density
MDavg	Average masseter density
MMA	Multifidus muscle area
MMD	Multifidus muscle density
MT	Mechanical thrombectomy
MRI	Magnetic resonance imaging
M1	M1 segment of the middle artery
NIHHS	National Institute of Health Stroke Scale
OSR	Open surgical repair
OR	Odds ratio
PACS	Picture archiving and communication system
PMA	Psoas muscle area
ΔPMA	Absolute PMA change
ΔPMA/BL	Relative PMA change (Absolute PMA change/Baseline PMA)
PMD	Psoas muscle density
PSMA	Paraspinous muscle area
SD	Standard deviation
SMM	Skeletal muscle mass
TAMA	Total abdominal muscle area
TAUH	Tampere University Hospital
Th12	Twelfth thoracic vertebra level
TPMA	Total psoas muscle area
TPMD	Total psoas muscle density
TLPMA	Total lean psoas muscle area

rAAA	Ruptured AAA
ROI	Region of interest
RMMA	Right multifidus muscle area
RMMD	Right multifidus muscle density
RPMA	Right psoas muscle area

ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:

I Lindström I, Khan N, Vänttinen T, Peltokangas M, Sillanpää N, Oksala N. Psoas muscle area and quality are independent predictors of survival in patients treated for abdominal aortic aneurysms. Ann Vasc Surg 2019;56:183–93.

II Lindström I, Protto S, Khan N, Sillanpää N, Hernesniemi J, Oksala N. Developing sarcopenia predicts long-term mortality after elective EVAR. J Vasc Surg 2020;71:1169-1178.

III Oksala NKJ, Lindström I, Khan N, Pihlajaniemi VJ, Lyytikäinen L. Pre-Operative Masseter Area is an Independent Predictor of Long-Term Survival after Carotid Endarterectomy. Eur J Vasc Endovasc Surg 2019;57:331–8.

IV Lindström I, Protto S, Khan N, Hernesniemi J, Sillanpää N, Oksala N. Association of masseter area and radiodensity with three-month survival after proximal anterior circulation occlusion. J Neurointerv Surg 2021;13:25-29.

AUTHOR'S CONTRIBUTION

A summary of the author's own contribution in original publications I-IV is presented below:

Contribution category	Study			
	I	II	III	IV
Research concept and design	x	x		x
Data collection	x	x		x
Statistical analysis and interpretation	x	x	x	x
Preparing figures and tables	x	x		x
Writing and revising the manuscript	x	x	x	x

1 INTRODUCTION

Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as a progressive and general loss of muscle mass and function (Cruz-Jentoft et al., 2019). The etymology of the term is derived from the Greek words "sarx" for flesh and "penia" for loss and poverty, and the term "sarcopenia" was first used in 1989 by Rosenberg (Rosenberg, 1989). As muscle mass and strength vary during the lifetime, sarcopenia can even occur earlier in life. However, it is more common in older age. The ageing of the population leads to an increased burden of sarcopenia and an increase in the incidence of ageing-associated conditions. The loss of skeletal muscle mass, sarcopenia, is associated with impaired outcomes after surgery. Patients with sarcopenia are particularly vulnerable to stressors, such as high-risk surgery, surgical complications and institutionalization. Sarcopenia, along with the ageing of the population, has gained special importance and interest, and there is a need for methods of recognizing high-risk patients before surgical interventions (Cruz-Jentoft et al., 2019). The first EWGSOP publication of the sarcopenia and updated consensus are widely used guidelines of sarcopenia in research area (Cruz-Jentoft et al., 2010, 2019).

A longer life expectancy is an important health goal worldwide, but at the same time, there are challenges in maintaining the quality of life and the capacity to live independently. The increasingly aging population also suffers a from varying comorbidities, and this has led to a situation where the older population is more fragile and associated with high mortality after surgical interventions. At the global level, between 2019 and 2050 65 years or older persons is estimated to double to 1.5 billion, when every six people would be 65 years or older worldwide (United Nations, Department of Economic and Social Affairs, 2020). The European Working Group on Sarcopenia in Older People has recommended increasing awareness of sarcopenia and its role when evaluating a patient's surgical candidacy (Cruz-Jentoft et al., 2019). The preoperative identification of and a systematic intervention for sarcopenia as a potential risk factor may be a novel approach to improving the surgical outcome. In a high-risk vascular surgery patient, the enhanced risk prediction methods may support patient survival, surgical results and cost-effectiveness. Along with surgical

methods, interventional radiology techniques have also developed, and there is a need to amplify the risk prediction for high-risk ischaemic stroke patients treated by means of mechanical thrombectomy. Several conventional surgical and anaesthesiologic predictive tools are generally applicable but do not perceiving sarcopenia or frailty, and are often impractical for surgeons. Sarcopenia adds a new dimension estimating postoperative survival.

The methods for estimating sarcopenia are varied; after the first study by the European Working Group on Sarcopenia in Older People in 2010, there has been increasing interest in examining the diagnostic criteria of sarcopenia. However, worldwide consensus is yet to be reached. The current challenge lies in the lack of defining sarcopenia in patients who are at a higher risk of death after invasive interventions, even though clinicians are more often aware of an increasing sarcopenic population. In order to be familiar with the clinical picture of sarcopenia on the one hand and, on the other, to understand the association between sarcopenia and survival, the evaluation method of sarcopenia should be objective, reproducible and convenient for clinical practice without adding to the costs. An overall clinical understanding of the influence of sarcopenia is beneficial when optimizing the postoperative survival of vascular and endovascular patients.

The most widely used methods for evaluating sarcopenia is the detection of low muscle mass, quality and strength (Cruz-Jentoft et al., 2019). Decreased muscle area and density in computed tomography angiography (CTA) had previously been considered to be a marker of sarcopenia. Before elective surgery or acute mechanical thrombectomy, patients undergo CTA imaging, which is used for operative planning. However, the patient's health and surgical risk may be evaluated from the same preoperative studies by measuring muscle size and density. In this thesis, the aim was to evaluate the reproducibility, reliability and association with mortality of muscle area and density measured from CTA in this challenging population, including vascular surgery patients and those treated by means of mechanical thrombectomy.

2 REVIEW OF THE LITERATURE

2.1 Sarcopenia

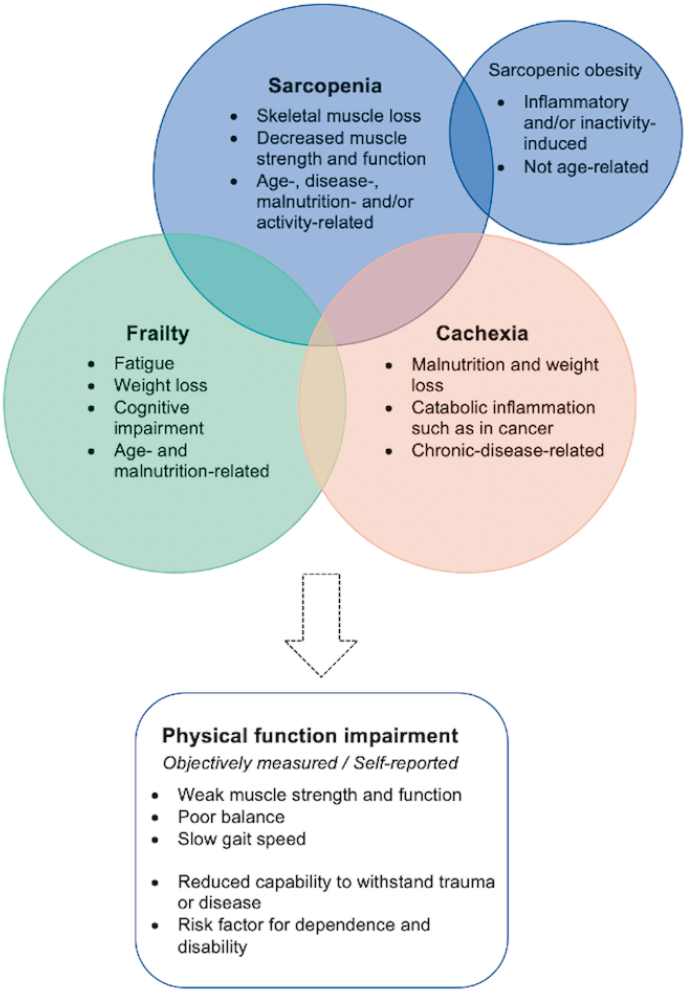
2.1.1 Definition

Three different terms, "sarcopenia", "frailty" and "cachexia", are used in the literature to depict age-related muscle loss and function, associated with disability in terms of mobility and daily activities, as well as hospitalization and mortality. Sarcopenia is defined as a syndrome characterized by a loss of muscle mass, function and strength, leading to physical disability, a poor quality of life and, finally, death (Cruz-Jentoft & Sayer, 2019). Sarcopenia is a significant contributor to frailty (Vellas et al., 2018). The definitions of frailty and sarcopenia overlap, and both syndromes have common manifestations in older adults, but the loss of muscle mass and function has also been observed in younger, middle-aged individuals people with physical disabilities, chronic diseases and malnutrition (Cederholm et al., 2017; Cruz-Jentoft et al., 2019). Nevertheless, frailty is more commonly referred to when the pathophysiologic background of the phenotype is defined, and the term is more easily used in the clinical setting because it is a clinical condition and caused by a decline in physiologic reserves, which leads to increased vulnerability. However, frailty is not limited to only physical disability but also includes social and cognitive aspects. (Keevil & Romero-Ortuno, 2015)

Sarcopenia differs from cachexia by the mechanism of underlying muscle mass decrease, and in sarcopenia, the muscle loss can be more moderate than in cachexia (Keevil & Romero-Ortuno, 2015). While sarcopenia is more often induced by a low-grade chronic inflammation due to ageing (Bano et al., 2017), in cachexia, in turn, the decrease in muscle mass is induced by the releasing of inflammatory cytokines in metabolic chronic diseases (Peterson & Mozer, 2017). Cachexia frequently occurs in patients suffering from diseases that are complicated by catabolic responses, such as cancer and end-stage chronic organ diseases, and it is characterized by a decrease in muscle mass with or without a loss of fat mass. Nutritional support cannot overturn the increasing catabolism in cachexia. (Sumbul

& García, 2014) The definitions of sarcopenia, frailty and cachexia are partially overlapping, and Figure 1 shows the relationships between these conditions. Common to all three is the presence of physical function impairment.

Figure 1. Definitions of sarcopenia, frailty, and cachexia overlap, with low physical function included in all three.



In 2019, the EWGSOP stated that muscle strength is the key characteristic of sarcopenia and the diagnosis requires detection of low muscle quality and quantity (Cruz-Jentoft et al., 2019). Sarcopenia is categorized as primary when no other specific reason is evident besides the condition being age-related and as secondary when the condition occurs due to chronic, inflammatory diseases in

individuals affected at a younger age. In comparison to the previous definition from 2010 (Cruz-Jentoft et al., 2010), the latest definition emphasizes muscle strength over muscle mass as the primary marker of sarcopenia (Cruz-Jentoft et al., 2019). However, muscle strength is associated with muscle mass, quality and consistency, and it is therefore justified to suggest that sarcopenia could also be detected by the measurement of muscle density from CT. Muscle quality is expected to be of significant importance in determining sarcopenia in the future. (Cruz-Jentoft et al., 2019) The evaluation of muscle quality has been considered to be inconvenient for the clinician due to the unavailability of feasible methods. The definition and diagnostic criteria were updated to increase awareness of and to enhance the treatment of sarcopenia, and the EWGSOP urged health care professionals to take action to better identify patients who are at a high risk of sarcopenia and to improve early detection and treatment (Cruz-Jentoft et al., 2019). Currently, sarcopenia has its own ICD-10 diagnosis code (Vellas et al., 2018), but official, universal guidelines for recognising this muscle disease in clinical work are still lacking.

2.1.2 Pathophysiology

The prevalence of sarcopenia is higher in older age groups (von Haehling et al., 2010). However, sarcopenia is a generalized skeletal muscle disorder and influenced by genetic and many other risk factors that people are exposed to during their lifetime (Cruz-Jentoft & Sayer, 2019), and the condition currently also affects younger adults. As early as in 1989, Rosenberg stated that "[n]o decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass" (Rosenberg, 1989). The most significant risk factor for the development of sarcopenia is malnutrition and physical inactivity. Other risk factors include smoking, genetic factors, hormonal factors and inflammation. (Rolland et al., 2008) It is suggested that the mechanism of sarcopenia includes both increased muscle catabolism and a reduction in the size and number of muscle myofibres (Cruz-Jentoft & Sayer, 2019). This leads to increased muscle protein turnover, remodelling and a loss of alpha-motor-neurons, which induces cell apoptosis (Rolland et al., 2008) and, consequently, muscle fibres are replaced with fatty infiltration. However, it is noteworthy that the mechanism that disturbs skeletal muscle homoeostasis remains to be clarified. Neither the chronological order of the reduction in muscle mass and tissue quality nor their pathogenic relationship is elucidated.

2.1.3 Clinical evaluation of sarcopenia

The clinical evaluation of sarcopenia is based on defining a loss of muscle mass and strength as well as lower physical performance. The loss of muscle mass and density is a clear starting point for developing sarcopenia, and according to recent guidelines, the effect of decreasing muscle density may exceed that of muscle mass loss (Cruz-Jentoft et al., 2019). Similarly, older individuals with low muscle function have been presented to be at a greater risk of losing their physical independence, as a marker of sarcopenia, than elderly people with low muscle mass (Carvalho do Nascimento et al., 2018). These findings suggest that new methods for evaluating sarcopenia are necessary, focusing not only on sarcopenia as muscle loss among aging people but also on the decrease in muscle strength and quality.

Currently, there are several specific methods available for the estimation of muscle mass and quality as markers of sarcopenia. The most commonly used and accessible methods are self-questionnaires as well as physical performance and muscle strength tests. The five-item SARC-F self-questionnaire was developed for clinicians to detect the risk of sarcopenia according the following five factors: strength, walking independence, chair stands, stair climb and history of falls. Ishii screening tool was presented to identify patients at a high risk of sarcopenia according to the EWGSOP sarcopenia criteria. They included three risk factors – age, grip strength and calf circumference – to estimate the probability of sarcopenia.

The more recent methods are objective muscle mass and quality (i.e. density) measurements via radiologic imaging, including dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI) and computed tomography (CT). Cut-off points for a diagnosis of sarcopenia vary, depending on the specific tests applied as well as the reference study population. The summary of clinical methods for estimating sarcopenia is shown in Table 1.

Table 1. Compilation of clinical methods for estimating sarcopenia.

Variable	Clinical practice /test	Diagnostic criteria for sarcopenia	Reference
Self-questionnaire	SARC-F	≥ 4 points	(Malmstrom et al., 2016)
Screening test	Ishii score	no cut-off	(Ishii et al., 2014)
Skeletal muscle strength	Hand grip test	men < 27 kg, women < 6 kg men < 26 kg, women < 16 kg	(Cruz-Jentoft et al., 2019) (Studenski et al., 2014)
	Knee flexion/extension	no cut-off	(Bijlsma et al., 2014)
Physical performance	Usual gait speed	< 0.8 m/s < 1.0 m/s	(Cruz-Jentoft et al., 2010) (Morley et al., 2011)
	Chair stand (5 rise-ups or 30 sec)	5 rise-ups or 30 sec	(Beaudart et al., 2016)
	The 400-m walk test	> 2 stops	(Cruz-Jentoft et al., 2019)
	Star climb power test	no cut-off	(Bean et al., 2007)
Skeletal muscle mass	Calf circumference	< 31 cm < 33 cm	(Landi et al., 2014) (Bahat et al., 2016)
	DEXA	ALM: men < 19.75 kg, women < 15.02 kg	(Studenski et al., 2014)
	BIA	ALM: no cut-off ASM: no cut-off ASM: men < 9.2 kg/m2, women < 7.4 kg/m2	(Scafoglieri et al., 2017) (Kyle et al., 2003) (Bahat et al., 2016)
	Ultrasound	Rectus femoris muscle Rectus femoris muscle Rectus femoris muscle and vastus lateralis muscle	(Mueller et al., 2016) (Thomaes et al., 2012) (Watanabe et al., 2013)
	CT	Mid-thigh muscle Psoas muscle All muscles of the axial slice	(Reinders et al., 2016) (J. Patel et al., 2020) (Derstine et al., 2018)
	MRI	Mid-thigh muscle Paraspinal muscles	(Maden-Wilkinson et al., 2013) (Kim et al., 2019)
Skeletal muscle quality	CT	Mid-thigh muscle All muscles of the axial slice	(Reinders et al., 2016) (Derstine et al., 2018)
	MRI	Mid-thigh muscle Paraspinal muscles	(Maden-Wilkinson et al., 2013) (Kim et al., 2019)

DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; ALM, appendicular lean mass; ASM, appendicular skeletal muscle mass.

The most cited definition and cut-off value for sarcopenia is that of the EWGSOP, which was recently updated in 2019. According to the EWGSOP, the gold standard for defining sarcopenia is appendicular muscle mass adjusted by the height squared, the hand grip test and walking speed test. (Cruz-Jentoft et al., 2019) The Asian Working Group for Sarcopenia (AWGS) drew up a similar classification (Chen et al., 2014) and released cut-off values more convenient for the Asian population's body size, lifestyle and cultural background. Previously, in 2014, the Foundation for the National Institutes of Health Sarcopenia Project (FNIH) used data from nine different studies on older patients to define a diagnostic threshold for sarcopenia (Studenski et al., 2014). They proposed that sarcopenia should be measured as appendicular lean muscle mass adjusted by the body mass index (BMI). The oldest cut-off values from 2011 were determined by the International Academy on Nutrition and Aging (IANA), and they did not consider the hand grip test as diagnostic for sarcopenia (Fielding et al., 2011). All these publications are comparable and summarized in Table 2.

Table 2. Compilation of the diagnostic criteria of sarcopenia.

Publication	Grip strength	Muscle mass	Physical performance
EWGSOP	< 27 kg (men) < 16 kg (women)	Appendicular lean mass*/height^2 < 7.0 kg/m^2 (men), <5.5 kg/m^2 (women)	Gait speed ≤ 0.8 m/s
AWGS	< 26 kg (men) < 18 kg (women)	Appendicular lean mass*/height^2 < 7.0 kg/m^2 (men), < 5.4 kg/m^2 (women)	Gait speed < 1.0 m/s
FNIH	< 26 kg (men) < 16 kg (women)	Appendicular lean mass*/BMI < 0.789 (men), < 0.512 (women)	Walking speed ≤ 0.8 m/s
IANA	N/A	Appendicular lean mass*/height^2 ≤ 7.23 kg/m^2 (men), ≤ 5.67 kg/m^2 (women)	Gait speed < 1.0 m/s

EWGSOP, European Working Group on Sarcopenia in Older People (Cruz-Jentoft et al., 2019); AWGS, Asian Working Group for Sarcopenia (Chen et al., 2014); FNIH, Foundation for the National Institutes of Health Sarcopenia Project (Studenski et al., 2014); IANA, International Academy on Nutrition and Aging (Fielding et al., 2011). *Measured by dual X-ray absorptiography.

Sarcopenia is challenging for surgeons to measure reliably in everyday practice, and it might be neglected, since the current clinical tools, such as muscle strength tests

(grip strength, chair rise test) and physical performance tests (gait speed test, 400-metre walking test), are time-consuming, need dedicated health care personnel, and there is a delay in receiving the results. Furthermore, body weight changes do not adequately reflect changes in muscle status (e.g. in cases of pathologic accumulation of fluid in the body, such as in ascites or pulmonary oedema, or when muscle tissue converts into adipose tissue). CT images are reliable for determining muscle mass and density, i.e. quality, potentially facilitating the detection of sarcopenia from CT images before the development of clinically noticeable signs (Batsis & Villareal, 2018).

2.1.4 The association of psoas and masseter muscles with sarcopenia

Measuring the whole-body skeletal muscle mass and strength, when diagnosing sarcopenia, is limited for different reasons. A CT study rarely includes the whole body, and the whole-body muscle analysis is laborious for the clinician. The efforts should focus on muscle measurements that are as simple, reliable and convenient as possible, which could represent sarcopenia. CT-measured low psoas muscle cross-sectional area has been related to the main risk factors of sarcopenia, such as impaired physical mobility and daily self-care ability as well as cognitive difficulty (Miller et al., 2014). The psoas muscle's utility as a sentinel muscle, independent of the other muscles, is based on the psoas muscle function as a main flexor of the hip and a stabilizer of the lumbar spine and hip joint. A weakness of the psoas muscle impairs walking, the maintaining of balance and standing up from a chair, and these, in turn, may weaken the recovery after surgery.

Masseter muscle area has been found to indicate sarcopenia in trauma patients and to correlate significantly with the psoas muscle (P. Hu et al., 2018). It appears that there is a relationship between the masseter muscle and sarcopenia according to a previous study that found masseter muscle thickness, chewing ability and dental status to be closely associated with hand and lower limb performance tests (Gaszynska et al., 2014). Furthermore, a low skeletal muscle index (muscle mass measured by BIA and divided by squared height), a risk factor for sarcopenia, has been found to be associated with decreased masseter muscle thickness (Umeki et al., 2017). Moreover, the individual differences in patients' backgrounds, ethics and the sexes may have an impact on skeletal muscles and the developing of sarcopenia.

2.1.5 The association of muscle parameters with postoperative survival

Seven previous studies of surgical patients have demonstrated an association between CT-measured muscular features and late survival in vascular surgery patients. Furthermore, three studies have investigated masseter muscle area as a predictive variable for mortality in brain trauma patients whose radiological studies were focused on the head. Two of the vascular surgery studies (Canvasser et al., 2014; Wallace et al., 2017) and two brain trauma studies (Tanabe et al., 2019; Wallace et al., 2017) reported the results of muscle parameter standardization by means of z-scoring in their mortality regression analyses, but the other studies arrived at their results in disparate units and no comparative conclusion can be reached. A compilation of key findings from previous studies is shown in Table 3. Muscle parameter results are covariate-adjusted hazard or odds ratios for mortality.

Table 3. Previous studies on the association of computed-tomography-measured muscular features and mortality in vascular surgical and trauma patients.

Study	Population	Surgery	n	Muscle/Location	Mean area (cm^2)	Follow-up	HR (95% CI)
Lee et al., 2011	AAA	elective OSR	262	PMA / L4	21.7 ± 7.3	2.3 y	0.33 (0.16–0.68) per $10cm^2$
Canvasser et al., 2014	surgical patients with abdominal CT	general or vascular surgery	1,309	PSMA / Th12	Men: 39.2 ± 11.1 Women: 28.2 ± 6.7	1 y	Men: OR 0.64 (0.47-0.88) * Women: OR 0.70 (0.50–.099) * (z-scored)
Drudi et al., 2016	AAA	elective EVAR (85%) or OSR	149	PMA / L4	24.0 ± 5.8	1.87 y	0.86 (0.79–0.93)
Wallace et al., 2017	Blunt-injury, age > 65	-	226	PMA average / L4	Men: 10.7 ± 2.8 Women: 6.5 ± 1.7	2 y	0.76 (0.60–0.96) (z-scored)
Shah et al., 2017	AAA	elective EVAR (96%) or OSR	137	TAMA / L4	Men: 58.5 Women: 52.9	3.8 y	N/A
Newton et al., 2018	AAA	elective EVAR	135	PMA / L4	26.8	5 y	N/A
Thurston et al., 2018	AAA	elective EVAR	191	PMA / L3	N/A	N/A	N/A
Indrakusuma et al., 2018	asymptomatic infrarenal AAA	EVAR (62%) or OSR	228, 124 were operated	PMA / L3	16.8 (median)	N/A	N/A
Wallace et al., 2017	Blunt-injury, age > 65	-	357	MA / 2 cm below zygomatic arch	Men: 4.2 ± 1.1 Women: 3.4 ± 0.8	2 y	0.68 (0.46–1.00) (z-scored)
Hu et al., 2018	Severe brain injury	-	108	MA / 2 cm below zygomatic arch	4.7 ± 1.1 (non-sarcopenic) 2.6 ± 0.5 (sarcopenic)	2.5 y	0.78 (0.62–0.97)
Tanabe et al., 2019	Trauma patients with head CT, age > 65	-	327	MA / 2 cm below zygomatic arch (z-scored)	Men: 4.4 ± 1.0 Women: 3.5 ± 0,8	1 y	2.0 (1.2–3.1) per SD less than mean (z-scored)

HR, hazard ratio; AAA, abdominal aortic aneurysm; OSR, open surgical repair; PMA, psoas muscle area; L4, fourth lumbar vertebra level; CT, computed tomography; PSMA, paraspinous muscle area; Th12, twelfth thoracic vertebra level; OR, odds ratio; EVAR, endovascular aneurysm repair; TAMA, total psoas muscle area; L3, third lumbar vertebra level; MA, masseter area; SD, standard deviation. * Result in OR. Results are adjusted for covariates specified separately in each study.

The first study included 262 AAA patients treated with elective open surgical repair (OSR), and psoas muscle area (PMA) was measured at the L4 vertebral level from preoperative CT images. PMA strongly correlated with survival (HR 0.33, 95% CI 0.16–0.68 per 10 cm^2 increase in total PMA). (Lee et al., 2011) The second study included a large cohort of different surgical patients (n = 1,309), not only vascular patients, and the investigators found paraspinal area measurements to be more easily attainable than psoas muscle measurements. Paraspinal muscle area at the Th12 level was measured from preoperative abdominal CT scans, and it was associated with one-year postoperative mortality (OR 0.64, 95% CI 0.47–0.88, for men and OR 0.70, 95% CI 0.50–0.99, for women). (Canvasser et al., 2014) The purpose in the third study of 149 AAA patients treated with EVAR or OSR was to replicate the previous results with a more homogenous population. The study found low PMA to be independently associated with greater mortality (HR 0.86, 95% CI 0.79–0.93) during follow-up (median 1.87 years) (Drudi et al., 2016). In a more recent cohort of 137 AAA patients treated with elective EVAR (96% of the patients) or OSR, the cross-sectional area of the total abdominal muscle area (TAPA), including the psoas muscles, was measured. There was no significant association with survival during long-term follow-up (median 3.8 years). However, the adjusted weight-standardised left psoas muscle area (LPMA) was independently associated with survival (HR 0.94, 95% CI 0.81–1.01). (Shah et al., 2017)

Since the first publication in 2011, several studies have stated the association of sarcopenia with survival in EVAR patients with different methods. In the a cohort of 135 AAA patients treated with elective EVAR, patients in the lowest PMA tertile had increased five-year mortality (OR 3.9, 95% CI 1.2–12.9) (D. Newton et al., 2018). The median follow-up for surviving patients was 2.25 years. Another study of 191 AAA patients treated with EVAR utilized PMA measured at the L3 level and normalized with height. Sarcopenia was defined as PMA < 500 mm^2/m^2. Sarcopenic patients had an increased risk of death (HR 1.73, 95% CI 0.84–3.58) after adjusting for classic risk factors. (Thurston et al., 2018) Contrary to the other previous studies, in a retrospective cohort of 124 AAA patients treated with EVAR (62% of the patients) or OSR, where sarcopenia was defined as a PMA lower than 14.56 cm^2 at the L3 vertebral level, no association with mortality was found (p = 0.311) (Indrakusuma et al., 2018). However, neither hazard rations nor the follow-up time were reported.

After 2016, when PMA was discovered to correlate with masseter area (MA) in elderly patients with blunt head trauma (Wallace et al., 2017), there has been an increasing interest in assessing MA as a marker of sarcopenia. In a study of 487 blunt-

injury trauma patients, both PMA and MA were measured from CT studies for 197 patients (Wallace et al., 2017). The average MA (mean of bilateral MA) at 2 cm below the zygomatic arch was associated with 2-year survival (HR 0.76, 95% CI 0.60 0.96) (Wallace et al., 2017). Similarly, in a cohort of 108 severe brain trauma patients, 30-day mortality was found to be linked to average MA (HR 0.78, 95% CI 0.62–0.97) (P. Hu et al., 2018), and another study including 327 trauma patients discovered a one-SD decrease from the mean to be linked to 1-year mortality (HR 2.0, 95% CI 1.2–3.1) (Tanabe et al., 2019).

When considering the sum of the predictive value of PMA and MA as sarcopenia markers – and their correlation with survival, which was found in almost all of the studies presented – it would be plausible consider that muscle density, i.e. muscle quality, is related to muscle area as well as to survival. Numerous studies have found low total psoas muscle area to independently associate with postoperative survival after different surgical procedures – for example, in patients who underwent transcatheter aortic valve transplantation (Yoon et al., 2021) or emergency abdominal laparotomy (Brandt et al., 2019) and also in cancer patients after elective colorectal surgery (Dolan et al., 2019). However, there is no clear consensus on whether muscle area, as well as density, is associated with mortality in vascular patients, specifically in AAA, carotid endarterectomy (CEA) and acute ischaemic stroke patients.

2.2 Abdominal aortic aneurysm

An abdominal aortic aneurysm (AAA) is generally defined as an over 3.0 cm dilation localized subdiaphragmatically in the aorta, the largest artery in the body (Chaikof et al., 2018). The prevalence of AAAs increases particularly in men after the age of 65 years. Other common risk factors increasing the risk of AAA are hypertension, diabetes, smoking as well as and peripheral and coronary artery disease. (Chaikof et al., 2018) According to large cohorts, the incidence of AAAs ranges from 4% to 7% in the general population (Lindholt et al., 2005; Norman et al., 2004) and most AAAs are detected at an asymptomatic stage during imaging studies performed for other medical conditions (Wanhainen et al., 2019). The risk of a potentially fatal aneurysm rupture correlates with the size and growth rate of the aneurysm. According to the updated guidelines, the AAA diameter threshold for elective AAA repair is ≥ 5.5 cm for men and ≥ 5.0 cm for women (Wanhainen et al., 2019). Currently, an AAA can be treated either by OSR or EVAR (Greenhalgh et al., 2010). EVAR shows early

benefit over open surgery in elective surgery (Thompson et al., 2012) as well as improved survival and quality in emergency settings when treating ruptured aneurysms (Zhang et al., 2016). However, EVAR was not associated with increased long-term survival compared to OSR treated patients (Lederle, F.A. et al., 2019). The surgical procedures for AAA are high-risk interventions (Carlyle et al., 2015), and an adequate survival prognosis for the patient is required in order to outweigh the risk of postoperative mortality. Commonly, OSR is classified as high-risk surgery, with mortality defined as more than 5%, and elective EVAR as intermediate-risk surgery with a mortality of 1%–5%. The 30-day perioperative mortality in AAA patients is evaluated to be between 1.4%–5.2% according to multicentre randomized trials. The outcomes are related to the selected method (EVAR or OSR) and the volume of AAA patients treated in the hospital. (Chaikof et al., 2018) Besides the treatment method, postoperative survival is influenced by several factors, such as age, sex, smoking, aneurysm rupture and comorbidities like renal insufficiency, congestive heart failure, diabetes and chronic pulmonary diseases (Beck et al., 2009; Grootenboer et al., 2010; Investigators, 2017; Mureebe et al., 2010). However, surgical and radiological technological developments have made it possible to offer invasive treatment to older and more multimorbid patients who need improved methods of risk prediction to enhance the survival results of EVAR and OSR procedures.

2.2.1 Endovascular aneurysm repair

EVAR is the treatment option for most elective patients suffering from an AAA. The EVAR technique, first described by Volodos in 1987, involves the placing of a stent graft within the aneurysm sac so that the stent graft extends sufficiently against the aortic wall above and below the aneurysm sac in sealing zones and prevents sac rupture by isolating the aneurysm sac from systemic circulation (England & McWilliams, 2013). After the publication by Parodi in 1991, EVAR achieved wider awareness among vascular surgeons (Parodi et al., 1991). The purpose of stent grafting is to exclude the aneurysm from the systemic circulation and to prevent aneurysm rupture (Paravastu et al., 2014). EVAR carries a lower risk of operative mortality (Beck et al., 2009; Greenhalgh et al., 2004, 2010; Lederle et al., 2009; Prinssen et al., 2004) and an early survival benefit over OSR (Greenhalgh et al., 2004; Investigators, 2017). The risk of death continues to be lower during the early postoperative years after elective EVAR compared to OSR (Greenhalgh et al., 2010;

Paravastu et al., 2014), but in the long term, the risk of mortality is increased in EVAR patients (Lederle, F.A. et al., 2019). The advantage of minimally invasive EVAR is that there is no open abdominal surgery, the need for intensive care is reduced and the hospital stay is shorter (Paravastu et al., 2014). However, the main disadvantage of EVAR is that patients need more frequent follow-up and as many as nearly one third require a re-operation later (Paravastu et al., 2014; R. Patel et al., 2016), mostly treated by endovascular technique (R. Patel et al., 2018).

Not all AAAs are anatomically or morphologically suitable for standard EVAR. Anatomical suitability is estimated by evaluating the length, shape and configuration of the aneurysm neck, as well as the access through the iliac arteries (Chaikof et al., 2018). The common reason for excluding a patient from standard EVAR is an aneurysm neck close to the origin of the renal arteries, or a case in which the arteries originate directly from the aneurysm sac (i.e. there is no aneurysm neck at all).

2.2.2 Open surgical repair for abdominal aortic aneurysm

OSR for an AAA is a surgical procedure performed via a laparotomy incision. The vascular graft is secured inside the aneurysm sac, placing graft proximally to the aorta above the aneurysm and distally to the aorta, iliac arteries or femoral arteries. (Wanhainen et al., 2019) Compared to EVAR, OSR is more invasive, but OSR-treated patients have shown similar (Lederle, F.A. et al., 2019) or lower mortality in the long term (R. Patel et al., 2016). The main indication for OSR is an unfavourable anatomy for EVAR, including a short or angulated AAA neck, multiple large accessory renal arteries, an additional iliac artery aneurysm, small iliac artery lumen or total occlusion due atherosclerosis and occlusive thrombus (Chaikof et al., 2018). The current expanding options for complex EVAR have decreased the volume of OSR treatment (R. Patel et al., 2016). However, it is reasonable to suggest OSR for young patients with a long life expectancy, since EVAR complications are reported to increase after 8–10 years and the long-term durability of the EVAR graft currently in use in not well known (Wanhainen et al., 2019).

2.3 Cerebrovascular disease

Cerebrovascular disease includes a variety of heterogenic conditions, diseases and disorders that affect the blood vessels of the brain and the cerebral circulation.

According to aetiology, cerebrovascular disease can be subdivided into two main categories: ischaemic events and cerebrovascular haemorrhages. Furthermore, ischaemic events are classified according to event location into the carotid or vertebrobasilar area, in addition to being classified by the duration of symptoms. An ischaemic stroke is an acute event, where a thrombus or an embolism causes an occlusion in an artery of the brain, and neurologic symptoms present over 24 hours and may be progressive. A transient ischaemic attack (TIA), in turn, typically lasts only a few minutes, after which the neurologic symptoms resolve. (Sorensen & Hakan, 2011). The inadequate cerebral blood supply is a result of thrombosis or embolism associated with arterial, cardiac or haematological disease, or with cerebral artery hypoperfusion due to carotid stenosis (A. R. Naylor et al., 2018).

Cerebrovascular diseases are important causes of morbidity and mortality: more than one in six people are affected by these conditions during their lifetime (Feigin et al., 2016). Furthermore, cerebrovascular disease represents the third leading cause of death worldwide after ischaemic heart disease and lung cancer (Naghavi, 2017). As vascular risk factors, smoking, physical inactivity, hypertension, high fasting glucose and total cholesterol are the most common risk factors for cerebrovascular disorders (Feigin et al., 2016). The total number of patients suffering from cerebrovascular disease will probably increase as the population ages over the coming decades. These conditions also cause secondary problems, including depression, dementia, epilepsy and impaired physical activity and balance (Dichgans & Leys, 2017).

2.3.1 Acute ischaemic stroke

To achieve equal understanding of the term "stroke" in clinical work and research alike, the Stroke Council of The American Heart Association/American Stroke Association published the last updated version of guideline for management of acute ischemic stroke (AIS) in 2018 (Powers et al., 2018). The consensus of stroke includes brain, spinal cord or retinal ischemic cell death (Sacco et al., 2013). The most typical stroke mechanism is ischaemic, but the term stroke also broadly includes intracerebral and subarachnoid haemorrhages (Powers et al., 2018). The clinical definition of ischaemic stroke entails a sudden loss of blood circulation in the central nervous system, mostly in brain parenchyma, which causes ischaemia and, consequently, an acute, persistent, focal neurological deficit. The infarct diagnosis is based on imaging and clinical evidence of a permanent stroke. The definitive

diagnosis is determined from a pathological examination of the tissue if autopsy is performed after death (Sacco et al., 2013).

A stroke is due to a potentially reversible embolic or thrombotic process preventing blood flow to the brain. Decreasing blood flow to the brain tissue initiates a complex cascade of events, leading to irreversible changes in the cells and, ultimately, cell death if circulation is not restored. (Lo et al., 2003) The fastest ischemic cellular death progress occurs within a few minutes at the centre of the stroke area, whereas more peripherally, the so-called ischaemic penumbra damages cells slowly due to collateral arteries (Lo et al., 2003). The National Institute of Health Stroke Scale (NIHHS) is the most commonly used classification in evaluating the severity of stroke according to clinical findings (Brott et al., 1989) and the Alberta Stroke Program Early CT Score (ASPECT) in defining the severity of early stroke findings in a brain CTA (Barber et al., 2000). Commonly, the middle cerebral artery (MCA) is involved in an acute stroke (Moustafa & Baron, 2008). The MCA supplies blood to a large area of the lateral cerebral cortex, a part of the basal ganglia and the internal capsule. According to supplied segments, the MCA is divided into four segments: M1, M2, M3 and M4. The main branch, the M1, supplies the basal ganglia, and damages to this area can cause deficiencies in motor control, learning motor skills, executive functions and regulating emotions. Immediate recanalization of a large vessel occlusion is required for a good neurological outcome (Mendelson & Prabhakaran, 2021). The treatment options for an AIS are intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) (Powers et al., 2018), and the choice of treatment is influenced by, for example, the symptoms of the stroke. Other endovascular treatment options are balloon angioplasty, stenting treatment and intra-arterial thrombolysis combined or not with MT.

2.3.2 Transient ischaemic attack

TIA is caused by temporarily impaired blood flow to the brain and a cerebral dysfunction, causing neurological dysfunction lasting less than 24 hours. The event is sudden and achieves the maximum symptoms almost immediately. Most often, the symptoms resolve within 10 minutes and only rarely last as long as 24 hours. The results of brain computed tomography imaging do not always correlate with a pathological infarction and may not indicate ischaemia despite a clinically defined stroke. (Easton et al., 2009) MRI technique is more sensitive to identify AIS than CT

(Lövblad et al., 1998) and patients suspected to have TIA should have MRI within 24 hours from the symptoms (Easton et al., 2009).

The diagnosis of a TIA is dependent on information on the type and duration of the neurological symptoms experienced by the patient (Coutts, 2017). The most important criteria for a TIA are symptom history, objective findings upon a neurologic examination and brain imaging findings. Transient monocular blindness, i.e. amaurosis fugax, is a common subtype of TIA. The lower or upper part of the visual field or the entire vision in one eye is lost. The vision loss can also be partial, such as a dimming or a blurring of the visual field. (Barnett et al., 1990) Other typical TIA manifestations include weakness or clumsiness of the limbs on one side of the body with or without numbness and a prickling sensation. Speech is sometimes described to be dysphasic or dysartric. If a patient's TIA presents with motor or speech symptoms, the risk of recurrent stroke is higher than in patients who present with other symptoms (Johnston et al., 2000). The risk of developing a stroke after a TIA is 20% within one month of symptom onset (Prasad, 2014).

2.3.3 Internal carotid artery stenosis due to the atherosclerosis

Carotid artery stenosis is a progressive narrowing of the artery caused by cholesterol-containing fatty plaques clogging the interior wall of the artery. The mechanism of developing atherosclerosis in the carotid artery is similar to the mechanism in coronary artery disease or peripheral artery disease in general, also including similar main risk factors, such as dyslipidemia, hypertension, diabetes, obesity, smoking and weak physical activity (Prasad, 2014). Increasing stenosis results alterations in local haemodynamic and may result in the formation of emboli and an occlusion, which can travel to the brain arteries and cause transient or more permanent ischaemia. Atherosclerotic plaques from the internal carotid artery and middle cerebral artery cause 25% of all strokes and constitute the main reason for recurrent ischaemic strokes before cardiac embolism (20%) (Ay et al., 2014). Between 10% and 15% of the asymptomatic internal carotid artery stenosis may be asymptomatic before recurrent stroke (A. R. Naylor et al., 2018).

2.3.4 Carotid endarterectomy

After stroke, TIA or amaurosis fugax caused by previously symptomatic carotid stenosis, surgical treatment of the atherosclerotic lesions in the cervical portion of

the inner lining of the internal carotid artery is carotid endarterectomy (Farrell et al., 1998). The goal of endarterectomy is secondary prevention, i.e. preventing carotid stenosis from causing a TIA or stroke. A less-invasive endovascular carotid stenting may be an alternative method for carotid stenosis. (A. R. Naylor et al., 2018) Carotid endarterectomy is mostly performed by opening the carotid artery longitudinally, removing the atherosclerotic lesions and closing the artery by means of suturing with or without sealing patch. Patients with a symptomatic 50%–99% internal carotid artery stenosis have an indication for endarterectomy (Liapis et al., 2009). In asymptomatic patients, the indications for surgery are more complicated with respect to optimizing the benefits and risks. The recently updated guidelines by the European Society for Vascular Surgery recommend the consideration of CEA for an asymptomatic 60%–99% stenosis if there is an increased risk of late ipsilateral stroke according to imaging characteristics and the patient's surgical risk is average at most. The main postoperative complications of CEA include a new stroke, myocardial infarction, haemodynamic instability and postoperative bleeding causing cervical haematoma. In symptomatic cases, surgical endarterectomy should be performed within 14 days after symptom onset. (A. R. Naylor et al., 2018)

2.3.5 Anterior mechanical thrombectomy

Endovascular mechanical thrombectomy (MT) has been demonstrated to be the standard choice in patients with an acute large vessel occlusion, i.e. proximal anterior circulation, ischaemic stroke (Bhogal et al., 2018; Powers et al., 2018). Most AIS patients are candidates for MT if the pre-stroke level is low, the occlusion is located in the internal carotid artery or the M1 branch of the MCA, the clinical severity of the symptoms is > 6 as measured by the NIHHS and the early ischaemic change in the brain CTA is > 6 as measured by ASPECT (Powers et al., 2018). Since 2014, several trials have investigated the efficacy and feasibility of MT. The MT time window after stroke symptom onset has been widened from six to up to 24 hours, and the number of patients treated with MT is increasing (Vidale et al., 2018). Alongside severe symptoms, patients presenting with mild symptoms have the benefit of rapid MT treatment before their collateral circulation is to be blocked up (Pfaff et al., 2016). Mechanical thrombectomy, like any other surgical procedure, carries treatment-related risks (e.g. symptomatic intracranial haemorrhage, artery dissection, new emboli), and patients selected for MT should be carefully evaluated in terms of the risk-benefit ratio.

3 AIMS OF THE STUDY

The aims of this thesis were as follows:

1. To clarify the reproducibility of muscle area and density measurements from computed tomography scans between clinicians and to find the most consistent parameters.

2. To determine the association of muscle area and radiodensity* as markers of sarcopenia with postoperative mortality in AAA patients treated with open surgery or EVAR.

3. To study the postoperative time course of potential changes in muscle status and their association with mortality in AAA patients treated with EVAR.

4. To study the association of masseter muscle area and radiodensity* as markers of sarcopenia with long-term postoperative survival in patients undergoing elective carotid endarterectomy.

5. To determine the association of masseter muscle area and radiodensity* as markers of sarcopenia with postoperative mortality in a cohort of acute stroke patients undergoing MT.

*Muscle area and radiodensity measured from CTA studies.

4 MATERIALS, SUBJECTS AND METHODS

4.1 Study settings

Studies I–IV had a retrospective cohort design. The patients were treated in Tampere University Hospital for a AAA during 2001–2014, for symptomatic internal carotid artery stenosis during 2004-2013 and for an acute ischaemic stroke during 2012–2018. Patient baseline clinical characteristics and time of death was collected from the Tampere University Hospital (TAUH) patient record data base, the results of the blood test from Fimlab Laboratories Ltd database and CT images from a picture archiving and communication system (PACS). In all of the studies, CTA imaging was used to measure muscle size and density for evaluating sarcopenia. Furthermore, in study II, 1–3-year follow-up CTA studies were employed to evaluate the progress of sarcopenia after EVAR. The baseline characteristics of the study populations are presented in Table 4.

4.2 Subjects and study protocol

Table 4. Study population, main objective, and primary outcome.

Study characteristics	Study I	Study II	Study III	Study IV
Study population	Treated AAA patients	EVAR-treated AAA patients	Treated ICA stenosis patients	ICA or M1 acute stroke patients treated with MT.
Study objective	Reproducibility of CTA muscle area and density and their association with postoperative survival.	Association of PMA and LPMA changes after EVAR with postoperative survival.	Reproducibility of MA and MD from CTA studies and their association with postoperative survival.	MA and MD evaluated from CTA studies and their association with 3-month survival.
Number of patients	301	122	242	312
Median age	74.4 (IQR 12.6)	77.9 (IQR 11.5)	71.0 (IQR 13.0)	69.2 (IQR 15.3)
Female	11%	10%	30%	37%
Muscle parameters	PMA, PMD, TPMA, TPMD, LPMA, TLPMA	PMA, LPMA, ΔPMA/BL, ΔLPMA/BL	MAavg, MDavg	MAavg, MDavg
Sample collection	2001–2014	2008–2016	2004–2010	2013–2018
End of follow-up	April 2015	September 2018	November 2017	December 2019
Median follow-up in years	2.7 (IQR 3.5)	6.0 (IQR 3.5)	5.7 (IQR 6.8)	2.3 (IQR 2.5)
All-cause mortality	94 (31.2%)	57 (46.7%)	104 (43.0%)	38 (12.2%)
Primary outcome				
Study I	PMD and LPMA at L2–L3 level; every 1-SD increase associated with a 22%–26% decrease in mortality during follow-up.			
Study II	For every 10% unit increase in ΔPMA/BL bilaterally, there was a 21% decrease in mortality during follow-up.			
Study III	A 1-SD increase in MAavg predicted a 24% decrease in long-term mortality after CEA.			
Study IV	A 1-SD increase in MDavg and MAavg was associated with a 39%–43% decrease in mortality during the first three months after MT.			

AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; ICA, internal carotid artery; M1, M1 segment of the middle artery; MT, mechanical thrombectomy; CTA, computed tomography angiography; CEA, carotid endarterectomy; MA, masseter area; MD, masseter density; PMA, psoas muscle area, PMD, psoas muscle density; TPMA, total psoas muscle area; TPMD, total psoas muscle density; LPMA, lean psoas muscle area; TLPMA, total lean psoas muscle area; ΔPMA/BL, relative psoas muscle area change; ΔLPMA/BL, relative lean psoas muscle area change; MAavg, average masseter area; MDavg, average masseter density.

4.2.1 Abdominal aortic aneurysm patients (I, II)

Three hundred and one patients with imaging data were randomly selected from a larger cohort (n = 959) of AAA patients treated at the TAUH vascular clinic between 2001 and 2014. The clinical data were collected from a prospectively constructed vascular registry and the TAUH patient records database that is linked to the National Population Register. The protocol of preoperative assessment included aortic imaging with contrast-enhanced CT for each patient. The main reason for patient exclusion was the unavailability of CT imaging of the abdominal area with a 0.63–3.00 mm slice thickness between 90 days before and 30 days after the operation. The treatment modality (OSR or EVAR) was selected by the vascular surgeons and interventional radiologists in a multidisciplinary meeting, and EVAR was generally preferred for older individuals and those with suitable anatomy (the length, shape and configuration of the aneurysm neck as well as the access route through iliac arteries) among the elective and the haemodynamically stabile ruptured cases.

4.2.2 The follow-up after EVAR (II)

After the AAA surgery, a one-month follow-up CT was performed for patients treated with EVAR, while patients treated with OSR were followed up clinically. Typically, EVAR patients' long-term follow-ups were performed at one year by means of ultrasound and at two years by means of CTA, and, if complications were not observed, annually by means of ultrasound after three years. Of the 301 randomly selected AAA patients, 220 were treated with EVAR. In these patients, the majority of exclusions were due to a missing follow-up CT study (n = 77), comprising patients whose follow-up was conducted in their nearest tertiary centres for practical reasons. Furthermore, 21 patients died during the first 10 months postoperatively before the first follow-up study. The final cohort consisted of 122 patients.

4.2.3 Internal carotid artery stenosis patients (III)

Of the 382 internal carotid stenosis patients treated with carotid endarterectomy, 242 comprised the final study population. Consecutive CEA patients treated from 2004 to 2010 at TAUH and were selected from vascular registry of TAUH. The excluded patients (n = 140) had no preoperative CTA available for the measurement of

masseter area and density, but their demographics, risk factors, indications and degrees of internal carotid stenosis did not differ significantly from those of included patients. The CEA patients with no applicable imaging data were operated on during the early years (2004–2006) when CTA was gradually achieving its role in clinical practice.

4.2.4 Mechanical thrombectomy patients (IV)

In a total of 312 patients presenting with an M1 or an ICA thrombus and treated with mechanical anterior thrombectomy were included in study IV. The position of the clot was determined with CTA and frequently also by means of CT perfusion (CTP) scanning. A multidisciplinary team, consisting of a stroke neurologist and a neurointerventional radiologist, made the selection of patients for MT. Older patients were not excluded due to age alone, but for example patients with a history of moderate or severe dementia and patients in palliative or end-of-life care were treated conservatively.

4.3 Clinical parameters/variables

The baseline variables including age, sex, body surface area (BSA) and cardiovascular risk factors were obtained from the vascular registry and the TAUH patient records database. Risk factor status was based on previous diagnoses (ICD-9 or ICD-10) and current medication: diabetes (diagnosis, insulin or oral antidiabetic medication), arterial hypertension (HTA, diagnosis or antihypertensive medication), coronary artery disease (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischaemia upon electrocardiography, and/or congestive heart failure), peripheral artery disease (PAD, diagnosis of peripheral vascular intervention, or amputation), pulmonary risk factors (diagnosis of chronic obstructive pulmonary disease), neurological risk factors (a previous stroke or TIA), dyslipidemia (diagnosis and/or statin medication), and smoking (current or former smoker within last 5 years). The results of the serum creatinine, haemoglobin (Hb) and c-reactive protein (CRP) blood tests were retrospectively collected from the Fimlab Laboratories Ltd database. Data on the American Society of Anesthesiologists (ASA) class and medication(s) were collected from a structured anaesthesia form completed at the time of the operation.

The primary clinical outcome was postintervention survival. The times of death were checked from the TAUH patient record database, which is linked to the National Population Register. Death certificates issued by a physician are mandatory in Finland, and there are no missing cases in the data on deaths.

4.4 Imaging parameters

CT and CTA imaging was routinely carried out for the patients according to hospital protocol in all studies. Abdominal aortic CT was performed as part of the preoperative clinical routine for all electively treated AAA patients. A one-month or earlier postoperative CT was used as the baseline imaging if the preoperative CT had been performed over 90 days before the operation, if the preoperative CT slice thickness was > 5 mm, or in rare cases of unstable, ruptured aneurysms, where immediate intervention was needed based on ultrasound imaging without concomitant CT imaging. Control CT imaging was habitually performed at one month and two years after EVAR in AAA patients. The parameters in AAA patients' abdominal aortic CT imaging were: 120 kV, 250 mAs, collimation 64 × 0.625 mm (64-row) or 120 kV, Auto MA (150-350 mAs), collimation 16 × 1.25 mm (16-row). The images' axial slices were reconstructed to the thickness of 1–3 mm. The contrast agent (Xenetix 350 mg/ml, Aulnay-sous-Bois, France) was administered through an antecubital 18-G cannula using a double-piston power injector with a flow rate of 3 ml/s, using 100 ml of contrast agent followed by 40 ml of saline. A manual real-time bolus was used when the contrast agent opacified the full diameter of the thoracoabdominal aorta during a deep-inspiration breath-hold.

All carotid endarterectomy patients (study III) and stroke patients treated with MT (study IV) were routinely subjected to brain CT and CTA prior to the intervention. The initial imaging protocol consisted of non-contrast-enhanced computed tomography, CTA and CTP images at the acute phase before mechanical thrombectomy. CT scans were obtained using two different multidetector scanners: the General Electric LightSpeed 16-row scanner (GE Healthcare, Milwaukee, WI, USA) and the Philips Brilliance 64-row scanner (Philips, Cleveland, OH, USA). The scanners were in equal use, and there was no selection of a specific scanner.

4.5 Image analysis

CT and CTA images were reviewed using medical imaging workstations (Carestream Vue PACS viewer version 11.4.0.1253, Rochester, NY, USA). Psoas and masseter area (mm^2) and mean radiodensity (Hounsfield Unit, HU) measurements were performed from images in the contrast-enhanced arterial phase. Psoas muscle measurements in AAA patients were performed at the L3 vertebral level on both sides, and the axial slice for each vertebral level was chosen at the level of origin of the transverse processes (Figure 2). Furthermore, in CEA and AIS patients' masseter measurements were performed after sagittal and coronal adjustment in brain CTA (Figure 3). CTA tilt alignment was selected according to tangents along the lower borders of the zygomatic arches in sagittal planes and along the lowest points of orbitae in coronal planes. Masseter area and radiodensity measurements were taken 20 ± 2 mm below the arches by outlining the outer surface of the masseter muscles along the fasciae. In the brain CT studies, the presence of teeth was evaluated from the CT images and scored in three categories: 1) no teeth, 2) any missing teeth and 3) no evidence of missing teeth.

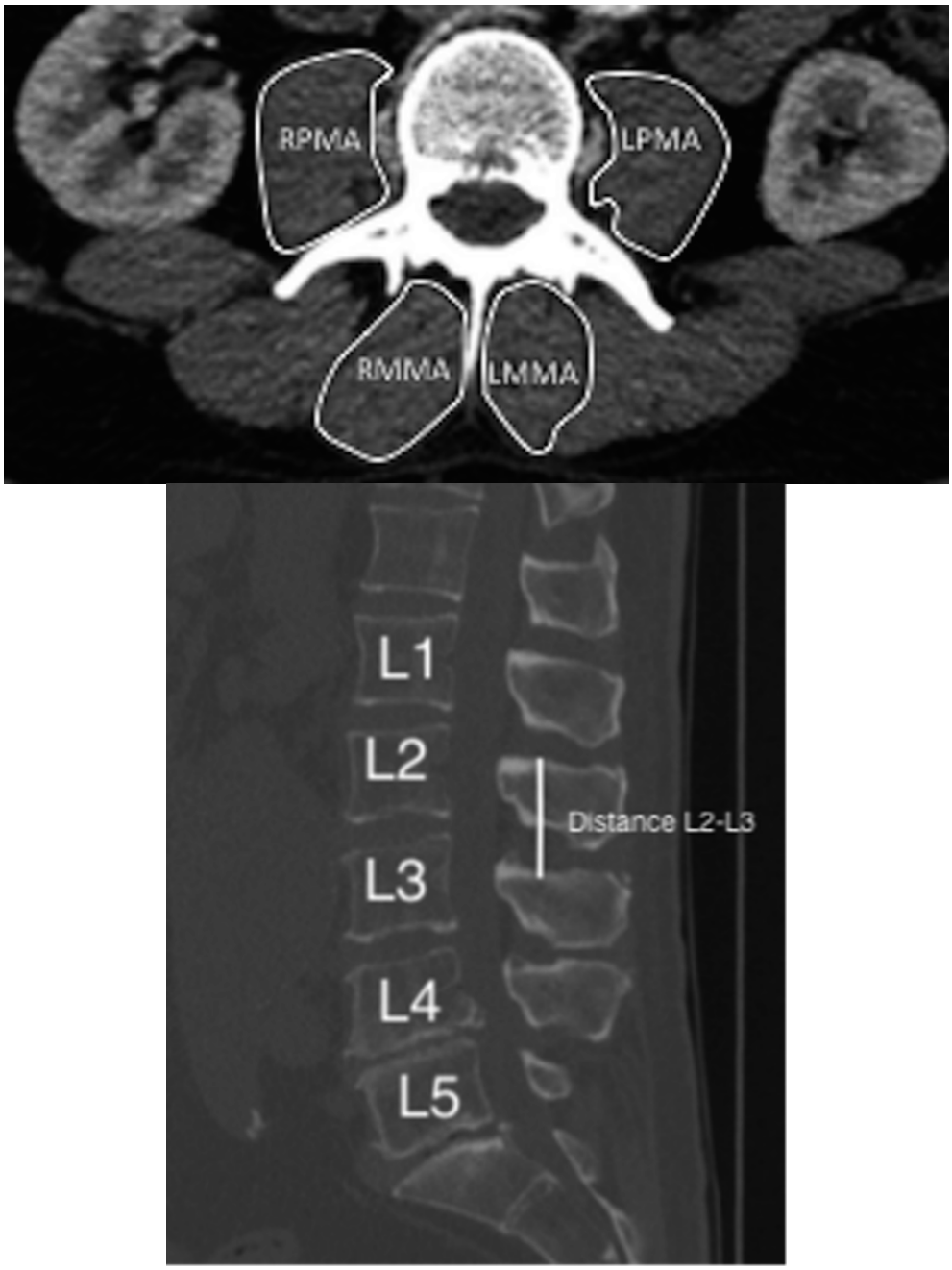
Three clinicians evaluated the reproducibility and prognostic value of the repeated measurements of the same psoas muscle area: a radiologist (10 years of experience), a vascular surgeon (15 years of experience) and a Bachelor of Medicine who had been instructed in investigating CT images. A test sample of 27 patients was first randomly selected, and the sample did not significantly differ from other patients. The clinicians were blinded to patients' outcomes, and the measurements were performed on both sides at the vertebral levels L2, L3, L4 and L5 independently by each clinician. The measurements were taken in the same fashion for MA by three independent clinicians, and the inter-observer reliability was based on intraclass correlation coefficient analysis (ICC) for both MA/MD and PMA/PMD measurements. In order to determine the intra-observer reliability by one independent clinician, 30 brain CTA images were randomly selected, and MA and MD were rated by a clinician in a repeated manner in study IV.

4.6 Sarcopenia evaluation from the CT images

Average muscle areas were determined by calculating the mean of the right and left muscle areas in mm^2. Similarly, muscle densities were calculated as means of the right and left sides in HU. Hounsfield Units are quantitative measurement of radiodensity used universally in CT images. HU scale based on water and air densities: 0 HU represents water and –1000 HU air. In this thesis muscle density thresholds for tissue characterization were set as follows: 20–80 HU for normal muscle, 1–19 HU for lower-density muscle, -1 to -29 HU for fatty muscle, and -30 to -50 HU for fatty connective tissue. Lean muscle area was defined as the product of muscle area and density (cm^2 x HU), which enabled accounting for both muscle area and density in the same variable. If the density was below 0 HU, lean muscle area was scored as zero.

Muscles were carefully outlined with a free-hand selection tool along the muscle fasciae, which subsequently produced a report yielding the cross-sectional area outlined by the regions of interest (ROIs) and the mean density in Hounsfield Units (HUs), along with standard deviation (SD). The image analysis programme automatically calculated the area (in mm^2) and density (in HU) along with SD across the ROI. Furthermore, psoas muscle volume was modelled for calculation as a 3D truncated cone, where the distance between vertebrae was the height of the cone and total muscle area was the base of the cone. The illustration of the psoas muscle measurements from CTA images are presented in Figure 2.

Figure 2. An illustration of muscle measurement at the L3 level and the distance between vertebrae.



RPMA = right psoas muscle area, LPMA = left psoas muscle area, RMMA = right multifidus muscle area, LMMA = left multifidus muscle area. Measurement in study I was performed by estimating gaps between spinal discs on transverse processes. Modified from Lindström et al., AnnVasc Surg 2019;56:183–93.

The MA and MD measurements were obtained from brain CTA scans. The MA measurements varied significantly according to head tilt. Therefore, the final area and radiodensity measurements were produced according to tangents along the lower borders of the zygomatic arches in the sagittal planes and along the lowest points of the orbitae in coronal planes (Figure 3). Masseter muscles were outlined along the outer surface of masseter muscle fascia from the axial planes 20 ± 2 mm below the zygomatic arches (Figure 4).

Figure 3. Demonstrating the imaging tilt adjustments before masseter muscle measurements. Sagittal and coronal tilt measurements.

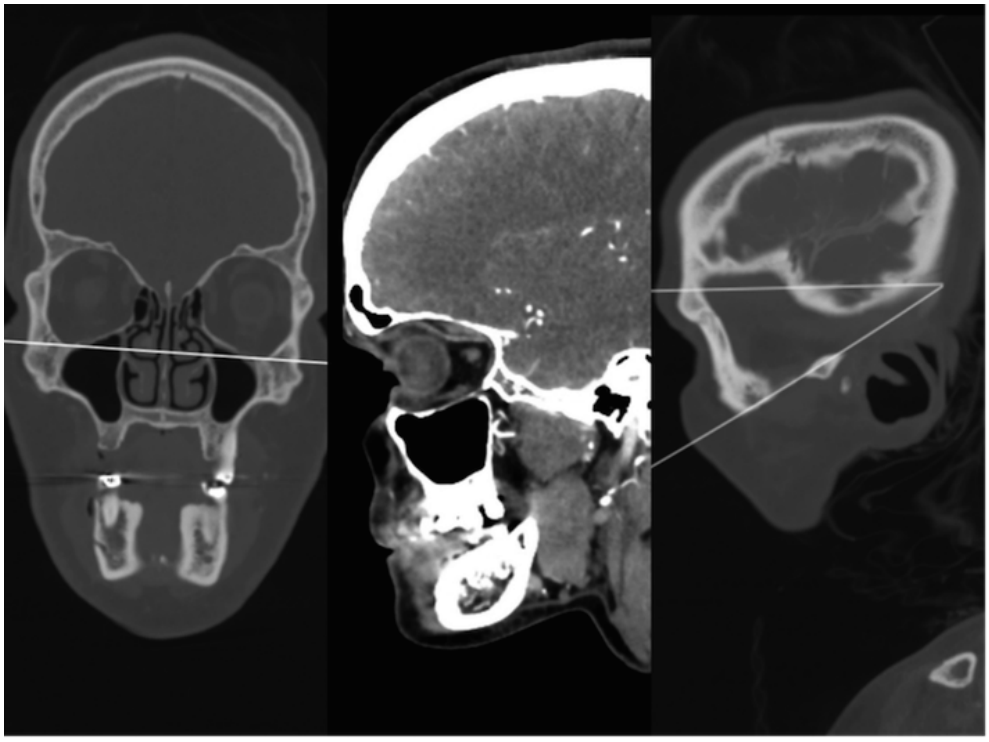
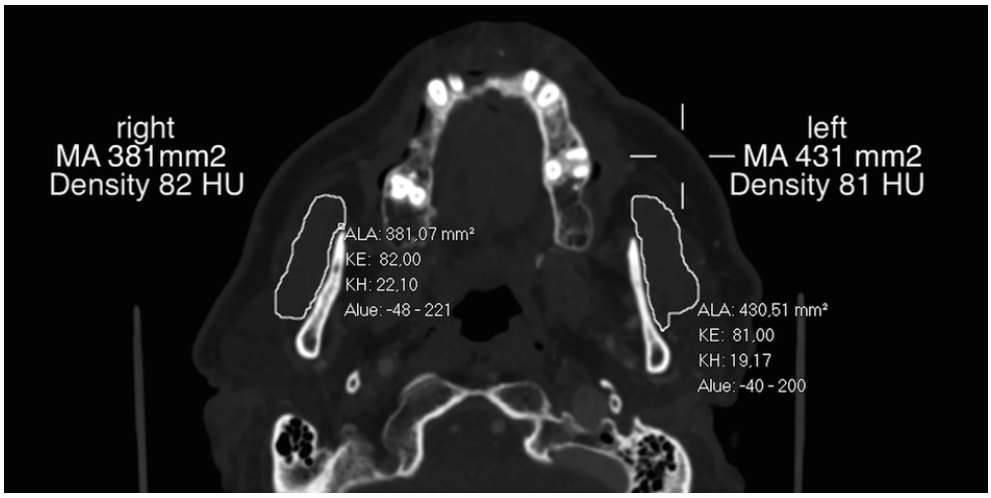


Figure 4. Axial measurements of masseter area by outlining the outer surface of muscle along the fascia.



4.7 Statistical analysis

The statistical software used for the analyses was SPSS 24 for Mac OS X. In all of the studies, data were tested for normality by applying Levene's test, and normal distributions of muscle values were visualized by using histograms. Based on normality, the parametric or non-parametric tests were selected. Student's T-test was selected for comparisons between normally distributed groups. Group comparisons of continuous variables were performed using the Wilcoxon signed-rank test and paired t-test for two dependent samples. The Mann-Whitney U-test was selected for non-Gaussian variables for two independent samples and the Kruskal-Wallis test for three or more independent samples.

The association of the muscle variables with survival after the operation was analysed using a Cox regression model first in the form of univariable analyses, therefore testing the proportional hazard assumption by log-minus-log plots. In multivariable models, independent factors with $p < 0.1$ were included as a univariable model (Table 5). A hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (CI) was calculated for each muscle variable and other covariates. When studying three-month mortality, binary logistic regression analysis was used, and patients were classified as being dead or alive at the three-month time point after the operation. The Pearson correlation coefficient was used to measure the linear association between muscle variables and the other risk factors included in the

multivariable analyses. The muscle variables were normalized with standardized z-scoring in all of the studies. Statistical significance was set at $p < 0.05$.

ICC was applied to muscle measurement reliability between clinicians, i.e. the intra- and inter-observer variability of the measured parameters (areas, densities). The two-way random single measurement model was selected, and both consistency and absolute agreement were calculated, along with a 95% CI (Zou, 2012). The ICC was categorized as poor (< 0.40), fair (0.40–0.59), good (0.60–0.74) or excellent (0.75–1.00) (Cicchetti, 1994). Table 6 summarizes the methods used in the studies.

Table 5. Risk factors included in multivariable Cox regression or binary logistic regression analyses.

The multivariable Cox regression analyses testing the independent associations of risk factors with mortality were as follows:	
Study I	Age, rAAA, smoking, stroke or TIA, serum creatinine level, ASA, anticoagulant medication, and statin medication.
Study II	Model 1: Age Model 2: Age, BSA, stroke or TIA
Study III	Age, sex, renal risk factor, indication, ipsilateral stenosis, teeth
The multivariable binary logistic regression analyses testing the independent associations of risk factors with 3-month mortality were as follows:	
Study IV	Age, diabetes, coronary artery disease, haemoglobin level

Table 6. Statistical methods used in studies I–IV.

Test	Study			
	I	II	III	IV
Levene's test	x	x	x	x
Pearson's chi-squared test	x	x	x	x
Student's t-test	x	x	x	x
Paired t-test		x		
One-Way ANOVA	x	x	x	
Mann-Whitney U-test	x	x	x	x
Wilcoxon signed-rank test	x	x	x	
Kruskal-Wallis test	x		x	x
Univariable Cox regression analysis	x	x	x	x
Multivariable Cox regression analysis	x	x	x	x
Binary logistic regression				x
Kaplan-Meier long-rank analysis		x	x	x
Pearson correlation coefficient	x	x	x	x
Intraclass correlation coefficient analysis (ICC)	x		x	x
Standardized z-scoring (muscle variables)	x	x	x	x

4.8 Ethical considerations

All studies were approved by the ethical committee of Pirkanmaa Hospital District Science Centre. The ethical principles of the Declaration of Helsinki were strictly conducted. In the retrospective studies, informed patient consent was not required or obtained. The patient data were collected from the pre-existing patient database, and no extra imaging control was arranged. Thus, patients were not exposed to radiation for this thesis and no harm was done.

5 RESULTS

The demographic data of the entire population is shown in Table 7.

Table 7. Characteristics of study patients in studies I–IV.

Patient characteristics	Study I n = 301	Study II n = 122	Study III n = 242	Study IV n = 312
Age, median years	74.4	77.9	71.0	69.2
Sex, male (%)	268 (89)	110 (90)	170 (70)	197 (63)
Height, median metres	1.76	1.74	1.72	N/A
BMI, median kg/m^2	26.6	26.1	26.8	N/A
BSA, median m^2	2.0	2.0	1.9	N/A
Risk factors				
Previous intervention, N (%)	20 (6.6)	7 (5.7)	N/A	N/A
Smoking, N (%)	71 (23.6)	26 (21.3)	68 (28.1)	N/A
Coronary artery disease, N (%)	158 (50.8)	73 (59.8)	128 (52.9)	43 (13.8)
Diabetes mellitus, N (%)	41 (13.6)	15 (12.3)	71 (29.3)	45 (14.4)
Hypertension, N (%)	192 (63.8)	76 (62.3)	186 (76.9)	132 (42.3)
Dyslipidemia, N (%)	132 (43.9)	56 (45.9)	135 (55.8)	N/A
Pulmonary disease, N (%)	68 (22.6)	29 (23.8)	25 (10.3)	N/A
Stroke or TIA, N (%)	34 (11.3)	10 (8.2)	210 (86.8)	312 (100)
Serum creatinine level, µmol/L	86	99	N/A	77
rAAA, N (%)	23 (7.6)	3 (2.5)	-	-
OSR, N (%)	81 (26.9)	0	-	-
EVAR, N (%)	220 (73.1)	122 (100)	-	-
Medication				
Antiaggregant, N (%)	148 (49.2)	63 (51.6)	N/A	N/A
Anticoagulant, N (%)	72 (23.9)	28 (23.0)	N/A	N/A
Oral antidiabetic, N (%)	26 (8.6)	14 (11.5)	N/A	N/A
Insulin, N (%)	19 (6.3)	5 (4.1)	N/A	N/A
Beta blocker, N (%)	179 (59.5)	72 (59.0)	N/A	N/A
Other antihypertensives, N (%)	184 (61.1)	78 (63.9)	N/A	N/A
Statin, N (%)	168 (55.8)	78 (63.8)	N/A	N/A

BMI, body mass index; BSA, body surface area; rAAA, ruptured abdominal aortic aneurysm; OSR, open surgical repair; EVAR, endovascular aneurysm repair; N/A, non-applicable.

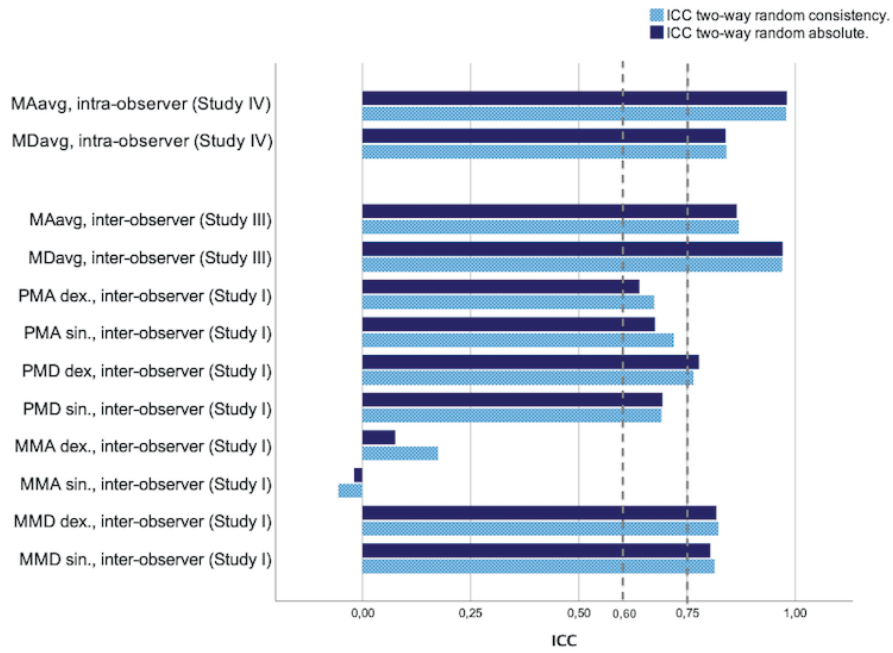
5.1 Reproducibility of the CT measurements (I, III, IV)

In order to test the reliability of the radiological muscle measurements, the inter-observer and intra-observer variability of the psoas and masseter parameters (areas and densities) were studied with the ICC analysis. The inter-observer variability of muscle parameters obtained by three independent clinicians was investigated in studies I and III. In study IV, the intra-observer variability of the repeated measurements performed by one clinician were determined. In the mentioned studies (I, III and IV), the variability was tested using 27–30 CT scans that were randomly selected from the study population.

In the AAA patients, the PMA and PMD measurements demonstrated good and excellent reproducibility. The ICC two-way random single measurement consistency agreement was 0.674–0.720 and the absolute agreement 0.640–0.676 for PMA at L3. For PMD, the consistency was 0.691–0.765 and the absolutely agreement 0.693–0.778. At the same level, multifidus area measurements did not achieve significant results, but PMA and PMD correlated with multifidus area and density at the same level, based on Pearson R ($R = 0.469$, $p < 0.05$, $R = 0.654$, $p < 0.01$).

Excellent results were found when comparing MA and MD measurements from CEA patients, as performed by three independent observers. The assessment of repeated measurements produced an ICC of 0.865–0.971, $p < 0.001$, for all parameters, indicating that the measurements were reliable. With regard to intra-observer reliability in study IV, MAavg and MDavg showed excellent correlations: ICC .839–.981, $p< 0.001$ (Figure 5).

Figure 5. Distributions of Intraclass correlation coefficient variability in muscle measurements in studies I, II and IV.



The Intraclass correlation coefficient (ICC) 0.60-0.74 was categorized as good and 0.75-1.00 as excellent.

5.2 Psoas muscle area in AAA patients (I)

Among the 301 patients treated for an AAA, 220 (73.1%) were treated with EVAR and twenty-three had a ruptured aneurysm. The median follow-up time was 2.70 years (IQR 3.54, range 0–8.9). Out of the 301 included AAA patients, 31.2% (n = 94) died, and none were lost during follow-up. According to the univariable Cox regression models, age, smoking (current or former smoker within last 5 years), a ruptured AAA, a previous stroke or TIA, serum creatinine level, ASA classification, as well as anticoagulant and statin medication predicted mortality and were incorporated in the multivariable analysis. Further adjustment was made for BMI and sex, which are known to be associated with PMA, but they did not affect the results.

The L3 left-sided PMD and total psoas muscle density (TPMD), the L3 right and left lean psoas muscle areas (LPMA) and the L3 total lean psoas muscle area (TLPMA), as well as the L2 right LPMA and TLPMA (HR 0.74–0.78, $p < 0.05$ to $p < 0.01$ per one SD), were independently associated with improved survival in the multivariable analysis. The most significant impact was found for the TLPMA parameter at the L3 level, for which every standard deviation increase was associated with a 26% decrease in the probability of death during follow-up. To explore the potential clinical value and generalizability of the results when the standard deviation of the local patients is measured and known, the muscle parameters were standardized by z-scoring. In the study population, one SD in total lean psoas area (TLPMA) was 269.4 cm^2HU.

In the analysis without ruptured AAA patients, the association of the most consistent muscle parameter, L3 TLPMA, with mortality was even stronger: the decrease in the probability of death was as high as 29% for every SD increase in L3 TLPMA. Further adjustment for the operative approach (EVAR vs OSR) or urgency (emergency vs elective) did not have any effect on the results.

5.3 Psoas muscle change after EVAR (II)

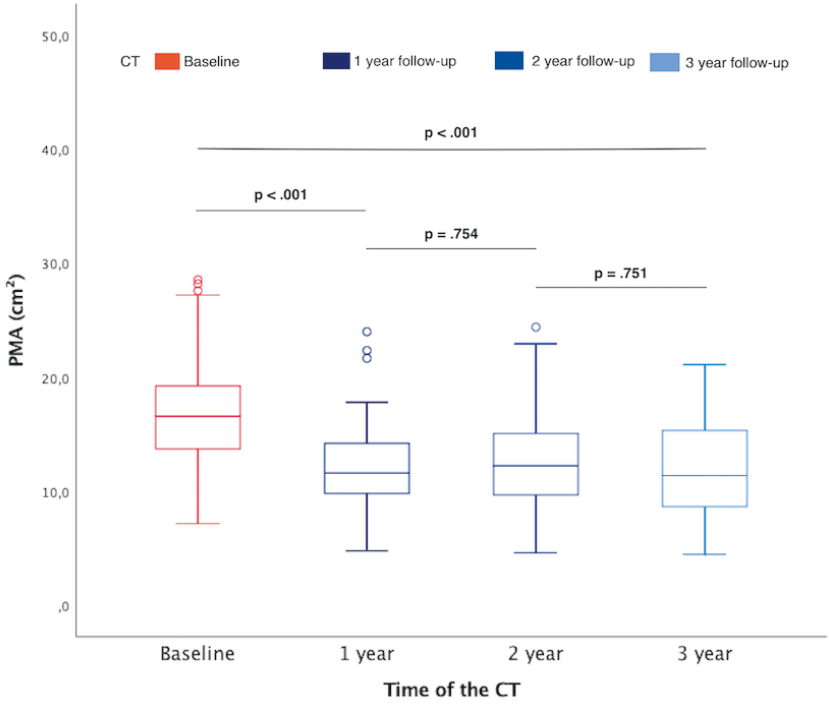
In study II, 122 EVAR-treated patients from study I were included. Cross-sectional analysis of the study II population was used to evaluated muscle parameter changes during follow-up (median 6.0 years, IQR 3.6). PMA, as well as LPMA, decreased significantly between the baseline CT and the first follow-up CT studies (PMA -4.4 cm^2 and LPMA -130.4 cm^2HU, $p < 0.001$ for both). When translated into percentual changes, these corresponded to a 26.8% decrease in ΔPMA and a 21.6% decrease in ΔLPMA. Age and sex were significantly associated with PMA and LPMA at the baseline, but similar significant associations were not found with absolute changes in muscle parameters (ΔPMA and ΔLPMA). Nevertheless, ΔPMA and ΔLPMA were associated with PMA and LMPA at the baseline, indicating that the absolute change is considerably associated with baseline muscle status and that the relative change may be considered to better represent the individual muscle loss process.

The PMA and LPMA values decreased clearly and statistically significantly during the first year after EVAR. However, in subsequent follow-up at two and three years, the median PMA and LPMA no longer decreased similarly to the decline between the baseline and the one-year CT studies (Figure 6). Furthermore, the relative muscle changes (ΔPMA/BL and ΔLPMA/BL) were not statistically significant between the

one-year and the two- or three-year follow-up studies. The relative change in PMA or LPMA in reference to the baseline did not seem to be markedly different between men and women.

For 37 patients who had CT studies available at several different time-points, an actual longitudinal analysis was performed. Overall, the greatest decreases in PMA (mean ΔPMA -4.1 cm^2, $p < 0.001$) and in LPMA (mean ΔLPMA -118.7, $p = 0.001$) arose during the first postoperative year.

Figure 6. Psoas muscle area at the baseline and at the 1-, 2- and 3-year follow-up imaging.



Modified from Lindström at al., J Vasc Surg 2020;71:1169-1178.

5.4 Association of psoas muscle changes with long-term mortality in EVAR patients (II)

In study II, EVAR patients' median duration of follow-up was 6.0 years (IQR 3.5, range 0.9–12.0 years), and their all-cause mortality was 46.7%. The association between long-term survival and follow-up PMA and LPMA, as well as the relative changes in PMA and LPMA, were analysed separately. In univariable analyses, both

follow-up PMA and LPMA were associated with mortality, but in multivariable analysis with other factors significant in univariable analyses (age, BSA and previous stroke or TIA; HR 0.77, 95% CI 0.56–1.05, p = 0.095), there was no longer any statistical significance. However, when the ΔPMA/BL and ΔLPMA/BL were added to the same model with the same risk predictors, the only factor independently associated with mortality was ΔPMA/BL (HR of 0.977 for one percent unit increase in ΔPMA/BL, 95% CI 0.960–0.995, p = 0.011) (Table 8). Effectively, this means that, with each 10% unit decrease in PMA between baseline and the first follow-up CT, the risk of death increases by one fifth. Even though sex, coronary artery disease (CAD), diabetes (DM), dyslipidemia, HTA and smoking were not statistically significantly associated with mortality in the univariable analysis, they were adjusted for in the multivariable analysis with age, BSA and ΔPMA/BL, since they are known to influence muscle size. However, the ΔPMA/BL results (HR 0.94, 95% CI 0.16-0.55) remained significant. The Kaplan-Meier curve demonstrated the long-term survival of the ΔPMA/BL tertiles, p < 0.010 (log-rank) (Figure 7).

Table 8. Comparison of relative muscle change and follow-up muscle parameters in the same Cox survival regression analysis.

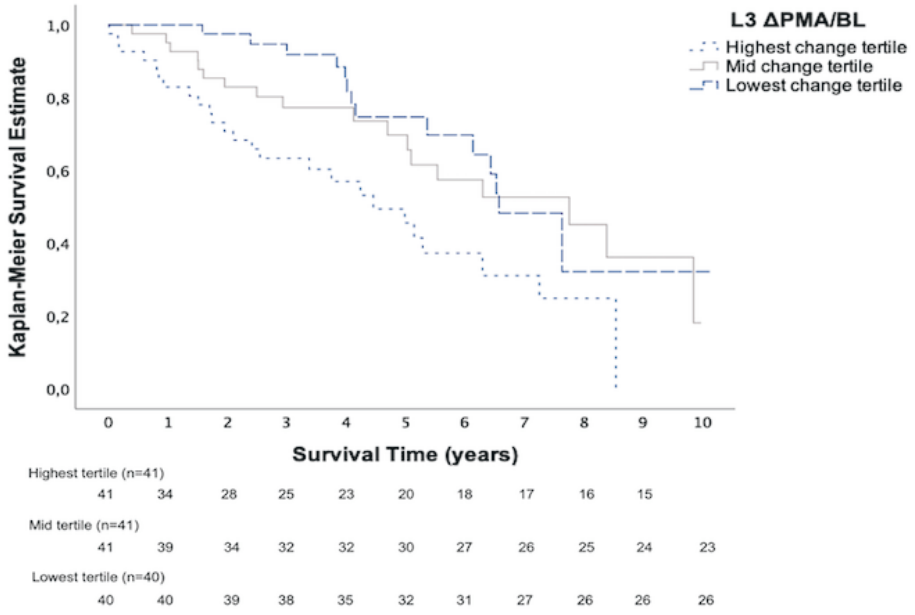
	Follow-up CT						Relative change					
Variables	L3 PMA			L3 LPMA			L3 ΔPMA/BL			L3 ΔLPMA/BL		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Unadjusted	0.609	0.45–0.83	.001	0.633	0.48–0.84	.001	0.975	0.96–0.99	.002	0.996	0.99–1.01	.628
Model 1	0.748	0.54–1.03	.078	0.735	0.54–1.00	.046	0.977	0.96–0.99	.009	0.996	0.99–1.00	.325
Model 2	0.784	0.55–1.12	.180	0.767	0.56–1.05	.095	0.977	0.96–0.99	.011	0.996	0.99–1.00	.348

Model 1: adjustments were made for age.

Model 2: adjusted for all factors associated with mortality in univariable analyses (p < 0.1): age, body surface area, stroke or transient ischaemic attack and muscle parameter.

PMA, psoas muscle area; LPMA, lean psoas muscle area; ΔPMA/BL, relative psoas muscle area change; ΔLPMA/BL, relative lean psoas muscle area change; HR, hazard ratio; CI, confidence interval. Modified from Lindström at al., J Vasc Surg 2020;71:1169-1178.

Figure 7. Overall survival of ΔPMA/BL tertiles in EVAR patients, Kaplan-Meier survival analysis, p < 0.01, n = 122.



ΔPMA/BL, relative psoas muscle area change.

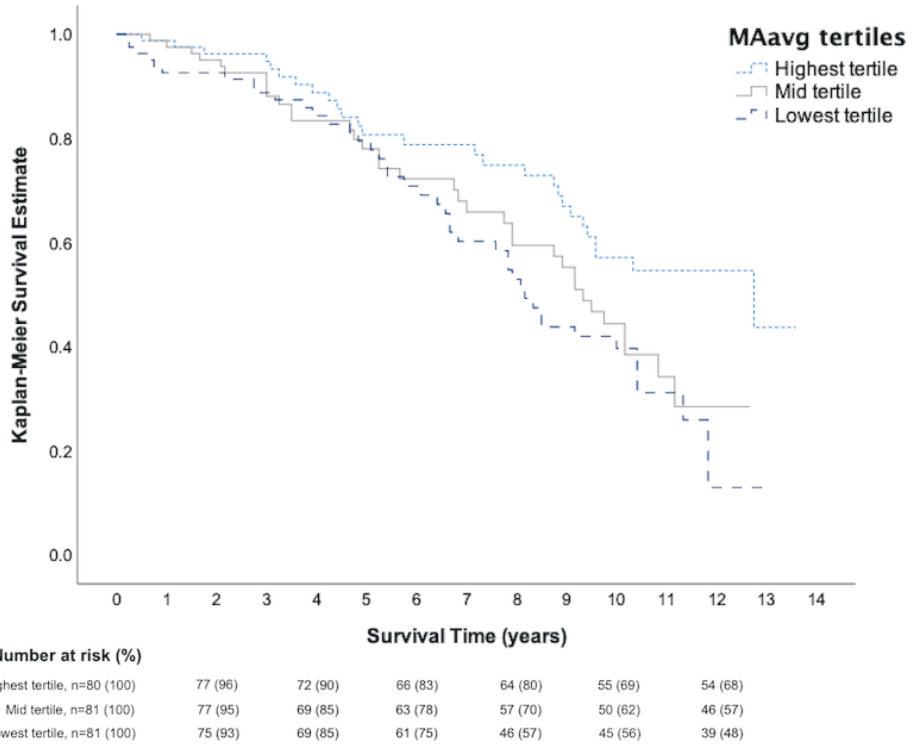
5.5 Masseter muscle in carotid endarterectomy patients (III)

In study III on CEA patients, the median follow-up time was 68.5 months (range 3–163 months). During this follow-up, 104 patients (43.0%) died. No patients were lost during follow-up.

Among all patients, the median average MA (MAavg) was 395.0 mm^2 (IQR 110.1) and density 53.5 HU (IQR 16.5). The oldest tertile had a statistically significantly smaller MAavg compared to the youngest tertile (362 vs 423 mm^2, $p < 0.001$), and women had a smaller MAavg than men (349 vs 420 mm^2, $p < 0.001$). Furthermore, MAavg correlated with BSA and teeth category ($p < 0.001$ for both). Similarly, the average MD (MDavg) was associated with sex (49 vs 55 HU, $p < 0.001$), dental status (48 vs 59 HU, $p < 0.001$) and age (49 vs 59 HU, $p < 0.001$). In contrast, BSA did not correlate with MDavg.

In the univariable Cox regression analysis, MAavg was significantly associated with mortality with every SD increase (HR 0.72, with 95% CI 0.59–0.88, p = 0.001), whereas no association was found for MDavg with mortality (HR 0.92, 95% CI 0.76–1.12, p = 0.423). Variable selection for multivariable analyses were made by checking the predictive value of all potential risk factors for mortality in univariable analyses, and those nominally connected (p < 0.1; age, BMI, BSA, renal risk factors, ipsilateral stenosis, indication category and dental status) were selected. After adjustment in multivariable analyses, increased MAavg was independently associated with lower mortality (HR 0.76, 95% CI 0.61–0.96, p = 0.023). The risk of death was inversely linear with MAavg and the risk growth exponential at the lowest end of the MAavg values. The cumulative survival of carotid endarterectomy patients after surgery was 79% at six years and 35% at 12 years (Figure 8).

Figure 8. The cumulative survival of carotid endarterectomy patients in mean masseter area tertiles.



MAavg, average masseter muscle area.

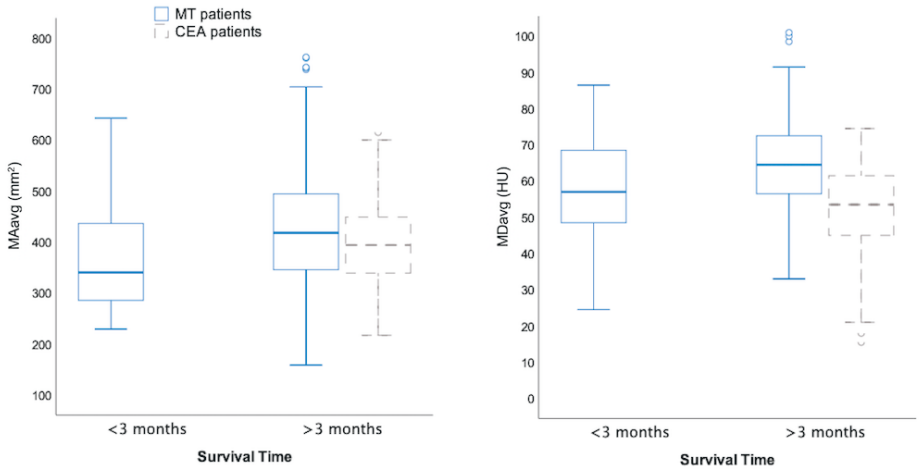
5.6 Masseter muscle in mechanical thrombectomy patients (IV)

In this cohort, a total of 312 patients were treated with MT for acute occlusions of the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (M1-MCA). The main occlusion was an M1 segment in 198 (63.5%) patients and an ICA segment in 74 (23.7%), while 40 (12.8%) patients had both an M1 and an ICA occlusion in their preoperative CTA images. The median follow-up time was 27.4 months (range 0–70.4 months). Most of the deaths occurred during the first three months after the intervention (n = 38 [12.2%], which was 62.3% of all deaths). The cause of deaths were not observed in this study. Patients who died within the first three months postoperatively had a smaller MAavg (433 vs 368 mm^2, p = 0.001) and MDavg (64.6 vs 57.3 HU, p = 0.001) than those alive three months after the intervention (Figure 9). Compared to CEA patients in study III, patients who survived for three months after MT had a greater MAavg and MDavg (Figure 9). As in study III, advanced age, female sex and poor dental status were linked to MA and MD decreases (Figure 10). The long-term mortality was 19.6% (n = 61) at the end of follow-up.

In the binary logistic regression analyses, MDavg and MAavg (OR 0.61, 95% CI 0.41–0.92, p = 0.018, and OR 0.57, 95% CI 0.35–0.91, p = 0.019; per 1-SD increase, respectively) as well as the Hb level (OR 0.98, 95% CI 0.96–1.00, p = 0.018–0.020) were independently associated with lower mortality at three months. In study IV, a 1-SD increase in MDavg and MAavg was associated with a 39%–43% decrease in the probability of death during the first three months after MT. Furthermore, including *a priori* risk factors (age, teeth, sex) emphasized the role of MDavg and MAavg as predictors of lower mortality in multivariable analyses, and the results were almost similar to those of the main analyses (MDavg OR 0.58, 95% CI 0.39–0.86, p = 0.007; MAavg OR 0.52, 95% CI 0.32–0.85, p = 0.009).

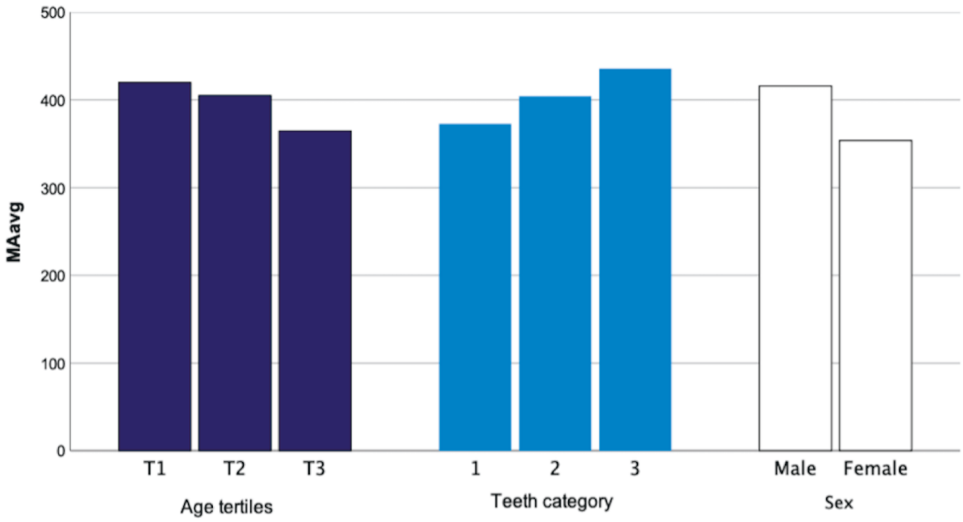
Overall, both MAavg and MDavg had an inverse relationship with mortality in Kaplan-Meier curves (from p < 0.001 to p = 0.002, log-rank) (Figure 11). The lowest end of the MDavg range demonstrated an increasing risk of death when the risk of death was presented across the full range of the standardized MDavg (Figure 12).

Figure 9. Comparison of mean masseter area and density between study III and IV patients.



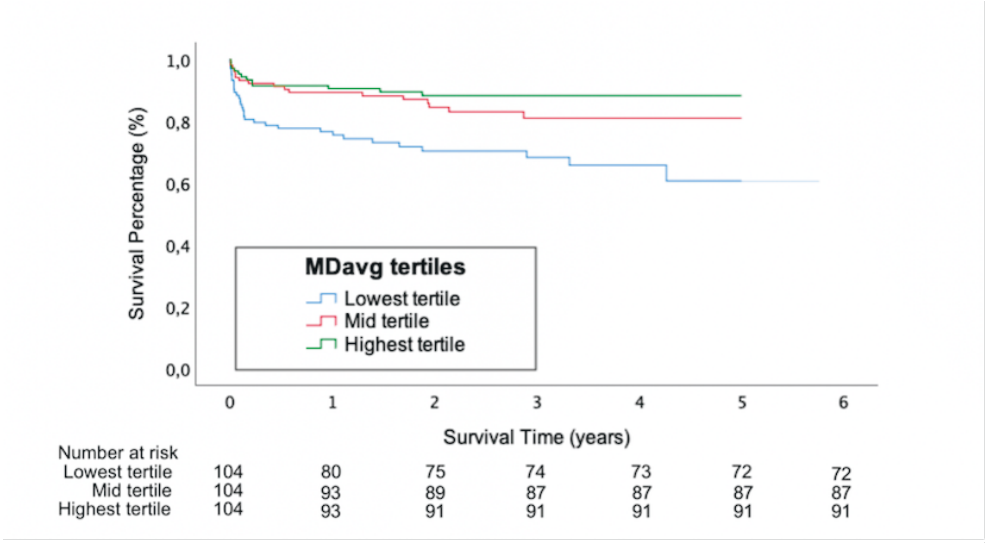
MT, mechanical thrombectomy; CEA, carotid endarterectomy.

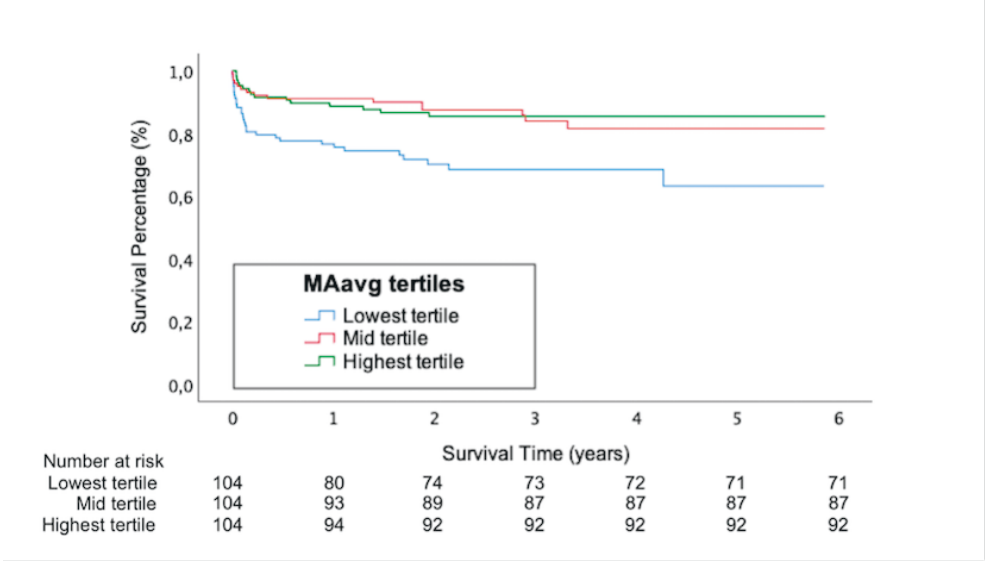
Figure 10. Mean masseter area distribution among acute ischemic stroke patients.



Tertiles: T1 = the youngest, T2 = middle and T3 = the oldest age tertile. Teeth category: 1 = no teeth, 2 = any missing teeth, 3 = no evidence of missing teeth.

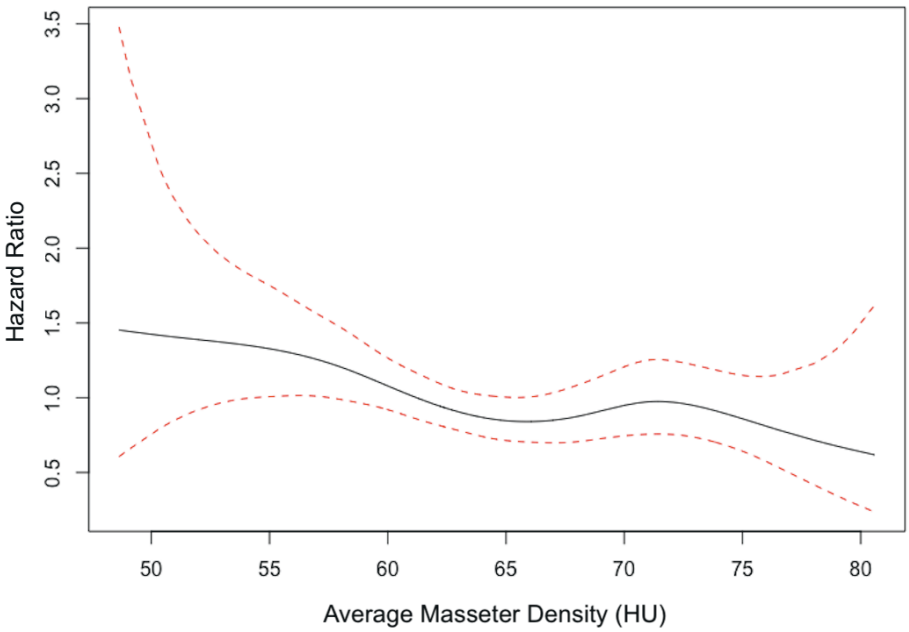
Figure 11. Kaplan-Meier survival curves of comparing mean masseter area and density in tertiles.





Acute ischemic stroke patients in the lowest tertile had significantly poorer survival ($p > 0.001$ for both MAavg and MDavg) according the log rank test. Modified from Lindström et al., J Neurointerv Surg 2021;13:25-29.

Figure 12. The risk of death across the full range of standardized masseter density in acute ischemic stroke patients.



The risk of death (hazard ratio) across the full range of average masseter density (HU). The model was standardized by age, diabetes mellitus, atrial fibrillation, local intracranial haemorrhage, dental status, Hb and serum creatinine level at the time of admission. Modified from Lindström et al., J Neurointerv Surg 2021;13:25-29.

5.7 Summary of the main results

A summary of the main results in studies I–IV is presented in Table 9.

Table 9. Summary of the main results.

Study	Surgery/intervention	Muscle variable	HR/OR (95%CI)	p
I	AAA treatment: OSR and EVAR	L3 TLPMA	0.74 (0.58–0.93)	< .05
II	AAA treatment: EVAR	L3 ΔPMA/BL	0.97 (0.96–0.99)	.011
III	Carotid endarterectomy	MAavg	0.76 (0.61–0.96)	.023
IV	Mechanical thrombectomy	MAavg	0.57 (0.35–0.91)	.019
		MDavg	0.61 (0.41–0.92)	.018

TLPMA, total lean psoas muscle area; ΔPMA/BL, relative psoas muscle area change; MAavg, average masseter area; MDavg, average masseter density; HR, hazard ratio; OR: odds ratio; CI confidence interval.

6 DISCUSSION

The studies included in this thesis focused on the relationship of CT-measured sarcopenia with postoperative survival in vascular patients suffering from an AAA or cerebrovascular disease. The size and density of the psoas and masseter muscles were reliably determined from routine CT scans, and they predict mortality after a high-risk vascular operation. Muscle area is known to predict postoperative survival after the operation, and the present thesis adds knowledge on the prognostic values of muscle quality i.e. density, besides muscle area, which is feasible in clinical work. Furthermore, the sarcopenia depicted by muscle status is a dynamic process, and changes in muscle status were addressed as markers of advancing frailty and decreased survival.

6.1 The association of the psoas muscle area and density with mortality in AAA patients (I, II)

In study I, psoas muscle area and radiodensity at L3 vertebral level were reliable, feasible and independent predictors of postoperative mortality in patients treated for an AAA. This thesis demonstrated that the association between sarcopenia and the other risk factors of mortality can be reliably estimated by measuring the psoas muscle area and radiodensity from CT scans; evidence on which has not been reliably available as regards vascular patients previously. PMA and PMD reached fair to excellent reproducibility at the L2 and L3 vertebral levels, which is in line with previous muscle reproducibility studies (Z. J. Hu et al., 2011; Zou, 2012) suggesting that these parameters are feasible for clinical use in vascular surgery patients. The reproducibility of multifidus muscle measurements was tested by means of ICC at the same vertebral level, but the results were weaker when compared to the measurements of the psoas muscles, which have a more perceptible fascia, making it easier to detect the psoas muscle outlines. Although the multifidus muscle measurements between clinicians did not achieve sufficient reproducibility, PMA and PMD correlated with multifidus muscle area and density at the L2–L3 vertebrae level.

Previously, other studies have found an association between psoas area and patient survival. Muscle quality, reflected by radiodensity, in turn, has not been investigated in vascular patients. In terms of muscle quality, the muscle lean values, which were defined as the product of muscle area and average density were analysed in study I. Estimating sarcopenia using only muscle area may be skewed due to the unheeded muscle density, i.e. fatty connective tissue volume in the muscle. Furthermore, evaluating both muscle area and density did not increase the clinicians' work, since both of these variables can be reported at the same time when outlining the muscle by the ROI.

The bilateral psoas muscle lean area at the L3 level was the strongest predictor of mortality, as a one-standard-deviation increase was associated with a 26% decrease in the probability of death during follow-up. When comparing the left and right muscle lean values separately, the left sides had greater areas and densities. This could possibly be due to the more common left-side dominance, as demonstrated in a cohort of healthy males (Stewart et al., 2010), or to the normal location of the aorta on the left side, with the strongest muscles providing a supportive structure around the aorta and the aneurysm, but the mechanism of how an AAA affects the surrounding musculature has not been explicated.

In surgery patients, Canvasser et al. (2014) (Canvasser et al., 2014) reported that the larger paraspinal muscle area at the twelfth thoracic vertebra (Th12) level, measured from preoperative abdominal CT scans, is associated with lower postoperative 1-year mortality. Their study included a large cohort of surgical patients, not only vascular patients, and they found paraspinal area measurement to be more easily attainable compared to the psoas muscles. Similarly, in study I, was found that the paraspinal and psoas muscle area at L4 level correlated with survival, but the psoas muscles measurements were more reliable than those of the paraspinal muscles, such as the multifidus muscles. Canvasser et al. used semiautomated measurement algorithms in muscle measurements, which is not available in clinical work, nor was the measurement reliability tested. Another possible explanation for the paraspinal muscle results of Canvasser et al. compared to the current AAA patients may lie in the more homogeneous patient sample in the studies presented herein, including only AAA patients, and in the longer follow-up.

Drudi et al. (2016) aimed to replicate the findings of Canvasser et al. on sarcopenia, but contrary to Canvasser et al., they used more homogenous data and included elective and open-surgery-treated abdominal aortic aneurysm patients. Drudi et al. stated that the psoas muscle area had not been examined before in abdominal aortic aneurysm patients and found a small psoas muscle area to be

independently associated with mortality during the follow-up of a median of 1.87 years. In a more recent papers, Newton et al. (2018) (D. Newton et al., 2018) found a small total psoas muscle area to be related with poorer survival in patients undergoing elective EVAR, and the 5-year survival was considerably longer compared to previous studies, suggesting that psoas muscle area also has a long-term association with postoperative survival. The result on the effect of PMA in study I is in line with Newton et al. (2018). Moreover, in elective EVAR patients, sarcopenia was defined as a < 500 mm^2 preoperative psoas muscle area and sarcopenic patients had impaired 3-year survival and longer hospitalisation, but sarcopenia did not correlate with an acute postoperative surgical complication according to Thurston et al. (Thurston et al., 2018). Contrary to the others, Indrakusuma et al. did not find independent statistical significance between AAA patients' survival and PMA at the L3 level, potentially due to the fact that 54% of the asymptomatic infrarenal AAA patients were operated (Indrakusuma et al., 2018). However, this study did not reported the analysis of overall survival.

6.2 Risk factors associated with investigated muscles parameters

Age and sex are known to be associated with mortality. Both are correlated with muscle area and density, and the present thesis adds to the knowledge of and clinical view on how frailty and muscle loss affect survival. In all the studies included in the present thesis, age had a significant inverse association with muscle areas and densities. The results verify the fact that PMA, PMD and LPMA could meet the definition of frailty and further supports their use as methods of frailty assessment (Chikwe & Adams, 2010; Drudi et al., 2016; Kalyani et al., 2014; Keevil & Romero-Ortuno, 2015). PMA, PMD and lean muscle values also had a tendency to be lower in women than in men, which is clearly also supported in previous studies (Janssen et al., 2000; Luckenbaugh et al., 2016; Marras et al., 2001). Furthermore, all muscle area parameters were found to be associated with BMI or BSA, which is supported by preceding evidence (Drudi et al., 2016), but, in some cases, muscle density was not associated with body size.

6.3 Muscle area and density changes during follow-up in EVAR patients (II)

Perioperatively (preferred CT imaging 0 to 90 days before EVAR) measured psoas muscle parameters were significantly associated with patient survival (D. Newton et al., 2018; Thurston et al., 2018), but there is no mention in the literature as to how objectively measured muscle density and area change after surgery in long-term follow-up, affecting the patient's risk of death. The up to one-third re-intervention rate of EVAR patients (Paravastu et al., 2014; R. Patel et al., 2016) indicates that long-term survival should be critically evaluated when considering whether the process of sarcopenia could not be slowed down by any interventions, especially for patients whose life expectancy is reduced and complex re-intervention is needed. Evaluating the progress of sarcopenia from CT scans could help clinicians to estimate the patient's physical fitness and rehabilitation capacity after the operation. Developed sarcopenia after EVAR may be a stronger risk factor for mortality than the muscle status at the time of the re-intervention.

After considering the baseline muscle status in study I, study II focussed on describing how PMA and LPMA advance after EVAR and how the muscle change predicts survival. The absolute muscle change in both PMA and LPMA was the strongest associated with baseline values, indicating that the larger and denser muscle can change in size more than the smaller and looser one in absolute terms, but the relative change was not dependent on baseline values. When looking at the absolute changes from baseline PMA or LPMA in the present analysis, there was no significant association with mortality. Therefore, the results support the hypothesis that the relative muscle change i.e. muscle absolute change as a percentage from the perioperative CT study most likely to measure the development of sarcopenia. The fact that the relative PMA change is a stronger predictor than follow-up PMA indicates that the already developed muscle loss is a more potent predictor of mortality than the muscle status at the follow-up.

However, PMA and LPMA decreased greatly during the first postoperative year, suggesting the fact that possible interventions to counteract the sarcopenia should be carried out even before the scheduled operation by means of, for example, nutritional interventions or physical activity (Beaudart et al., 2017). Currently, the role of the progress of sarcopenia in vascular patients is not understood, but it has been suspected in cachectic cancer patients that sarcopenia could be slowed down or even reversed (Fearon et al., 2011; Prado et al., 2013). Whether or not this would be possible in a sarcopenic vascular surgical patient cohort undergoing treatment for

an AAA remains to be investigated. If the progress of consequences of sarcopenia cannot be slowed down by any interventions, the long-term mortality and high number reoperations should be assessed critically before a primary and reoperation, if the estimated end of life is near. However, although decreased PMA is one of the relative risk factors indicating poor survival, it alone is hardly sufficient to facilitate an acceptable assessment of repeated interventions. Alongside the patient's overall state of health and previous known risk factors, relative PMA change can be considered as an independent indicator after the operation in relation to other risk factors affecting overall health. That being said, a subgroup of patients known to have inferior survival after EVAR could be identified efficiently. More research with larger samples is required to investigate the specific threshold for PMA reduction needed to affect impaired survival over other risk factors.

6.4 Masseter muscle

6.4.1 Long-term survival in CEA patients (III)

The presented results of study III showed a similar association between sarcopenia and long-term mortality to the one previously demonstrated in AAA patients, but in the current study III, preoperatively measured masseter muscle area was associated with long-term mortality in elective carotid endarterectomy patients, whereas MD was not associated with mortality. In line with the psoas measurements in AAA patients, masseter muscle and density were also easily and reliably measured from routine preoperative CTA images after sagittal and coronal adjustment below the zygomatic arch.

The identification of sarcopenia in patients with only brain CTs available, the use of MA has been demonstrated in the identification of sarcopenia (Wallace et al., 2017). The sarcopenia defined by means of MA has been previously presented by Hu et al. in elderly blunt trauma patients (P. Hu et al., 2018) as well as Wallace et al. after severe brain trauma (Wallace et al., 2017). The mean MAavg in the current studies III and IV differs from the MAavg values obtained in these previous trauma studies. However, in the study by Hu et al., the study population was younger (65.4 years vs 69.2–71.0 years) and the proportion of men was higher (73.1% vs 63.1%–70.2%), and, consequently, the mean MA was larger. Hu et al. defined sarcopenia as a 1-SD decrease from the sex-based mean, and they reported a significantly increased

risk for 30-day mortality among sarcopenia patients compared to non-sarcopenic patients (80.0% vs 50.6%). In the study by Wallace et al., the study population was older (80.0 vs 69.2–71.0 years) and the MA was comparable with the current CEA patients, but the MA was smaller than in the younger AIS patients. Wallace et al. found MA to increase the 2-year mortality after blunt trauma (HR 0.79, 95% CI 0.60–-0,96). The findings in previous studies are not directly comparable to the present thesis due to the different age and sex distributions, which, according to the present results, can affect MAavg.

Furthermore, dental status has been proposed to have a stronger correlation with the masseter muscle parameter than ageing or skeletal muscle index in the elderly (Yamaguchi et al., 2018), but the previous trauma studies did not take into account the potential effect of dental status on MA (J. P. Newton et al., 1993) or of the jawing ability on overall functional status (Kimura et al., 2013). The European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2019) has recommended the evaluation of not only muscle area but also muscle density when assessing adverse outcomes in high-risk patients. MD was not evaluated in the previous trauma studies, but according to the present results, MD correlated with age, sex and the presence of teeth.

In study III, MAavg was strongly associated with BSA and the presence of teeth and MDavg with age, sex and the presence of teeth. Age has also previously been shown to correlate with masseter muscle, but the association with survival is mostly uninfluenced by age, indicating that MA could be regarded as having independent prognostic value after trauma or carotid endarterectomy. Hu at al. analysed the association of MA with mortality between the sexes and suggested that women had a lower MAavg threshold for the sarcopenic area, increasing the risk of 30-day mortality in comparison with men after brain trauma (P. Hu et al., 2018). In the current study on CEA patients, the association of MAavg with mortality persisted despite adjustment for sex, which could confirm the findings. In addition, most of the perioperative and long-term risk factors in CEA patients mentioned in large studies and clinical trials (A. R. Naylor, 2012; A.R. Naylor, 2009) were considered in the analysis: age, BMI, BSA, sex, DM, HTA, CAD, dyslipidemia, renal insufficiency, peripheral artery disease, diagnoses of obstructive pulmonary disease, smoking, ipsilateral and contralateral stenosis, and indication for surgery (asymptomatic, amaurosis, TIA, ischaemic stroke). The effect of age, sex and dental status on MA and MD in this study was very similar compared to previous observations (J. P. Newton et al., 1993), indicating that the results are valid. Both age and MA were associated independently with mortality in the same multivariable survival analysis,

which implies their considerably predictive values as regards long-term survival despite each other.

6.4.2 Three-month survival in patients treated by MT (IV)

Wallace et al. (2017) and Hu et al. (2018) did not report short- and long-term mortality separately in either study, but in the survival curves, there was a trend towards most of the death occurring during the first months, as was also observed in study IV. In study IV, during the first three months after anterior mechanical thrombectomy of ICA and M1-MCA occlusions patients, a 1-SD increase in MAavg and MDavg was associated with a respective 43% and 39% decrease in the probability of death. When only patients surviving over three months were considered, no association of MAavg and MDavg with mortality could be demonstrated.

The findings regarding the association of MAavg and MDavg with short-term mortality in study IV differ from the evidence from study III concerning long-term mortality in patients treated by elective CEA. MDavg was associated with mortality during the first three months in study IV, whereas significant association with long-term mortality was not found in study III. This, in turn, could be due to fat infiltration in the masseter muscles being the first phase in the development of sarcopenia even before the MA decreases, supported by the fact MD value was the stronger muscle parameter that predicted 3-month survival in study IV. One potential reason for the results is that the patients' sample selection is not comparable. The AIS patients are treated by MT immediately, but (mostly) elective ICA stenosis patients are treated within two weeks from the onset of symptoms. Additionally, the included patients treated by MT in study IV had higher mean MD compared to the CEA patients (63.7±12.4 vs 53.5±16.5 HU) and the higher proportion of men among the CEA patients. It would be plausible to assume that the common occurrence of stenosis also in the external carotid artery had an association of influence on masseter muscle perfusion and radiodensity measurements. Another explanation could lie in the possibility that AIS patients' neuronal plasticity may have the most significant influence on recovery during the first weeks and months after stroke (Cramer & Riley, 2008), and it is possible that MAavg and MDavg associations might have an only short-term association in AIS patients.

6.5 Future prospects

The role of sarcopenia in vascular patients is probably underestimated, since there continues to be a lack of knowledge on the consequences of sarcopenia after operative treatments. The methods for estimating sarcopenia vary to a great extent. The clear clinical impact of CT-measured muscle parameters is difficult to verify because there continues to be a lack of consensus on whether it is even possible to influence the cross-sectional area or density of the psoas or masseter muscles with any interventions. However, there is already evidence that the frailty could be slowed down or even reversed in cancer patients, and it is worthwhile to consider whether sarcopenia is possibly preventable. The objectively measured muscle area and quality can be the first markers of early-stage sarcopenia before the development of clinically noticeable signs. Finally, as pre- and postoperative diet and physical interventions were not routinely performed, a target for future research should be to investigate whether interventions after surgery or thrombectomy will have a beneficial effect on postoperative survival. This thesis presents an optional method to detect muscle parameters and their changes as markers of sarcopenia in the future studies.

This thesis consists of retrospective studies, and the results need to be validated in further independent cohorts. Future work should aim to establish a clear clinical cut-off value for critical reduction in muscle size and density in relation to postoperative survival and to determine when the predictive value as regards the surgery or intervention does not exceed the benefits received by the patient according the preoperative muscle state. Since CT measurements are objective, reproducible and convenient for the clinician without adding costs, the method facilitates the expansion of the sarcopenia risk prediction to other surgical fields that treat aging patients with multiple comorbidities and in which the estimation of the prognosis may be demanding.

7 STUDY STRENGHTS AND LIMITATIONS

The primary limitation of the present thesis is that it based on individual retrospective studies. The part of the data and muscle measurements was assembled retrospectively, which may introduce bias. However, the prospectively collected vascular and thrombectomy registers were audited annually for data loss and consistency, but despite this, there were still some shortcomings in the data on risk factors. The mortality data of the patients was gathered from the Finnish causes of death register (Statistics Finland), which contains all deaths in Finland.

This thesis aimed at exploring the association between muscle parameters and mortality. However, the actual predictive value of the results would only be raised if the results could be replicated in other independent vascular patient cohorts. It is remarkable that the muscle area has previously been suggested to have an association with mortality and, thus, the predictive value of psoas and masseter parameters as regards mortality would seem justified. The prior hypothesis did not specify a clear cause-and-effect relationship between muscle parameters and mortality. It cannot be determined in practice, as the connection between these is not properly known, there are many confounding factors influencing muscle parameters and experimental studies are not performed. Therefore, adequate study samples were not defined in advance, but the sufficiency of the samples was observed by power calculations afterwards.

In all studies, patients were treated in a single hospital, and the results are not directly generalizable to other hospitals. However, the muscle measurements were z-scored in order to archive more clinical value and to generalize the results. When the muscle standardized deviation of the local patients is known, the muscle results could help in determining the sarcopenia. Moreover, it would be interesting to analyse the clinical parameters of sarcopenia, such as physical exercise, muscle strength and nutritional status, possibly to counteract developing sarcopenia, but these were not available.

In study II, the cohort sample was small, since the entire AAA population was not investigating owing to unavailable follow-up CT images. However, in study II, the operation baseline CT imaging and follow-up imaging was performed in the same hospital with the same imaging method, providing a more reliable estimate of the

CT-measured muscle changes. The 5-year survival rates between included and excluded patients did not differ significantly, and the baseline characteristics were similar, indicating only small and non-existent selection bias.

In all studies, the CT imaging timing and volume of contrast agent may have had an influence on muscle density measurements, in addition to muscle perfusion and the haemodynamic state. Density measurement may be overestimated in small patients with hyperkinetic perfusion, when compared to a larger patient with slower perfusion. Additionally, females were underrepresented in the studies, owing to the different epidemiology of vascular diseases, and the results are therefore less generalizable for the female population. The power of retrospective data is insufficient to draw reliable conclusion about which sarcopenia muscle parameter is indisputably the most accurate. Such a conclusion needs to be validated in larger independent cohorts whose power is sufficient to prove the difference between the muscle parameters.

8 CONCLUSIONS

The primary aim of these studies was to determine the association of sarcopenia, represented by muscle area and quality measured from CT images, with postoperative survival in patient with AAA or cerebrovascular disease. This thesis supports the following conclusions:

1. Psoas and masseter muscles measurements from CT images were reliable and applicable in clinical work. The intraclass correlation results (ICC) for reproducibility ranged from good and excellent: psoas measurements ICC > 0.640 and masseter measurements ICC > 0.865, p <0.001 for all.

2. PMA and LPMA at the L2–L3 vertebral level are independent predictors of mortality in patients treated for an AAA. At the strongest level of association, this entails that, for every one-standard-deviation increase in bilateral psoas muscle lean area at L3 level, there was a 26% decrease in the probability of death during follow-up (HR 0.74, 95% CI 0.58-0.93).

3. After EVAR, the psoas muscle decreased significantly both in terms of psoas muscle area, with a 27% decrease, and lean psoas muscle area, with a decrease of 22%. The most significant loss of skeletal muscle occurs during the first postoperative year after. The relative psoas muscle change (ΔPMA/BL) from baseline was independently associated with mortality during follow-up. For every 10% unit increase in ΔPMA/BL, there was a 21% decrease in the probability of death during follow-up.

4. The average masseter area (HR 0.76, 95% CI 0.61-0.96), but not the density, is independently associated with postoperative long-term survival in CEA patients.

5. MAavg and MDavg are independent predictors of 3-month survival after MT for ICA or M1-MCA occlusions in acute stroke patients. A 1-SD increase in MDavg was associated with a 39%–43% decrease in the probability of death during the first three months after the intervention.

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ORIGINAL PUBLICATIONS

PUBLICATION I

Psoas muscle area and quality are independent predictors of survival in patients treated for abdominal aortic aneurysm

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Psoas Muscle Area and Quality Are Independent Predictors of Survival in Patients Treated for Abdominal Aortic Aneurysms

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Background: Sarcopenia is associated with mortality after abdominal aortic aneurysm (AAA) repair. The reliability of computed tomography (CT) core muscle areas and quality—that is, densities and their association with postoperative survival in patients undergoing AAA treatment—were retrospectively studied.

Methods: Psoas muscle area (PMA) and multifidus area and psoas muscle density (PMD) and multifidus density were measured from CT images and analyzed to lean values. Results were standardized by *z*-scoring. Measurement reliability was ascertained using intraclass correlation coefficient analysis (3 independent observers). Clinical data were collected from an institutional database and the hospital's patient record database.

Results: The study included 301 patients (89% male, mean age 74.4 years, endovascular treatment 73.1%, rupture 7.6%). Median duration of follow-up was 2.70 (interquartile range 3.54) years and mortality 31.2%. Age, female gender, and body mass index were associated with PMA, PMD, and lean psoas muscle area (LPMA). L3 left PMD, total psoas muscle density, right and left LPMA, lean total psoas muscle area (LTPMA), and L2 right LPMA and LTPMA (hazard ratio 0.74−0.78 per 1 standard deviation, $P < 0.05$ to $P < 0.01$) were independently associated with improved survival in multivariable analysis.

Conclusions: L2−L3 PMD and LPMA are reliable, feasible, and independent predictors of mortality in patients treated for AAA. For every standard deviation increase in these standardized *z*-score muscle parameters, there was a 22%−26% decrease in the probability of death during follow-up.

INTRODUCTION

Surgical procedures for abdominal aortic aneurysms (AAAs) are high-risk interventions with considerable postoperative mortality. Survival is influenced by several factors such as urgency of operation, age, gender, and comorbidities like renal insufficiency, congestive heart failure, and chronic obstructive pulmonary disease.[1−5] The effect of treatment modality, open versus endovascular aortic repair (EVAR), has been somewhat controversial but EVAR has shown early survival benefit

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over open surgery in elective surgery and better long-term survival, cost-effectiveness, and quality of life when treating ruptured aneurysms in the emergency setting.[6–12] Development of surgical and anesthesiologic techniques along with aging of the population has led to vascular surgical patient material becoming more challenging which in turn emphasizes the need for improved methods of risk prediction in order to optimize patient safety, operative results, and cost-effectiveness.

Frailty, the age-associated decline in overall physiologic reserve and function, is associated with subclinical cardiovascular disease and appears to be superior to conventional anesthesiologic or surgical risk scores in estimating postoperative survival.[13–16] Muscle mass measures are one way of assessing frailty and skeletal muscle depletion referred to as sarcopenia has been demonstrated as an independent predictor of postoperative mortality.[16–21] Core muscle mass estimates have been found to be associated with postoperative survival even in patients undergoing elective AAA repair and sarcopenia has been noted to be associated with worse survival after elective EVAR and open surgery.[22–26] The methods for estimating both frailty and sarcopenia vary and the current challenge lies in defining an approach that is objective, reproducible, and convenient for the clinician without adding costs.[13,16] Furthermore, there is a need for evidence on the effect of sarcopenia as an indicator of muscle quality on survival of AAA patients undergoing invasive treatment including urgent and emergency cases. Psoas muscle area (PMA) can be applied as a quantitative method of estimating core muscle mass and sarcopenia and it correlates with postoperative complications and mortality.[23,27] It should be noted that PMA correlates negatively with age and positively with weight.[23] Similarly, paraspinal muscle area has been used in core muscle evaluation and is associated with postoperative survival.[28,29] Taken together, previous evidence on the effect of sarcopenia on survival of AAA patients is limited to elective patients and on PMA. In addition, data on reproducibility of the measurement, the value of other muscles and muscle quality as reflected by density is not available.

The purpose of this study is, first, to ascertain the reproducibility of core muscle area and quality—that is, density measurement from computed tomography (CT) scans of AAA patients by 3 independent observers—and to select the most consistent parameters. Second, the study sought to determine the association of sarcopenia represented by these density and lean area parameters with postoperative mortality in a cohort of patients treated for AAA with open surgery or EVAR electively or in an urgent or emergency setting. To explore more clinical association between psoas area and quality, we performed muscle parameter standardization by *z*-scoring.

METHODS

Patients

For this study, a total of 301 patients were randomly selected from a larger cohort of patients ($n = 959$) undergoing AAA treatment at the Tampere University Hospital (TAUH) vascular clinic between 2001 and 2014. The data were collected from a prospectively constructed institutional database and TAUH patient record database. The clinic's protocol of preoperative assessment entailed aortic imaging with contrast-enhanced CT for each patient. Additional CT imaging was conducted postoperatively as part of the follow-up at 1 month and 2 years in patients who underwent EVAR. The treatment modality, open or endovascular surgery, was selected by the treating vascular surgeon often in collaboration with an interventional radiologist in a multidisciplinary meeting. The study adhered to the ethical principles of the Declaration of Helsinki and was approved by Pirkanmaa Hospital District Science Center Approval. Due to the nature of the study, no informed patient consent was required or obtained. A total of 100 patients were first evaluated and it was found that a 6–10% change in parameter values caused a significant difference in mortality. It was therefore decided to measure 201 additional patients yielding a sufficient sample. Patients without available CT imaging of the abdominal area between 90 days before and 30 days after the operation with 0.63- to 3.00-mm slice thickness were excluded. The excluded patients had less dyslipidemia (28.9% vs. 43.9%, $P < 0.001$) and coronary artery disease (CAD) (41.5% vs. 50.8%, $P = 0.007$), but no significant differences were observed in other demographic parameters.

Imaging Parameters

CT scans were obtained using 2 different multidetector scanners: General Electric LightSpeed 16-row scanner (GE Healthcare, Milwaukee, WI) and Philips Brilliance 64-row scanner (Philips, Cleveland, OH). Scanners were in equal use and patients were not selected to a certain scanner. Abdominal aortic CT imaging was performed using the following parameters: 120 kV, 250 mA, collimation 64 × 0.625 mm

(64-row) or 120 kV, Auto MA (150−350 mA), collimation 16 × 1.25 mm (16-row). Contiguous slices were reconstructed to a thickness of 1−3 mm in the whole scanning range. The contrast agent (Xenetix 350 mgI/mL, Aulnay-sous-Bois, France) was administered through an antecubital 18-gauge cannula using a double-piston power injector with a flow rate of 3 mL/s using 100 mL of contrast agent followed by a 40-mL saline flush. Real-time bolus tracking was used and the acquisition was triggered when the contrast agent opacified the full diameter of the thoracoabdominal aorta. The acquisition was performed during deep-inspiration breath-hold.

Image Analysis, Variables, and Measurements

The CT images were reviewed using dedicated medical imaging workstations (Carestream Vue PACS viewer version 11.4.0.1253, Rochester, NY). Density and area measurements were performed from contrast-enhanced arterial phase images and axial slices of 0.63−3.00 mm thickness were used. The distance between the transverse processes was measured from sagittal reformats reconstructed with the multiplanar reformat feature of the viewer software. Preferentially, the preoperative aortic imaging study was utilized. When preoperative images with the desired slice thickness were unavailable, the 1-month or earlier follow-up aortic CT was evaluated (21.9% of cases). Of these, 90.9% were elective and 95.5% were EVAR.

A test sample of 27 patients was first randomly selected and evaluated independently by 3 clinicians: a radiologist (10 years of experience), a vascular surgeon (15 years of experience), and a junior doctor who had been previously given appropriate instructions. The purpose was to extensively test the reliability and prognostic value of repeated measurement of the same muscle area in the clinical work. All evaluators were blinded to the patients' outcome and test patients' characteristics did not significantly differ from the remaining patients. The remaining patients were evaluated by a single interpreter based on observations from the test sample. The measurements were performed on both sides at 4 vertebral levels: L2, L3, L4, and L5. A representative axial slice for each vertebral level was chosen at the level of origin of the transverse processes. Regions of interest (ROIs) that separately outlined the psoas and multifidus muscles on both sides were carefully drawn with a free-hand tool that subsequently produced a report giving the cross-sectional area outlined by the ROI and the mean density in Hounsfield Units (HUs) along with

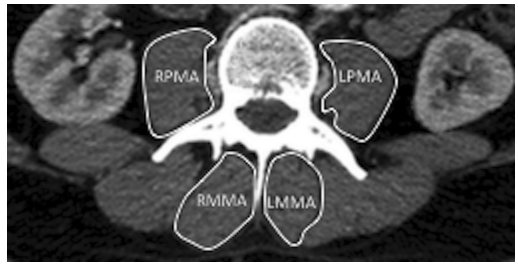

Fig. 1. Muscle measurement. Outlining the region of interest: psoas (and multifidus) muscles on both sides. Area was measured in mm^2. RPMA, right psoas muscle area; LPMA, left psoas muscle area; RMMA, right multifidus muscle area; LMMA, left multifidus muscle area.

standard deviation (SD) (Figs. 1 and 2). The idea was to isolate the muscle according to the anatomical boundaries in axial images. Free-hand selection of ROI measured the area and mean density.

Total muscle areas were formed by adding the right and left muscle areas and total muscle densities were calculated as means on each sides at the same vertebral level. Distance between vertebrae was measured between the caudal margins of the transverse processes in the sagittal plane of the mid part of the transverse process of the more cranial vertebra. The side with longer distance was chosen for measurements if there was a visible difference. After confirmation of reproducibility, which ranged from fair to excellent (being fair in 2 types of CT measurements), the remaining 274 patients were evaluated by a single interpreter based on the observations gathered from the test sample. Density thresholds for tissue characterizations were set as follows: 20−80 HU normal muscle, 1−19 HU lower density muscle, 0 HU water, −1 to −29 HU fatty muscle, and −30 to −50 HU fatty connective tissue. Contrast between psoas muscle tissue and adipose tissue is considerable as a consequence of prominent fascia and muscle measurements can be done as a semiautomated procedure. Isolation using HU-based segmentation would not work in a muscle with fatty streaks and subfascial fat because the region-growing algorithm would not be able to discriminate the intramuscular fat from the surrounding fat. Inside the free-hand ROI, HU-based segmentation into fat and muscle would be possible. However, the density−area product was elected in line with previous reports.[23,29]

Lean muscle area was estimated by the product of total muscle area with average density ($cm^2 \times HU$). This value was scored as 0 if the average density was below 0 HU. Lean muscle area was estimated by the product of total muscle area with average density

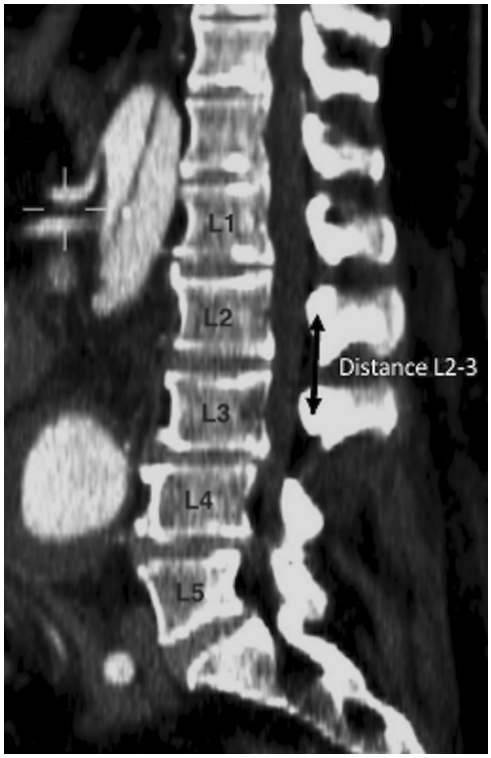

Fig. 2. Illustration of the measurement used for this study between vertebrae L2 and L3. Estimating gaps between spinal discs on transverse processes from the bottom of the more cranial vertebra.

($cm^2 \times$ HU) which enabled accounting for both muscle area and density on the same variable. Lean muscle area was scored as 0 if the average density was below 0 HU. The study center's medical imaging workstation was not able to directly measure lean variables. The psoas muscle volume was modeled for calculations as a 3-dimensional truncated cone, where distance between vertebrae was the height of the cone and total muscle area was the area of the base of the cone.

Statistical Analysis

The statistical software used for analyses was SPSS 24 for Mac OS X. Intraclass correlation coefficient analysis (ICC) was applied to ascertain reliability, that is, interobserver variability of the parameters (areas, densities, and distance) measured by 3 independent observers. Not all observers traced the ROI twice, therefore intraobserver variables are not shown. The 2-way random single measurement model was selected and both consistency and absolute agreement were calculated along with 95% confidence intervals (CIs).[30] ICC was rated as poor (<0.40), fair (0.40−0.59), good (0.60−0.74), or excellent (0.75−1.00). A test sample size of approximately 10% of the whole sample (>20 patients) is typical in testing the functionality of a study as the measurement error decreases significantly at this threshold. In this study, post hoc statistical power estimates were calculated for the ICC values as assurance probabilities as proposed by Zou.[31] The assurance probability is alternative to power analysis when ICC results are the primary outcome and it indicates the probability that the lower limit of the CI is no less than the obtained value. In this study, assurance probability results were excellent (0.80−0.92) in almost all of the statistically significant measurements indicating that the 27-patient test sample applied was sufficient.

The distributions of the measured variables were visualized using histograms and analyzed for normality using Levene's test. Predictors of survival were analyzed using Cox regression first in univariable analyses and then testing the proportional hazards assumption by log-minus-log plots, and consequently in a multivariable model including parameters with $P < 0.1$ in univariable analysis as covariates. Muscle parameters were entered as continuous variables to the Cox regression analysis. Multivariable regression was adjusted as covariates for age, ruptured AAA, smoking, previous stroke or transient ischemic attack, creatinine level, American Society for Anesthesiologists (ASA) score, statin, and anticoagulant medication. Multivariable analyses were also calculated by standardized *z*-scoring variables and analyses were adjusted for the same variables. Statistical significance was set at $P < 0.05$.

RESULTS

Patient Demographics

The final study population consisted of 301 patients treated for AAA at TAUH between 2001 and 2014. The demographic data, risk factors, procedural variables, and medication are presented in Table I. There were no patients with missing data. The majority of patients was male, presented with CAD and hypertension, underwent an elective procedure, received EVAR, was classified as ASA 3, and had statin medication.

Reproducibility of the CT Measurements

The distance between L2 and L3 vertebrae was clearly the most consistently measured one among

the different vertebral levels based on ICC analysis (consistency 0.599, 95% CI 0.25−0.86; absolute agreement 0.588, 95% CI 0.25−0.85; Table II). Thus, muscle volume and density measurements were performed on these 2 levels. The measurements demonstrated fair to excellent reliabilities, mostly in the range of good reproducibility (Table II). Consistency was 0.535−0.686 and absolute agreement 0.446−0.585 for PMA at L2, and 0.672−0.720 and 0.640−0.676 at L3, respectively. For PMD, the consistency was 0.769−0.816 and absolute agreement 0.776−0.793 at the L2 level and 0.691−0.765 and 0.693−0.778, correspondingly, at the L3 level. PMAs measured at these levels had moderate to high correlation to the areas of the multifidus muscles at the same levels based on Pearson R (L2: $r = 0.719$, $P < 0.01$, L3: $r = 0.469$, $P < 0.05$). A similar finding was observed when densities were compared (L2: $r = 0.512$, $P < 0.01$, L3: $r = 0.654$, $P < 0.01$).

Association of Age, Gender, and BMI with the CT Measurements

Clinical features were similar between men and women in terms of demographics, risk factors and procedural variables, but men used significantly more antihypertensive medication ($P = 0.04$). When comparing sides (dexter versus sinister), the left-sided parameters were significantly higher: L2 PMA (5.2 ± 2.0 vs. 5.5 ± 1.9 cm^2), L2 PMD (29.3 ± 12.6 vs. 31.7 ± 11.8 HU), L3 PMA (8.2 ± 2.6 vs. 8.5 ± 2.5 cm^2), L3 PMD (32.0 ± 12.0 vs. 33.4 ± 11.3 HU), L2 lean PMA (155.2 ± 93.1 vs. 175.4 ± 93.1 $cm^2 \times$ HU), L3 lean PMA (253.3 ± 138.2 vs. 287.8 ± 135.9 $cm^2 \times$ HU) showed significant differences ($P < 0.01$ for all).

Table III presents the actual median values of measured muscle areas and densities. Furthermore, the effects of age, gender, and BMI are presented on the measured CT parameters. Aging had an overall inverse effect on PMA, PMD, lean area and volume, and lean volume. Female gender was associated with decreased PMA, lean area, density and volume, and lean volume. Finally, BMI was associated with increased PMA and volume (Table III).

Association of CT Measurements with Mortality

The follow-up lasted until April 2015 with the median duration of follow-up being 2.70 (interquartile range [IQR] 3.54) years. Ninety-four (31.2%) patients died and none were lost during follow-up. Parameters with a tendency to predict survival in univariable analyses (Supplementary Table I) were checked by log-minus-log plots to confirm proportional hazards assumption and were thereafter incorporated into the multivariable analysis (Supplementary Table II). Results were also confirmed by further adjusting the multivariable model with BMI and gender known to associate with PMA and the results remained the same (Supplementary Table III). To explore more clinical association between PMD or lean area and outcome, the multivariable analysis after muscle parameter standardization by z-scoring was performed (Table IV). L3 left side PMD and total psoas muscle density (TPMD), L3 right and left lean psoas muscle area (LPMA), L3 lean total psoas muscle area (LTPMA), and L2 right LPMA and LTPMA (hazard ratio [HR] 0.74−0.78 per 10 HU) per 1 SD ($P < 0.05$ to $P < 0.0.01$) were independently associated with improved survival in multivariable analysis. The most effective muscle parameter was L3 LTPMA, for

Table I. Patient demographics and risk factors

Features	Sample ($n = 301$)
Demographics	
Age (years)	74.4 ± 9.4
Male (%)	268 (89%)
Height (m)	1.76 ± 0.08
BMI (kg/m^2)	26.6 ± 4.4
Risk factors	
Previous intervention	20 (6.6%)
Smoking	71 (23.6%)
CAD	158 (50.8%)
DM	41 (13.6%)
HTA	192 (63.8%)
Dyslipidemia	132 (43.9%)
Pulmonary disease	68 (22.6%)
Stroke or TIA	34 (11.3%)
Creatinine level (μmol/L)	86 ± 83
Procedural variables	
rAAA	23 (7.6%)
OR	81 (26.9%)
EVAR	220 (73.1%)
ASA 2	16 (5.3%)
ASA 3	176 (58.5%)
ASA 4	92 (30.6%)
ASA 5	17 (5.6%)
Medication	
Antiaggregant	148 (49.2%)
Anticoagulant	72 (23.9%)
Oral antidiabetic	26 (8.6%)
Insulin	19 (6.3%)
Beta blocker	179 (59.5%)
Other antihypertensives	184 (61.1%)
Statin	168 (55.8%)
Glucocorticoid	19 (6.3%)

DM, diabetes mellitus; HTA, hypertensio arterialis; OR, open repair of abdominal aortic aneurysm; rAAA, ruptured abdominal aortic aneurysm; TIA, transient ischemic attack.

Table II. Intraclass correlation coefficient analysis of CT measurements

Variable	ICC[a]	95% CI	ICC[b]	95% CI	*P*-value
L2					
dx psoas muscle					
Area	0.686	0.36–0.89	0.585	0.21–0.85	<0.001
HU	0.816	0.58–0.94	0.793	0.54–0.93	<0.001
sin psoas muscle					
Area	0.535	0.17–0.83	0.446	0.10–0.77	0.002
HU	0.769	0.50–0.92	0.776	0.51–0.93	<0.001
dx multifidus muscle					
Area	−0.113	−0.34 to 0.29	−0.036	−0.10 to 0.14	0.758
HU	0.705	0.40–0.90	0.675	0.36–0.89	<0.001
sin multifidus muscle					
Area	−0.117	−0.34 to 0.31	−0.051	−0.15 to 0.20	0.726
HU	0.690	0.37–0.89	0.698	0.39–0.90	<0.001
L3					
dx psoas muscle					
Area	0.674	0.35–0.89	0.640	0.31–0.87	<0.001
HU	0.765	0.49–0.92	0.778	0.52–0.93	<0.001
sin psoas muscle					
Area	0.720	0.42–0.91	0.676	0.35–0.89	<0.001
HU	0.691	0.37–0.89	0.693	0.38–0.89	<0.001
dx multifidus muscle					
Area	0.175	−0.16 to 0.61	0.076	−0.06 to 0.38	0.167
HU	0.823	0.59–0.94	0.818	0.59–0.94	<0.001
sin multifidus muscle					
Area	−0.055	−0.30 to 0.39	−0.019	−0.10 to 0.19	0.595
HU	0.814	0.58–0.94	0.804	0.57–0.94	<0.001
L4					
dx psoas muscle					
Area	0.812	0.57–0.94	0.740	0.40–0.92	<0.001
HU	−0.036	−0.29 to 0.41	−0.036	−0.30 to 0.41	0.553
sin psoas muscle					
Area	0.028	−0.25 to 0.48	0.027	−0.24 to 0.46	0.416
HU	0.772	0.50–0.93	0.786	0.52–0.93	<0.001
dx multifidus muscle					
Area	0.050	−0.24 to 0.50	0.046	−0.21 to 0.47	0.372
HU	0.811	0.57–0.94	0.801	0.56–0.94	<0.001
sin multifidus muscle					
Area	0.199	−0.14 to 0.62	0.185	−0.12 to 0.60	0.138
HU	0.843	0.63–0.95	0.849	0.65–0.95	<0.001
L5					
dx psoas muscle					
Area	0.916	0.79–0.97	0.862	0.57–0.96	<0.001
HU	0.784	0.52–0.93	0.766	0.50–0.92	<0.001
sin psoas muscle					
Area	0.351	−0.02 to 0.73	0.350	−0.01 to 0.72	0.032
HU	0.798	0.55–0.94	0.811	0.57–0.94	<0.001
dx multifidus muscle					
Area	0.757	0.48–0.92	0.653	0.26–0.88	<0.001
HU	0.719	0.42–0.91	0.736	0.44–0.91	<0.001
sin multifidus muscle					
Area	0.756	0.48–0.92	0.756	0.48–0.92	<0.001
HU	0.716	0.41–0.90	0.719	0.42–0.91	<0.001
L2–L3 distance	0.599	0.25–0.86	0.588	0.25–0.85	0.001
L3–L4 distance	0.257	−0.10 to 0.66	0.268	−0.10 to 0.68	0.084
L4–L5 distance	0.310	−0.05 to 0.70	0.287	−0.04 to 0.68	0.050

dx, dexter; sin, sinister.
[a]Model: ICC 2-way random consistency.
[b]Model: ICC 2-way random absolute.

Table III. The effect of age, gender, and BMI on CT measurements and the actual medians

	Age			Gender		BMI				
	T1	T2	T3			T1	T2	T3		
	65.1	74.4	82.4	Male	Female	22.9	26.0	31.1	Median	SD
Distance between L2 and L3 (cm)	34.8	34.0	33.6[a]	34.5	31.2	34.3	34.3	34.3	34.3	3.2
L2										
dx PMA (cm^2)	5.8	4.9	4.3[a]	5.2	3.0	4.2	4.8	5.6[b]	4.9	2.0
dx PMD (HU)	33.5	28.0	24.0[a]	30.0	22.0[c]	33.0	28.0	29.0	30.0	12.6
dx lean PMA (cm^2 × HU)	187.6	147.4	109.8[a]	154.4	68.9	134.3	148.0	158.4	147.8	93.1
sin PMA (cm^2)	6.0	5.5	4.6[a]	5.6	3.6	4.7	5.5	6.0[b]	5.5	1.9
sin PMD (HU)	37.0	30.0	31.0[a]	32.0	28.0	34.5	30.0	31.0	31.0	11.8
sin lean PMA (cm^2 × HU)	207.6	166.4	147.4[a]	182.8	114.2	169.6	166.6	178.4	170.3	93.1
TPMA (cm^2)	11.7	10.7	8.9[a]	10.9	6.9	8.9	10.6	11.6[b]	10.6	3.6
TPMD (HU)	34.8	29.0	27.3[a]	31.3	28.0	32.8	29.5	29.5	30.5	11.3
Lean TPMA (cm^2 × HU)	388.3	309.2	254.4[a]	330.7	451.0[c]	294.8	309.5	329.1	314.0	177.1
L3										
dx PMA (cm^2)	9.1	8.0	7.1[a]	8.1	5.1	6.9	8.1	9.1[b]	7.9	2.6
dx PMD (HU)	37.0	32.0	29.0[a]	33.0	28.0[c]	34.5	33.0	32.0	33.0	12.0
dx lean PMA (cm^2 × HU)	310.1	242.4	187.8[a]	266.2	121.8[c]	221.6	257.3	260.0	253.5	138.2
sin PMA (cm^2)	9.5	8.2	7.6[a]	8.6	5.4[c]	7.5	8.5	9.5[b]	8.3	2.4
sin PMD (HU)	38.0	33.0	32.0[a]	35.0	33.0	37.0	34.0	33.0	34.0	11.3
sin lean PMA (cm^2 × HU)	344.5	280.0	225.4[a]	301.2	157.7[c]	266.6	280.2	301.2	282.0	135.9
TPMA (cm^2)	18.5	16.3	14.6[a]	16.8	11.0[c]	14.5	16.5	18.5[b]	16.3	4.9
TPMD (HU)	37.3	32.5	29.5[a]	33.5	29.0	34.8	32.5	33.0	33.0	10.8
Lean TPMA (cm^2 × HU)	653.4	522.2	414.2[a]	556.5	768.3[c]	523.3	540.6	548.4	532.1	262.7
Right psoas volume (cm^3)	26.3	22.2	18.5[a]	23.0	12.8[c]	19.0	22.5	25.0[b]	21.8	8.2
Lean volume (cm^3 × HU)	849.3	701.7	491.5[a]	715.4	338.1[c]	617.3	706.7	707.8	684.8	402.6
Left psoas volume (cm^3)	25.9	23.7	20.9[a]	24.4	13.7[c]	20.5	23.9	26.2[b]	23.7	7.8
Lean volume (cm^3 × HU)	933.8	7,765.9	622.6[a]	824.0	423.9	748.1	760.1	843.8	785.8	398.6
Total psoas volume (cm^3)	52.0	45.9	40.0[a]	47.2	26.9[c]	39.7	45.8	50.5[b]	45.5	15.6
Lean total volume (cm^3 × HU)	1,770.0	1,514.4	1,141.7[a]	1,566.9	747.3[c]	1,428.4	1,505.2	1,577.0	1,495.2	769.0

Values presented are medians. Volumes have been calculated between L2 and L3 vertebrae.
dx, dexter; sin, sinister; T, tertile.
[a]The oldest tertile has statistically significant difference compared to the youngest tertile ($P < 0.05$, one-way analysis of variance or Kruskal–Wallis test).
[b]The highest tertile has statistically significant difference compared to the lowest tertile ($P < 0.05$, one-way analysis of variance or Kruskal–Wallis test).
[c]Females have statistically significant difference compared to males ($P < 0.05$, independent-samples *t*-test or chi-squared test).

which for every SD increase means 26% decrease in the probability of death during follow-up. *Z*-scoring decreased muscle parameter skewing compared to authentic muscle parameters (Supplementary Table II). Further adjustment of the model with operative approach (EVAR versus open repair) or urgency (emergency versus elective) did not have any effect on the results. Furthermore, multivariable analysis was also performed with *z*-scored muscle parameters and after exclusion of ruptured AAA patients. In these analyses, L3 TPMD (HR 0.68–1.01) and L2 LTPMA (HR 0.60–1.01) demonstrated slightly decreased significance, but the most consistently associated muscle parameter L3 LTPMA strengthened and every SD increase was associated with a 29% decrease in the probability of death. Ruptured AAA patients did not have statistically significant effect on the results. The effect of pre-postoperative imaging was also tested by univariable Cox regression analysis and no association with survival was found.

DISCUSSION

Muscle size and quality are significant predictors of postoperative mortality. However, the optimal method for estimating these in a reliable and convenient way is yet to be determined and the evidence regarding vascular surgical patients remains limited. This study demonstrated the association of muscle quality with mortality in patients treated for AAA

Table IV. Multivariable Cox regression analysis of overall survival

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.05[a]	1.03−1.09	1.05[a]	1.02−1.09	1.05[a]	1.02−1.08
rAAA	5.07[a]	2.17−11.84	5.04[a]	2.15−11.81	5.16[a]	2.21−12.01	4.82[a]	2.10−11.10	4.91[a]	2.14−11.29	4.78[a]	2.09−10.92	4.91[a]	2.14−11.26
Smoking	1.09	0.62−1.92	1.12	0.64−1.98	1.07	0.61−1.89	1.06	0.60−1.88	1.07	0.61−1.89	1.02	0.58−1.80	1.05	0.60−1.84
Stroke or TIA	1.82	1.00−3.30	1.83[b]	1.00−3.34	1.76	0.97−3.19	1.75	0.96−3.17	1.77	0.97−3.22	1.81	0.99−3.28	1.80	0.99−3.26
Creatinine	1.03[a]	1.02−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.02−1.05	1.03[a]	1.01−1.05
ASA	1.11	0.76−1.61	1.12	0.77−1.62	1.16	0.81−1.67	1.17	0.81−1.68	1.15	0.80−1.66	1.13	0.79−1.63	1.14	0.79−1.64
Medication														
Anticoagulant	1.13	0.71−1.81	1.12	0.70−1.79	1.08	0.68−1.73	1.10	0.69−1.76	1.11	0.70−1.78	1.11	0.70−1.78	1.11	0.70−1.77
Statin	0.67	0.44−1.03	0.67	0.44−1.02	0.66[b]	0.43−1.00	0.66	0.43−1.00	0.66	0.43−1.02	0.66	0.43−1.01	0.67	0.44−1.02
CT parameter *z*-score														
L3 sin PMD	0.76[c]	0.63−0.93	−		−		−		−		−		−	
L3 TPMD	−		0.78[b]	0.64−0.95	−		−		−		−		−	
L2 dx LPMA	−		−		0.78[b]	0.61−0.99	−		−		−		−	
L2 LTPMA	−		−		−		0.78[b]	0.61−1.00	−		−		−	
L3 dx LPMA	−		−		−		−		0.76[b]	0.60−0.95	−		−	
L3 sin LPMA	−		−		−		−		−		0.75[b]	0.59−0.94	−	
L3 LTPMA	−		−		−		−		−		−		0.74[b]	0.58−0.93

Creatinine level and HU values are transformed to one-tenth values. The effect of area and volume parameters is presented as per cm^2 and cm^3, respectively. HR estimated from Cox hazard regression model.

dx, dexter; rAAA, ruptured abdominal aortic aneurysm; sin, sinister; TIA, transient ischemic attack; TPMA, total (sin and dx) psoas muscle area.

[a]Indicates significant difference $P < 0.001$.

[b]Indicates significant difference $P < 0.05$.

[c]Indicates significant difference $P < 0.01$.

in 1- to 5-year follow-up using PMD, PMA, and LPMA at the level of the L2 and L3 vertebrae as markers that can be reliably and swiftly measured from CT scans. In this study, the strongest cut-off value affecting prognosis was a 1 SD increase in the psoas muscle lean area bilaterally at the L3 level. Specifically, at a cut-off value for total psoas lean area of 269.4 cm^2 or greater at the L3 level was associated with a 26% decrease in the probability of death during follow-up. Results can be generalized in the clinical work, when the muscle standardized deviation of the local patient series is measured and known. Other research has studied the association between muscle area and patient outcome, but in this study, attention was paid also to lean values including both muscle area and density ($cm^2 \times$ HU). Preoperative CT images within 90 days before the operation were preferred, but if these were unavailable the 1-month or earlier postoperative images were used. It was verified that the timing of CT imaging was not significantly associated with survival. It was additionally ascertained that PMD is negatively associated with age and female gender in patients undergoing AAA repair.

The fair to excellent reproducibility of PMA and PMD measurements at L2–L3 vertebral levels as shown by ICC analysis is in line with previous studies and suggests that these parameters can be reproducibly estimated from routine preoperative CT scans.[32,33] PMA and PMD correlated with multifidus area and multifidus density at L2–L3 levels. Reproducibility of multifidus muscles areas was tested by ICC at the same vertebral level, but the results were weaker. These findings most likely result from the challenges of outlining the ROIs of the multifidus muscles if there is no perceptible fascia. Apart from left lean muscle volumes the study patients presented with greater muscle areas and densities on the left side compared to the right. Previously, PMA has been found to be greater on the dominant side in a study cohort of healthy males.[34] A study investigating the potential causes of paraspinal muscle asymmetry in men found only some inconsistent associations with muscle laterality, including handedness.[35] Whether the asymmetry noted in this study was influenced by the AAA via different mechanisms remains to be elucidated. With regards to factors associated with the investigated muscle parameters, the significant inverse association of age with PMA and PMD fits well to the very definition of frailty and further supports the use of muscle mass and quality estimates as methods of frailty assessment.[13,14,23,36] The tendency of women toward lower PMA, PMD, and lean muscle volume compared to men is supported by preceding evidence.[37–39] This study found that in addition to age, BMI is associated with increased PMA and total PMA, which is seconded by current literature.[23] A similar correlation has been noted before in lung cancer patients undergoing pneumonectomy.[21] The multivariable models were adjusted with age, gender, BMI, operative approach, and urgency, and with all significant factors found in univariable analyses these adjustments had no effect on the association of psoas muscle parameters with survival which further confirms the independent role of these parameters as predictors of mortality.

Previous work on the effect of sarcopenia on survival in vascular surgical patients includes a study by Canvasser et al.,[29] which stated that paraspinal muscle area at Th12 level measured from preoperative abdominal CT scans is associated with postoperative 1-year mortality. Paraspinal muscle area measurements were used as the group found them more easily attainable from routine imaging compared to psoas muscle measurements for a larger group of surgical patients. Additionally, paraspinal muscle area was noted to correlate well with total PMA at the L4 level. Despite the substantial study cohort ($n = 1{,}309$), the percentage of vascular surgical patients was only 13.5, the study excluded outpatients and those subjected to emergency surgeries, and did not provide data on AAA patients. In comparison, the study cohort in this study is more homogenous entailing only patients subjected to AAA repair, includes both elective and emergency cases, patient data are comprehensive, and the follow-up is longer (2.70 years, IQR 3.54). Previous studies on AAA patients have a comparable follow-up and are in line with the present findings thus consolidating evidence on the predictive value of PMA in postoperative survival of elective patients ($n = 149$) treated mainly with EVAR (85%; HR 0.86 per cm^2),[23] elective patients ($n = 137$) treated mainly with EVAR (96%),[26] and elective patients ($n = 262$) treated with open repair.[22] In more recent papers, Newton et al.[24] found sarcopenia to be associated with worse survival in patients ($n = 135$) undergoing elective EVAR (odds ratio 3.9, $P = 0.027$) and Thurston et al.[25] presented similar findings in an elective all-male EVAR cohort (odds ratio 2.37, $P = 0.011$). Shah et al.[26] included postoperative CT images within 3 months after operation in case of missing preoperative images in 12% of cases and the group discovered reduced left PMA at the L4 level to be independently associated with mortality which is supported by the results of the present study.[26] Contrary to other works, Indrakusuma et al.[40] did not find an association between low PMA at the level of L3 and survival in AAA patient. In a study of 228 elective, asymptomatic infrarenal AAA patients, only 124

underwent AAA repair and 62% of 124 patients were treated by EVAR. Their study did not include patients who had symptomatic pain or ruptured AAA and multivariable analysis of significant univariable parameters and overall survival was not presented. Advantageously, the present study adds on previous knowledge by providing data on the value of PMD and lean PMA parameters, indicating that in addition to area, muscle quality also has predictive value. Furthermore, the present study applied both authentic and *z*-scored values to control for skewing and to enhance more clinical importance to the results. Low muscle size and density are potential variables when considering the fitness of a patient for operation, particularly for a high-risk operation.

The results presented in this article should be interpreted in the context of a single-center retrospective study. The vascular registry used is, however, constructed prospectively and annually audited. Furthermore, patients treated before 2005 were mainly excluded from the study since CT slice thickness of 1−3 mm was not routinely used in this center before 2005, possibly causing patient selection. The 1-month or earlier follow-up aortic CT was used in 21.9% of cases and it is unlikely that a significant change in muscle mass or quality would have developed during that time. Furthermore, the timing of the imaging was not found to be associated with survival in a Cox regression analysis. The timing and volume of the contrast agent, and the hemodynamic state of the patient may have influenced the density measurements. Densities measured in small patients with hyperkinetic circulation may be overestimated compared to large patients with slow circulation. Another likely yet small contributor to selection bias may have been that in rare cases of unstable patients requiring immediate intervention, the decision to operate was based solely on ultrasound without concomitant CT imaging. The strengths of the present study lie in a large and homogenous patient cohort comprising elective and urgent or emergency cases and patients treated with open surgery and EVAR, structural collection of data, and a noticeable follow-up time.

CONCLUSION

L2−L3 PMD and LPMA offer a valuable adjunct to postoperative risk prediction in patients treated for AAA and they can be reliably and swiftly measured without added costs. At strongest, this means that for every SD increase from psoas muscle lean value bilaterally at L3 level, there is a 26% decrease in the probability of death during follow-up. In clinical use, PMD and LPMA standardized *z*-scoring help to perceive prognosis when SD is known.

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APPEDIX

Supplementary Table I. Univariable Cox regression analysis of overall mortality

Risk factor	HR	95% CI
Age	1.06[a]	1.04−1.09
Gender	1.05	0.56−1.98
Height	1.00	0.97−1.02
BMI	0.97	0.92−1.02
rAAA	3.25	1.76−6.00
Previous operation	1.05	0.43−2.60
Smoking	0.64[b]	0.38−1.09
CAD	1.31	0.87−1.97
DM	1.31	0.74−2.31
HTA	0.92	0.61−1.39
Dyslipidemia	0.70	0.46−1.07
Pulmonary disease	0.95	0.58−1.55
Stroke or TIA	1.79[c]	1.01−3.18
Creatinine level	1.00[a]	1.00−1.01
EVAR	1.28	0.79−2.07
ASA	1.70[a]	1.26−2.29
Medication		
Antiaggregant	1.08	0.72−1.62
Anticoagulant	1.50[b]	0.96−2.34
Oral antidiabetic	0.96	0.45−2.09
Insulin	0.80	0.32−1.96
Beta blocker	1.04	0.69−1.57
Other antihypertensives	1.06	0.70−1.60
Statin	0.61[c]	0.41−0.92
Glucocorticoid	1.76	0.85−3.66

HR estimated from Cox hazard regression model. Variables demonstrating significant associations with mortality on univariate analysis ($P < 0.1$) were incorporated into multivariate analysis.

DM, diabetes mellitus; HTA, hypertensio arterialis; rAAA, ruptured abdominal aortic aneurysm; TIA, transient ischemic attack.

[a]Indicates significant difference $P < 0.01$.

[b]Indicates significant difference $P < 0.1$.

[c]Indicates significant difference $P < 0.05$.

Supplemenatry Table II. Multivariable Cox regression analysis of standardized *z*-scoring

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.06[a]	1.03−1.09	1.05[a]	1.03−1.09	1.05[a]	1.02−1.09	1.05[a]	1.02−1.08
rAAA	5.07[a]	2.17−11.84	5.04[a]	2.15−11.81	5.16[a]	2.21−12.01	4.82[a]	2.10−11.10	4.91[a]	2.14−11.29	4.78[a]	2.09−10.92	4.91[a]	2.14−11.26
Smoking	1.09	0.62−1.92	1.12	0.64−1.98	1.07	0.61−1.89	1.06	0.60−1.88	1.07	0.61−1.89	1.02	0.58−1.80	1.05	0.60−1.84
Stroke or TIA	1.82	1.00−3.30	1.83[b]	1.00−3.34	1.76	0.97−3.19	1.75	0.96−3.17	1.77	0.97−3.22	1.81	0.99−3.28	1.80	0.99−3.26
Creatinine	1.03[a]	1.02−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.01−1.05	1.03[a]	1.02−1.05	1.03[a]	1.01−1.05
ASA	1.11	0.76−1.61	1.12	0.77−1.62	1.16	0.81−1.67	1.17	0.81−1.68	1.15	0.80−1.66	1.13	0.79−1.63	1.14	0.79−1.64
Medication														
Anticoagulant	1.13	0.71−1.81	1.12	0.70−1.79	1.08	0.68−1.73	1.10	0.69−1.76	1.11	0.70−1.78	1.11	0.70−1.78	1.11	0.70−1.77
Statin	0.67	0.44−1.03	0.67	0.44−1.02	0.66[b]	0.43−1.00	0.66	0.43−1.00	0.66	0.43−1.02	0.66	0.43−1.01	0.67	0.44−1.02
CT parameter														
L3 sin PMD	0.79[c]	0.66−0.94	−		−		−		−		−		−	
L3 TPMD	−		0.80[b]	0.66−0.96	−		−		−		−		−	
L2 dx LPMA	−		−		0.97[b]	0.95−1.00	−		−		−		−	
L2 LTPMA	−		−		−		0.99[b]	0.97−1.00	−		−		−	
L3 dx LPMA	−		−		−		−		0.98[b]	0.96−1.00	−		−	
L3 sin LPMA	−		−		−		−		−		0.98[b]	0.96−1.00	−	
L3 LTPMA	−		−		−		−		−		−		0.99[b]	0.98−1.00
CT parameter *z*-score														
L3 sin PMD	0.76[c]	0.63−0.93	−		−		−		−		−		−	
L3 TPMD	−		0.78[b]	0.64−0.95	−		−		−		−		−	
L2 dx LPMA	−		−		0.78[b]	0.61−0.99	−		−		−		−	
L2 LTPMA	−		−		−		0.78[b]	0.61−1.00	−		−		−	
L3 dx LPMA	−		−		−		−		0.76[b]	0.60−0.95	−		−	
L3 sin LPMA	−		−		−		−		−		0.75[b]	0.59−0.94	−	
L3 LTPMA	−		−		−		−		−		−		0.74[b]	0.58−0.93

Creatinine level and HU values are transformed to one-tenth values. The effect of area and volume parameters is presented as per cm^2 and cm^3, respectively. HR estimated from Cox hazard regression model.

dx, dexter; rAAA, ruptured abdominal aortic aneurysm; sin, sinister; TIA, transient ischemic attack; TPMA, total (sin and dx) psoas muscle area.

[a]Indicates significant difference $P < 0.001$.

[b]Indicates significant difference $P < 0.05$.

[c]Indicates significant difference $P < 0.01$.

Supplementary Table III. Multivariable Cox regression analysis of overall mortality

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
Variables	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09	1.06[a]	1.03–1.09
Gender	0.61	0.31–1.19	0.57	0.29–1.12	0.47[b]	0.23–0.95	0.49[b]	0.24–0.98	0.48[b]	0.24–0.96	0.43[b]	0.21–0.88	0.44[b]	0.22–0.89
BMI	0.98	0.93–1.03	0.98	0.93–1.04	1.00	0.95–1.05	1.00	0.82–1.05	0.99	0.94–1.05	1.00	0.94–1.05	0.99	0.98–0.99
CT parameter														
L3 sin PMD	0.76[c]	0.63–0.91	–		–		–		–		–		–	
L3 TPMD	–		0.76[c]	0.63–0.92	–		–		–		–		–	
L2 dx LPMA	–		–		0.96[c]	0.94–0.99	–		–		–		–	
L2 LTPMA	–		–		–		0.98[c]	0.97–1.00	–		–		–	
L3 dx LPMA	–		–		–		–		0.97[c]	0.96–0.99	–		–	
L3 sin LPMA	–		–		–		–		–		0.97[a]	0.95–0.99	–	
L3 LTPMA	–		–		–		–		–		–		0.98[a]	0.98–0.99

Creatinine level and HU values are transformed to one-tenth values. The effect of area and volume parameters is presented as per cm^2 and cm^3, respectively. HR estimated from Cox hazard regression model. Other covariates included in the model are rAAA, smoking, stroke or TIA, creatinine, ASA, anticoagulant, and statin.
dx, dexter; rAAA, ruptured abdominal aortic aneurysm; sin, sinister; TIA, transient ischemic attack; TPMA, total (sin and dx) psoas muscle area.
[a]Indicates significant difference $P < 0.001$.
[b]Indicates significant difference $P < 0.05$.
[c]Indicates significant difference $P < 0.01$.

PUBLICATION II

Developing sarcopenia predicts long-term mortality after elective endovascular aortic repair

Lindström, I., Khan, N., Vänttinen, T., Peltokangas, M., Sillanpää, N., Oksala, N.

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Developing sarcopenia predicts long-term mortality after elective endovascular aortic aneurysm repair

Check for updates

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ABSTRACT

Background: Preoperatively detected sarcopenia as reflected by psoas muscle area (PMA) is associated with postoperative mortality after abdominal aortic aneurysm (AAA) repair. We studied, whether changes in PMA and lean PMA (LPMA) after endovascular aortic repair (EVAR) are associated with postoperative survival.

Methods: In 122 AAA patients treated between 2008 and 2016 (90% male; median age, 77.8 years; interquartile range, 11.5; rupture 2.5%) PMA and LPMA at L3 level were measured retrospectively from preoperative and 1- and 3-year follow-up computed tomography (CT) studies. The median duration of follow-up was 6.0 years (interquartile range, 3.5) and all-cause mortality was 46.7%. Association of radiologic muscle parameters with all-cause mortality was evaluated with Cox regression. Clinical data were collected from an institutional database and patient record databases.

Results: There was a significant decrease in PMA and LPMA at L3 level (mean, -4.4 cm^2 [-26.8%] for PMA and -130.4 cm^2 $\times$ Hounsfield units [-21.6%] for LPMA, respectively; $P < .001$) and the greatest decline occurred during the first postoperative year after EVAR. Relative PMA change during follow-up (ΔPMA/baseline CT muscle parameter) was independently associated with mortality in multivariable analysis (hazard ratio, 0.977 for a 1% unit increase; 95% confidence interval, 0.960-0.995; $P = .011$).

Conclusions: The most significant loss of skeletal muscle occurs during the first year after EVAR. The relative change in PMA from baseline is an independent predictor of mortality. For every 10% unit increase in ΔPMA/baseline CT muscle parameter bilaterally, there was a 21% decrease in the probability of death during follow-up. Early detection (from CT studies) and prevention of sarcopenia may potentially improve survival in EVAR-treated patients. (J Vasc Surg 2020;71:1169-78.)

Keywords: Abdominal aortic aneurysm; CT measurement; Sarcopenia; Psoas muscle

Increasing interest in patient selection for abdominal aortic aneurysm (AAA) repair has subsequently set the focus on developing novel and improved risk stratification methods. The basis of risk assessment in aneurysm patients is formed by the balance between the risk of rupture, associated mostly with aneurysm diameter, and the operative risks. Especially after the introduction of endovascular aortic repair (EVAR) characterized by low operative mortality[1-5] and early survival benefit over open repair (OR),[4-6] the value of considering life expectancy and quality is highlighted. Survival after elective EVAR is influenced by several known factors such as age, sex, and comorbidities like diabetes mellitus, renal insufficiency, congestive heart failure, and chronic obstructive pulmonary disease.[2,7-9] During the early years after operation, the risk of perioperative death after elective EVAR is smaller than that of OR,[1,3-5,10] but the long-term mortality is greater in EVAR patients compared with OR patients.[11] The ability to identify the factors that independently affect patients' late survival will help to optimize patient and treatment selection. Because EVAR is associated with a reintervention rate of up to nearly one-third,[10,11] more information is needed to identify patients who truly benefit from additional procedures.

Sarcopenia, the age-associated decrease in skeletal muscle mass, quality, and strength, seems to be useful when estimating postoperative survival in addition to perioperative and surgical risk scores.[12-16] It has been proven to be an independent risk factor of postoperative mortality also after EVAR,[15,17-23] although there is a lack of consensus regarding the definition of sarcopenia and the methods for estimating it vary a great deal.[12,15,24] Psoas muscle area (PMA) and lean PMA (LPMA) estimated from axial computed tomography (CT) slices can, however, be considered as one of the most valid and

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reproducible methods to be applied in clinical work with low or nonexistent financial costs.[16,25]

The early recognition of sarcopenia and adequate interventions enable postponing the progression of the condition and positively influence the quality of life.[26-28] Detecting the depletion of the skeletal muscle area may help vascular surgeons to better identify high-risk patients and implement preventive preoperative therapies to improve the postoperative outcome. Our previous study showed that preoperatively measured L2 to L3 PMA and LPMA are valuable adjuncts in the prediction of postoperative survival in AAA patients with an LPMA increase of one standard deviation (SD) at L3 level found to be associated with a 26% decrease in the probability of death during follow-up.

These data indicate that sarcopenia as depicted by muscle status is a dynamic and potentially reversible process and could be regarded as an important factor when deciding on reoperations after EVAR. The purpose of this study was to address these issues using changes in PMA and LPMA as markers of advancing frailty in a cohort of patients treated for AAA with EVAR.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective analysis of prospectively collected registry data
- **Key Findings:** After 122 endovascular aortic aneurysm repairs, the absolute and lean psoas muscle area (PMA) at L3 level decreased (median, −4.4 cm^2 [−26.8%] and −130.4 cm^2 × Hounsfield units [−21.6%], respectively; $P < .001$). The greatest decrease occurred during the first year. During follow-up, relative PMA change was independently associated with mortality (hazard ratio, 0.977 for a 1% unit increase; $P = .011$). The absolute change in lean PMA and PMA were mostly associated with baseline muscle size.
- **Take Home Message:** The most significant loss of skeletal muscle occurs during the first year after endovascular aortic aneurysm repair. The relative change in PMA from baseline is an independent predictor of mortality. The absolute change is strongly modulated by baseline muscle size, suggesting that relative change is perhaps the best way to depict individual muscle loss.

METHODS

This retrospective study adhered to the ethical principles of the Declaration of Helsinki and was approved by the Pirkanmaa Hospital District Science Center. Owing to the nature of the study no informed patient consent was required or obtained.

Patients. This study is based on a subsample from the 301 randomly selected patients from all consecutive patients treated for AAA (n = 956) by OR or EVAR in the Tampere University Hospital between 2006 and 2016. The size of the original study sample (n = 301) was designed to be sufficiently powered to observe a significant association between psoas muscle parameters and mortality among patients treated for AAA (with a power of 0.95 and alpha of 0.05 for detecting significant differences between population tertiles).[22] For the specific purpose of this observational study, only the randomly selected patients treated by EVAR (n = 220) were considered. The final cohort included EVAR patients with available preoperative CT imaging 90 days before or 1 month after the index operation as well as follow-up CT imaging at the earliest 10 months postoperatively with no reinterventions between the CT scans. Exclusions were made for OR and missing follow-up CT scans. Furthermore, EVAR patients were excluded if they died before the first scheduled follow-up. Fig 1 presents an overview of the study sample and inclusion and exclusion criteria.

Our protocol of preoperative assessment entailed aortic imaging with contrast-enhanced CT for each patient. Control CT imaging was habitually conducted at 1 month and 2 years after EVAR. Patient selection for EVAR as opposed to open surgery was at the discretion of a multidisciplinary team led by a vascular surgeon. Overall, EVAR was preferred for older patients with a suitable anatomy in the elective setting. Anatomic suitability, in turn, was assessed by evaluating the length, shape, and configuration of the aneurysm neck as well as the access route through the iliac arteries. With respect to rupture/emergency cases, those with a suitable anatomy for a traditional endovascular approach and who were hemodynamically stable at admission were habitually treated with EVAR.

Image analysis, variables, and measurements. The CT images were reviewed using dedicated medical imaging workstations (Carestream Vue PACS viewer version 11.4.0.1253, Rochester, NY). Imaging techniques and appliances used for obtaining contrast enhanced aortic CT images have been described previously[22] (Supplementary Material, online only). The density and area of psoas muscles were measured from the arterial phase images from axial slices of 0.63 to 3.00 mm in thickness. Baseline and follow-up CT studies performed preoperatively or within 1 month of the operation, and 1 to 3 years after the operation were analyzed. Preferentially, the preoperative CT imaging study was used, but when preoperative images with the desired slice thickness were unavailable, the 1-month or earlier follow-up CT studies were evaluated (31.1% of cases) as the baseline imaging. Postoperative CT images were acquired as part of routine follow-up and inclusion criteria was at least 10 months between the operation and follow-up

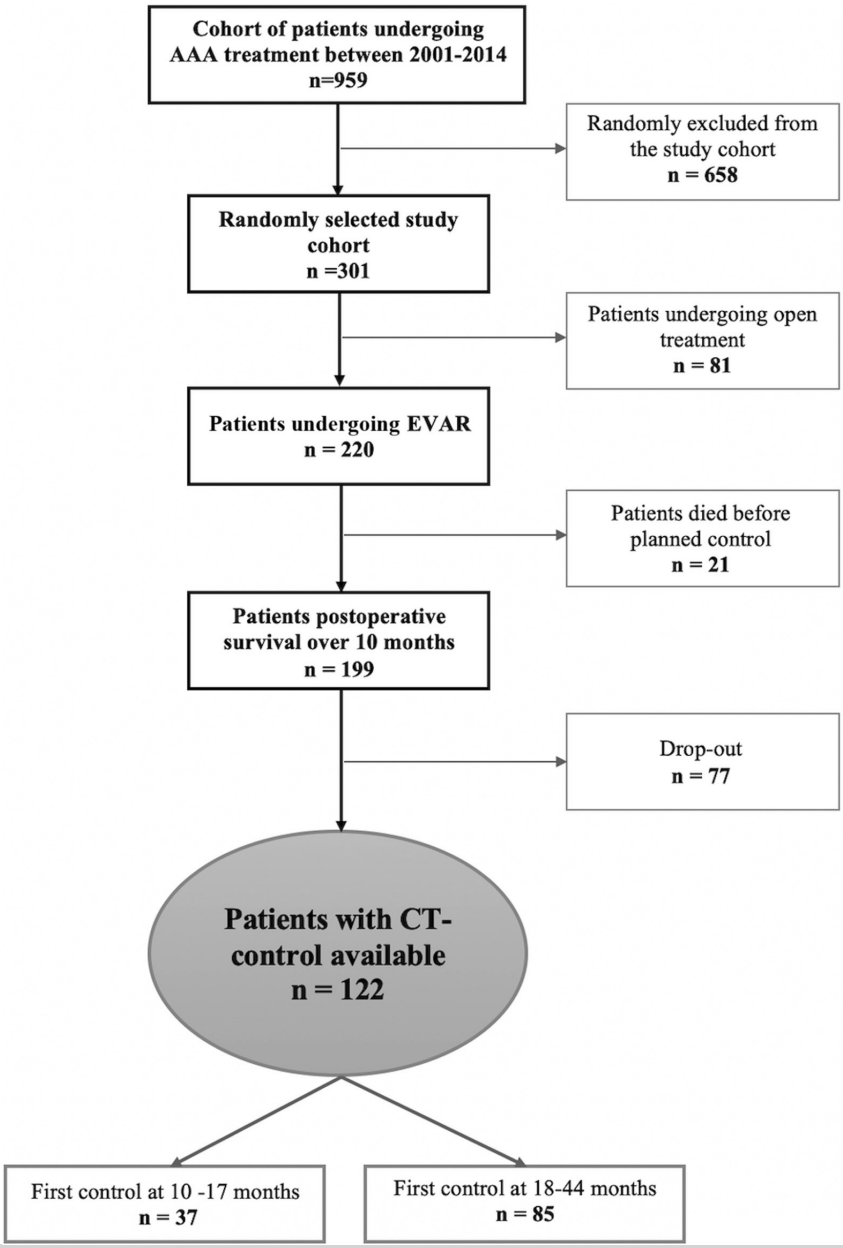

Fig 1. An overview of sample and inclusion/exclusion during the study. *AAA*, Abdominal aortic aneurysm; *CT*, Computed tomography; *EVAR*, endovascular aneurysm repair.

imaging. When various follow-up CT images were available (1, 2, and 3 years postoperatively), the earliest follow-up CT was used. The mean time difference between CT images was 1.9 years (SD, 0.61; median, 2.1; minimum, 10.5 months; maximum, 3.9 years).

The baseline and follow-up muscle parameters were evaluated by a single clinician observer who was blinded to patient outcome. In our previous study, the reproducibility and prognostic value of the repeated measurement of the psoas muscles at the L2 to L3 level

was tested and the method was deemed applicable to routine clinical work.[22] PMA was measured from axial one image slice at the L3 level. A representative axial slice for each vertebral level was chosen at the level of origin of the transverse processes. Regions of interest (ROIs) that separately outlined the psoas muscles were manually drawn freehand from both sides individually and they were combined to represent total PMA. The idea was to isolate the muscle according to the anatomic boundaries in axial images. This technique produced a report giving the cross-sectional area outlined by the ROI and the mean density in Hounsfield units (HUs) along with the SD.

The overall muscle density was calculated as the mean of both sides at the same vertebral level. Threshold limitations for the ROI were not set to avoid excluding intramuscular fat. Density thresholds for tissue characterizations inside the ROI were set as follows: 20 to 80 HU normal muscle, 1 to 19 HU lower density muscle, 0 HU water, −1 to −29 HU fatty muscle, and −30 to −50 HU fatty connective tissue. LPMA was defined as the product of muscle area and average density ($cm^2 \times$ HU). If the muscle density was 0 or below, the lean value was set as zero.

The difference between the baseline CT (CT1) and follow-up CT (CT2) parameter values (Δparameter) was calculated by subtracting the baseline muscle parameter value from the follow-up value. Relative change in the muscle values (Δparameter/baseline CT muscle parameter [BL]), in turn, was calculated as follows: Δparameter/BL.

Statistical analysis. Statistical analyses were performed with SPSS 25 for Mac OS X (Apple, Cupertino, Calif). The data were tested for normality applying Levene's test and the distribution of the muscle parameters were visualized using histograms. The Student *t*-test was conducted to test muscle parameters between different timepoints. For data not normally distributed nonparametric tests were selected. Group comparisons of continuous variables were performed using the Mann-Whitney *U* test for two independent samples, the Wilcoxon signed-rank test, and paired *t*-test for dependent samples, and the Kruskall-Wallis test for two or more independent samples.

The association of the variables with overall survival after the follow-up was analyzed with the Cox regression analysis first by univariable analyses (Supplementary Table I, online only). All variables were checked with log-minus-log plots to confirm proportional hazard assumption. Furthermore, Pearson correlation coefficient was computed to evaluate the linear correlation between the other variables and each muscle parameter and if the correlation was $P < .5$, the parameter was chosen for multivariable analyses using backward selection algorithm. The multivariable models testing the independent associations of risk factors with mortality were as follows: model 1 was adjusted only for age and model 2 for all factors associated with mortality in univariable analyses ($P < .1$).

Muscle parameters were calculated as absolute values and muscle parameter changes both as absolute and relative values. The absolute muscle parameters were normalized with standard z-scoring for multivariable Cox regression analysis. Using this standardization (mean value set to zero with value one denoting one SD from mean) all reported hazard ratio (HR) estimates for mortality correspond to a one SD increase in the exposure variables. Results were regarded as statistically significant if $P < .05$. Intraclass correlation coefficient for the muscle area measurements was tested in our previous study and it was found to be excellent for the used parameters[22] (Supplementary Table II, online only).

RESULTS

Patient demographics. The study cohort consisted of 122 patients. Follow-up lasted until September 1, 2018 (minimum, 10 months; maximum 12 years). The mean ± SD age at the time of follow-up was 77.0 ± 8.7 years and the majority of patients (90.0%) were male. At the time of intervention hypertension (62.3%) and coronary artery disease (59.8%) were the most prevalent baseline conditions. The mean ± SD aneurysm diameter was 6.1 ± 12.3 (median, 59 mm; interquartile range, 11). Procedural variables were similar between men and women (Table I). As expected, men were on average taller and had higher body surface area (BSA) than women. Women were significantly older (mean 74.3 years vs 82.3 years; $P = .001$).

The majority of exclusions were due to OR (n = 81) or missing EVAR follow-up CT scans (n = 77), comprising mainly patients whose follow-up was conducted in their nearest tertiary centers for practical reasons. Nevertheless, these excluded EVAR patients did not differ significantly in the demographic parameters compared with the included patients (Supplementary Table III, online only). Furthermore, there was no difference in the five-year survival rate between excluded and included patients ($P = .210$), suggesting that the exclusion of these 77 patients did not result in significant selection bias. Patients without follow-up CT scans at 10 months or later after EVAR owing to early death (n = 21) had significantly lower psoas muscle density bilaterally (mean, 25.8 HU vs 31.4 HU; $P = .021$) and worse renal function (mean creatinine 156 vs 104; $P = .015$) when compared with included patients. Otherwise there were no significant differences in baseline features. Patients' pharmacotherapy is presented in Supplementary Table IV (online only). As compared with the cohort in our previous study,[22] the present cohort was more often prescribed statin medication

Table I. Patient demographics and risk factors

Features	Sample (N = 122)
Demographics	
Age, years	77.0 ± 8.7
Male	110 (90)
Height, m	1.74 ± .07
BMI	26.9 ± 4.1
BSA, m^2	1.99 ± 0.18
Risk factors	
Previous intervention	7 (5.7)
Smoking	26 (21.3)
CAD	73 (59.8)
DM	15 (12.3)
Hypertension	76 (62.3)
Dyslipidemia	56 (45.9)
Pulmonary disease	29 (23.8)
Stroke or TIA	10 (8.2)
Creatinine level, μmol/L	99 ± 66
Procedural variables	
AAA diameter, mm	61.3 ± 12.3
AAA neck length, mm	35.0 ± 18.1
AAA neck diameter, mm	23.9 ± 8.0
rAAA	3 (2.5)
ASA 2	8 (6.6)
ASA 3	82 (67.2)
ASA 4	29 (23.8)
ASA 5	3 (2.5)
Time of the first FU CT control, years	
1	38 (31.1)
2	78 (63.9)
3	6 (4.9)
Δt between baseline and FU CT scans, years	1.9 ± 0.6
Number of all FU CT-controls	
Baseline	122
1 year	38
2 year	96
3 year	19

AAA, Abdominal aortic aneurysm; *ASA*, American Society for Anesthesiologists classification; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CT*, computed tomography; *DM*, diabetes mellitus; *FU*, follow-up; *RAAA*, ruptured abdominal aortic aneurysm; *TIA*, transient ischaemic attack.
Results are presented as mean ± standard deviation or number (%).

(50.3% vs 63.9%, $P < .019$), but no other significant differences in pharmacotherapy were observed.

As previously demonstrated,[22] age and sex were significantly associated with muscle parameters at baseline (Supplementary Table V, online only) with age being inversely correlated with PMA and LPMA ($P < .001$ for both) and men having higher PMA and LPMA compared with women.

Table II. Psoas muscle parameters at the L3 level at baseline and in the follow-up computed tomography (*CT*) scan

Variable	PMA, cm^2	LPMA, $cm^2 \times U$
Baseline CT		
Mean	16.7	537.7
SD	4.4	254.9
Minimum	7.15	0.0
Maximum	28.6	1570.8
FU CT		
Mean	12.5	407.2
SD	4.2	197.5
Minimum	4.5	0.0
Maximum	24.4	905.1
Difference (FU minus baseline)		
Mean	−4.4	−130.4
SD	3.7	183.6
P value	<.001[a]	<.001[a]

FU, Follow-up; *LPMA*, lean psoas muscle area; *PMA*, psoas muscle area; *SD*, standard deviation.
Paired *t*-test for identifying significant differences of mean values between baseline and follow-up CT images.
[a]Statistically significant.

Changes in muscle parameters between the perioperative and the first follow-up CT. The absolute changes in psoas muscle parameters between the perioperative CT and the first follow-up CT are presented in Table II, which shows that the mean values for both absolute PMA as well as LPMA decreased significantly between the imaging studies ($P < .001$). These differences in absolute values translate into proportional changes of −26.8% in ΔPMA and −21.6% in ΔLPMA.

Despite the significant associations observed between age, gender. and psoas muscle parameters at baseline, they were not associated with absolute change in psoas muscle parameters (ΔPMA and ΔLPMA; Supplementary Table V, online only). The only variables associated with ΔPMA and ΔLPMA were PMA and LPMA values at baseline. The fact that absolute change is strongly modulated by baseline muscle size suggests that relative change is perhaps the best way to depict individual muscle loss. Furthermore, all the survival analyses were tested by excluding postoperative studies as the baseline demonstrating the sensitivity of the analyses and the results remained practically the same (Supplementary Material, online only).

The association between follow-up time and muscle parameter changes. In a cross-sectional analysis of the measurement of the entire study population, PMA and LPMA values at the 1-year follow-up were clearly and statistically significantly lower compared with the baseline (Fig 2). However, in subsequent measurements at follow-up visit at 2 or 3 years the population median

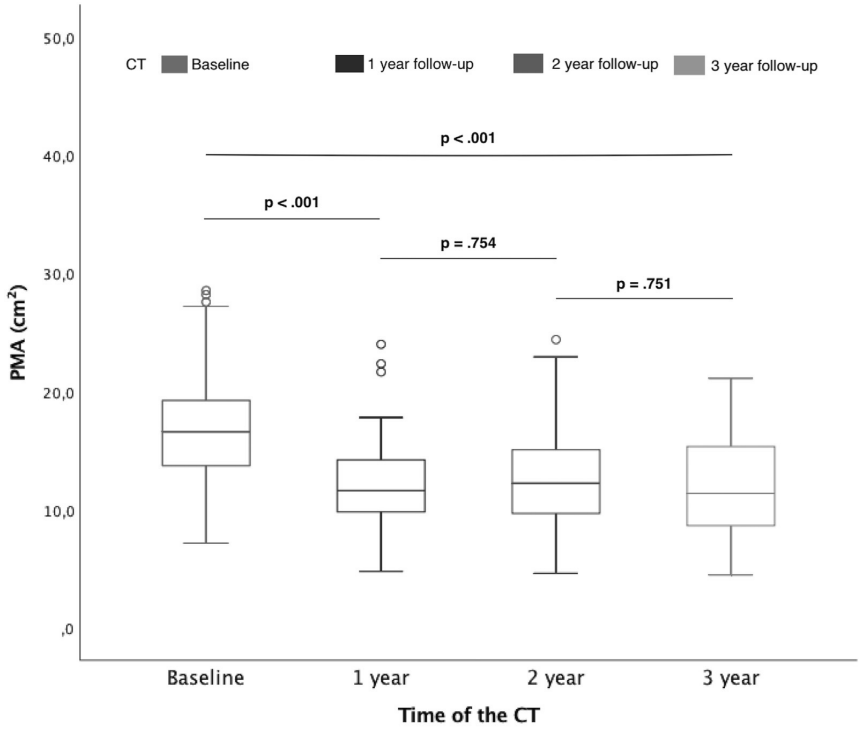

Fig 2. The association of psoas muscle area (PMA) at baseline with PMA at the 1-, 2-, and 3-year follow-up imaging. Comparisons of PMA between baseline and 1-year follow-up and baseline and 3-year follow-up as well as comparisons between 1- and 2-year follow-up and 2- and 3-year follow-up were all cross-sectional and performed by applying the *t*-test. The cross-sectional method was selected owing to the fact that all patients were not habitually subjected to follow-up computed tomography (*CT*) imaging every year.

values no longer decreased as substantially as during the first time interval (Fig 2). Similarly using cross-sectional data, ΔPMA/BL and ΔLPMA/BL were not significantly different between the 1- to 2-year or 3-year follow-up studies, which is shown for the PMA in Fig 3. Table III shows ΔPMA and ΔLPMA during follow-up among patients with repeated measurements (n = 37) from baseline to different time points (actual longitudinal data). The greatest decrease in PMA (mean ΔPMA, −4.1 cm^2; $P < .001$) and LPMA (mean ΔLPMA, 118.7; $P = .001$) occurred during the first postoperative year after EVAR.

Association of CT measurements with mortality. The median follow-up time was 6.0 years (interquartile range, 3.5) and the overall mortality rate was 46.7% (57/122 patients; Fig 4). Both PMA and LPMA were significantly associated with long-term mortality. LPMA persisted even after adjusting for age (HR, 0.74; 95% confidence interval [CI], 0.54-1.00). However, this was not the case after accounting for other factors found significant in the univariable analyses—age, BSA, and stroke or transient ischemic attack (HR, 0.77; 95% CI, 0.56-1.05; $P = .095$; Table IV). Interestingly, when ΔPMA/BL and ΔLPMA/BL were added to the model, the only independent risk factor identified was ΔPMA/BL (HR of 0.977 for a 1% unit increase in ΔPMA/BL with 95% CI between 0.960 and 0.995; $P = .011$), indicating that previously developed sarcopenia is a stronger predictor of mortality than the state of muscle at follow-up (Table V). The magnitude of the association translates into an increase in the risk of death by approximately one-fifth, with each 10% unit decrease in PMA between baseline and the first follow-up. Results were also confirmed by further adjusting the multivariable model with age, gender, BSA, CAD, diabetes mellitus, dyslipidemia, hypertension, and smoking, which are known to influence muscle size and the result for ΔPMA/BL was even stronger (Supplementary Table VI, online only). Further adjustment of PMA measured at the time of EVAR did not change the significant association between ΔPMA/BL and mortality, but showed that baseline PMA was no longer an independent risk factor for mortality in this population of patients surviving to the first CT control.

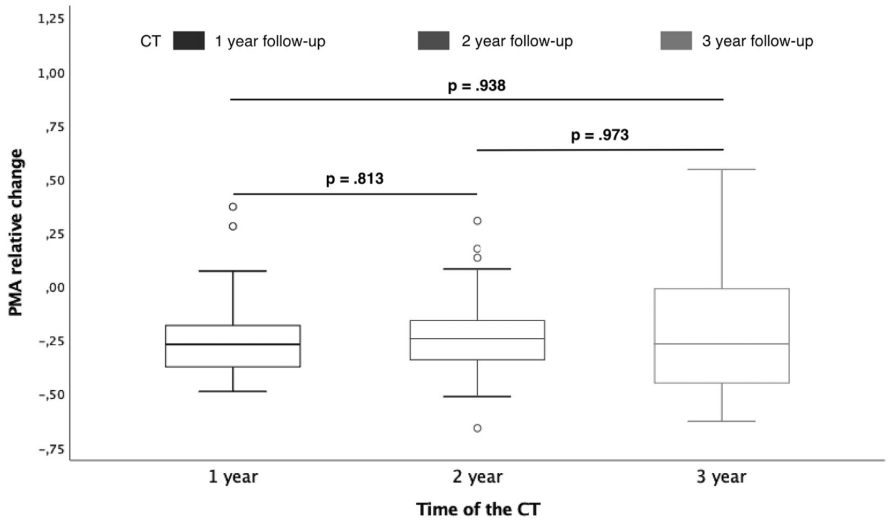

Fig 3. The association between relative psoas muscle area (PMA) changes (ΔPMA/BL) at the 1-, 2-, and 3-year follow-up imaging. Comparison between relative PMA changes were cross-sectional and performed with the Mann-Whitney *U* test. *BL*, Baseline computed tomography (*CT*) muscle parameter.

Table III. Comparison psoas muscle parameters at L3 level between consecutive computed tomography (*CT*) studies

	L3 ΔPMA, cm^2	L3 ΔLPMA, $cm^2 \times HU$
Difference baseline − 1-year FU (n = 37)		
Mean difference	−4.1	−118.7
P value	<.001[a]	.001[a]
Difference 1-year − 2-year FU (n = 17)		
Mean difference	−1.3	−66.8
P value	.003[a]	.012[a]
Difference I year− III year FU (n = 13)		
Mean difference	0.7	−20.1
P value	.056	.055

FU, Follow-up; *ΔPMA*, psoas muscle area change; *ΔLPMA*, lean psoas muscle area change.
Muscle parameters changes were measures between baseline and the follow-up CT studies. Paired *t*-test for identifying significant difference between mean values.
[a]Statistically significant.

DISCUSSION

This is, to the best of our knowledge, the first study to describe how sarcopenia as depicted by the decrease in PMA and lean muscle area advances after EVAR and how this change in muscle area predicts survival. The most significant factor associated with the absolute decrease in these parameters is baseline psoas muscle size. After considering the baseline muscle status, the relative decline in psoas muscle surface areas is the strongest muscle parameter associated with long-term survival after EVAR.

The present study demonstrated that PMA and LPMA decreased most significantly during the first year of follow-up. Furthermore, the relative change of PMA was independently associated with long-term survival after EVAR. In our data, every 10% unit decrease in relative PMA change from baseline increased the probability of death by 21% after clinical follow-up. The fact that the loss of skeletal muscle occurred mostly during the first year suggests that possible interventions to counteract sarcopenia should be used early or even potentially before the operation, for example, via nutritional intervention and physical exercise.[28] This is highlighted by the fact that up to one-third of EVAR patients need reoperations.[10,11] Thus, methods for improving survival by targeted interventions after these procedures could prove highly beneficial. Supporting this finding, previous studies have shown that the process of sarcopenia could be slowed down or even reversed in cachectic and sarcopenic patients with cancer.[29,30]

Taking into account the significant number of reoperations often required after EVAR, if the process of sarcopenia could not be slowed down by any intervention, long-term survival should be evaluated critically before subjecting patients to repeated interventions near the end of their life. However, using only one risk factor such as developing sarcopenia is hardly sufficient to stratify patients when considering eligibility or ineligibility for possible repeat interventions. Nevertheless,

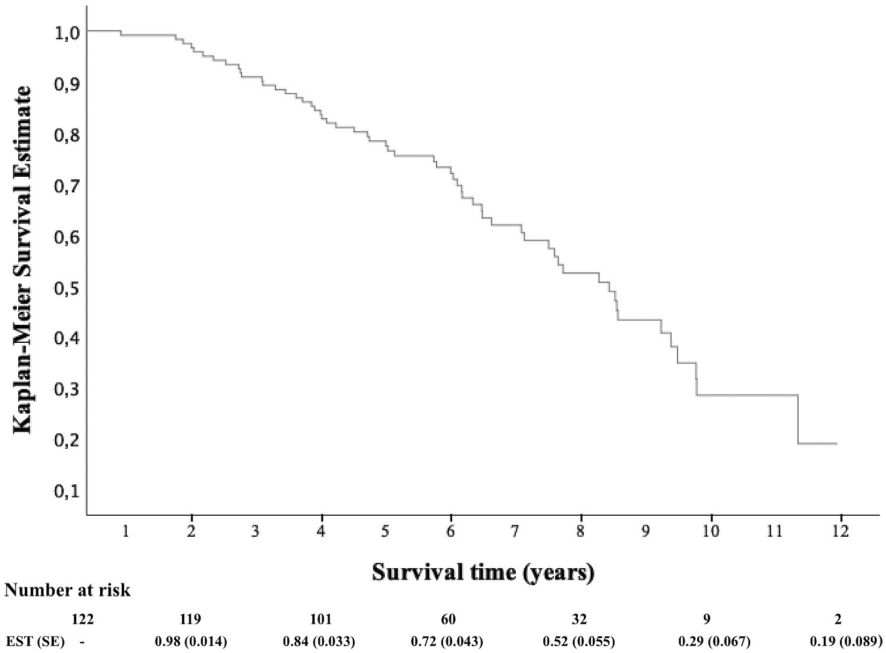

Fig 4. Overall survival with Kaplan-Meier method, N = 122. *EST*, Estimated survival; *SE*, standard error.

decreased relative PMA can be considered as one of the indicators of impaired survival and it is possible prognostic value should be evaluated in relation to the patient's overall state of health (ie, other major factors associated with perioperative and postoperative survival).[10,11] Unfortunately, the size of the present study does not allow for inferring any clear clinical thresholds for critical reduction in muscle size in relation to survival and more research is required applying larger sample sizes.

When comparing the sexes, women had a tendency to have smaller PMA and LPMA at baseline and follow-up, which fits well to previous studies.[22,31-35] However, the relative change in PMA or LPMA in reference to baseline did not seem to be markedly different between men and women. In fact, the strongest factor that associated with the absolute change in LPMA and PMA was baseline muscle size. The explanation for this finding is most likely that larger muscle can change more in size than smaller muscle in absolute terms, but the relative change is constant regardless of baseline muscle size. Therefore, the relative change is most likely the most accurate measure of developing sarcopenia, a hypothesis supported by the results of this study.

Previous studies have demonstrated the association between preoperatively measured PMA and late survival in EVAR and OR-treated AAA patients.[6,14,16,22,35,36] Only one previous study has failed to demonstrate a significant association.[37] However, previous research has not paid attention to postoperative changes in muscle size after the operation. According to our results, it is important to observe muscle depletion when considering prognostic relevance of sarcopenia because EVAR patients are at risk of requiring reoperation. Supporting this finding, in our analyses the baseline PMA or LPMA were not associated significantly with mortality if the dynamic change in them was considered in the analysis. Additionally, purely weight and thus resulting BSA changes do not adequately reflect changes in body composition in cases of muscle tissue conversion to adipose tissue or pathologic accumulation of fluid, such as ascites or pulmonary edema. Sarcopenia could be detected from CT images before the development of clinically noticeable signs of advanced muscle loss (eg, weight or BMI), enabling early preventive measures.

Baseline CT images 0 to 90 days before EVAR were preferred, but in 31.1% of cases 1 month or earlier postoperative images had to be used as baseline CT scans because preoperative imaging studies were unavailable. Considering the finding that sarcopenia seems to advance most rapidly during the first postoperative year, it is plausible that the inclusion of patients with only postoperative images available possibly caused bias toward weaker results.

This single-center retrospective observational study has inherent limitations. Owing to its retrospective nature,

Table IV. Unadjusted and adjusted associations between z-scored muscle parameters and survival using cox-regression in follow-up computed tomography (*CT*) studies

	Follow-up CT					
	L3 PMA			L3 LPMA		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted	0.609	0.45-0.83	.001	0.633	0.48-0.84	.001
Model 1	0.748	0.54-1.03	.078	0.735	0.54-1.00	.046
Model 2	0.784	0.55-1.12	.180	0.767	0.56-1.05	.095

CI, Confidence interval; *LPMA*, lean psoas muscle area; *PMA*, psoas muscle area.
Model 1 adjustments were made for age. Model 2 was adjusted for all factors associated with mortality in univariable analyses ($P < .1$).
The effect of area is presented as cm^2 and lean values as $cm^2 \times$ Hounsfield Units. Hazard ratio (HR) estimated from Cox hazard regression model. The reported hazard ratios for muscle parameters correspond a 1-standard deviation increase. CI of the estimated HR.

Table V. Survival analysis of muscle parameters changes with calculation of hazard ratios (*HRs*) using Cox regression

	L3 ΔPMA/BL			L3 ΔLPMA/BL		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted	0.975	0.96-0.99	.002	0.996	0.991-1.005	.628
Model 1	0.977	0.96-0.99	.009	0.996	0.989-1.004	.325
Model 2	0.977	0.96-0.99	.011	0.996	0.989-1.004	.348

BL, Baseline CT muscle parameter; *CI*, confidence interval; *ΔLPMA*, lean psoas muscle area relative change; *ΔPMA*, psoas muscle area relative change.
Model 1 was adjusted for age. Model 2 was adjusted for all factors associated with mortality in univariable analyses ($P < .1$).
Muscle parameter changes (Δparameter) were obtained by subtracting baseline parameter values from the first follow-up CT studies. The effect of parameter changes were calculated as ratios of the baseline values. HR estimated from Cox hazard regression model. CI of the estimated HR.

missing data such as follow-up weight, nutritional habits, and physical exercise could not be analyzed. However, the vascular registry providing the clinical baseline data was collected prospectively by treating physicians. As mentioned, the entire EVAR population of the previous study was not investigated, owing to unavailable follow-up CT images. However, we found no differences in the 5-year survival rate between excluded and included EVAR patients and there was no significant difference in the overall baseline profiles, suggesting only minimal or nonexistent selection bias. Because CT images were used, the timing and volume of the contrast agent may have influenced the density measurements besides muscle perfusion. Additionally, as with the majority of AAA studies, women were underrepresented owing to the epidemiology of the condition, which can make the results less generalizable to female patients.

CONCLUSIONS

Dynamic PMA measurements offer an easily applicable prognostic tool for vascular surgeons in the clinical setting and relative muscle change (in reference to baseline) seems to be the best way to evaluate individual muscle loss. The greatest decline in skeletal muscle size occurs during the first postoperative year. Whether the role of sarcopenia in patients undergoing endovascular treatment for AAA as a risk factor is more of a modifiable or a prognostic one requires further research in this patient cohort.

AUTHOR CONTRIBUTIONS

Conception and design: IL, SP, NK, NS, JH, NO
Analysis and interpretation: IL, JH, NO
Data collection: IL, SP, NK, NS, NO
Writing the article: IL, NO
Critical revision of the article: SP, NK, NS, JH, NO
Final approval of the article: IL, SP, NK, NS, JH, NO
Statistical analysis: IL, JH
Obtained funding: NO
Overall responsibility: NO

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APPENDIX (online only).

Supplementary material: Survival analyses with and without 30-day or earlier postoperative computed tomography (CT) scanning as a baseline study

Up to 31.1% of the patients had a 30-day or earlier postoperative computed tomography (CT) study as the baseline study on account of the unavailability of preoperative imaging with the required slice thickness. Nevertheless, no differences in psoas muscle area (PMA) and lean psoas muscle area (LPMA) were noticed between preoperative studies and postoperative studies at the baseline. Furthermore, all the survival analyses were tested by excluding postoperative studies as the baseline demonstrating the sensitivity of the analyses and the results remained practically the same. In these analyses, *P* values did not markedly differ and there were almost no changes in significances which were set at $P < .05$ (Modified Tables IV and V). Only in the L3 ΔPMA model 2 the result was slightly more than the appointed significance (for all patients: hazard ratio [HR], 0.784; 95% confidence interval [CI], 0.55-1.12; $P = .18$, and without postoperative baseline CTs: HR, 0.708; 95% CI, 0.45-1.00; $P = .055$).

Modified Table IV (online only). Adjusted and unadjusted associations between z-scored muscle parameters and survival using Cox regression in follow-up computed tomography (*CT*) studies both in whole cohort and excluding postoperative baseline CT studies

	Follow-up CT					
	L3 PMA			L3 LPMA		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted (all patients)	0.609	0.45-0.83	.001	0.633	0.48-0.84	.001
Unadjusted (no postoperative baseline CTs)	0.545	0.37-0.80	.002	0.533	0.36-0.80	.002
Model 1 (all patients)	0.748	0.54-1.03	.078	0.735	0.54-1.00	.046
Model 1 (no postoperative baseline CTs)	0.517	0.26-1.05	.066	0.634	0.41-0.98	.040
Model 2 (all patients)	0.784	0.55-1.12	.180	0.767	0.56-1.05	.095
Model 2 (no postoperative baseline CTs)	0.708	0.45-1.11	.132	0.661	0.43-1.03	.066

CI, Confidence interval; *HR*, hazard ratio; *LPMA*, lean psoas muscle area; *PMA*, psoas muscle area.
Model 1 adjustments were made for age. Model 2 was adjusted for all factors associated with mortality in univariable analyses ($P < .1$).
The effect of area is presented as cm^2 and lean values as $cm^2 \times$ Hounsfield units. The HR is estimated from the Cox hazard regression model. The CI is of the estimated HR.

Modified Table V (online only). Survival analysis of muscle parameters changes with calculation of hazard ratios (*HR*) using Cox regression both in whole cohort and excluding postoperative baseline computed tomography (*CT*) studies

	L3 ΔPMA/BL			L3 ΔLPMA/BL		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Unadjusted (all patients)	0.975	0.96-0.99	.002	0.996	0.99-1.01	.628
Unadjusted (no postoperative baseline CTs)	0.978	0.96-0.99	.026	0.993	0.98-1.01	.229
Model 1 (all patients)	0.977	0.96-0.99	.009	0.996	0.99-1.00	.325
Model 1 (no postoperative baseline CTs)	0.979	0.96-1.00	.048	0.989	0.98-1.00	.102
Model 2 (all patients)	0.977	0.96-0.99	.011	0.996	0.99-1.00	.348
Model 2 (no postoperative baseline CTs)	0.980	0.96-1.00	.055	0.988	0.99-1.00	.080

BL, Baseline CT muscle parameter; *CI*, confidence interval; *ΔLPMA*, lean psoas muscle area relative change; *ΔPMA*, psoas muscle area relative change.
Model 1 was adjusted for age. Model 2 was adjusted for all factors associated with mortality in univariable analyses ($P < .1$).
Muscle parameter changes (Δparameter) were obtained by subtracting baseline parameter values from the first follow-up CT studies. The effect of parameter changes were calculated as ratios of the baseline values. The HR is estimated from the Cox hazard regression model. The CI is of the estimated HR.

Supplementary Table I (online only). Univariable Cox regression analysis of overall mortality

Risk factor	HR	95% CI	*P* value
Age	1.08	1.04-1.12	<.001[a]
Gender	1.16	0.52-2.57	.719
Height	0.98	0.95-1.02	.338
BSA	0.24	0.05-1.18	.079[b]
Previous operation	1.57	0.57-4.36	.387
Smoking	0.78	0.40-1.52	.470
CAD	1.01	0.59-1.72	.969
DM	0.85	0.36-1.98	.699
Hypertension	0.77	0.45-1.33	.352
Dyslipidemia	0.71	0.41-1.22	.212
Pulmonal disease	1.00	0.54-1.87	.991
Stroke or TIA	3.62	1.49-9.77	.004[a]
Creatine level	0.99	0.99-1.01	.245
Aneurysm diameter	1.02	0.99-1.04	.148
Aneurysm neck length	1.01	0.99-1.03	.333
Aneurysm neck diameter	1.01	0.98-1.04	.470
ASA score			
I	0.76	0.23-2.49	.649
II	1.40	0.41-4.78	.594
III	1.86	0.19-18.08	.593

ASA, American Society for Anesthesiologists Classification; *BSA*, body surface area; *CAD*, coronary artery disease; *CI*, confidence interval; *DM*, diabetes mellitus; *EVAR*, endovascular aortic repair; *HR*, hazard ratio; *rAAA*, ruptured abdominal aortic aneurysm; *TIA*, transient ischaemic attack.
The HR is estimated from the Cox hazard regression model. The CI is of the estimated HR. Variables demonstrating significant associations with mortality on univariate analysis ($P < .1$) were incorporated into multivariate analysis.
[a]< .01.
[b]$P < .1$.

Supplementary Table II (online only). Intraclass correlation coefficient (*ICC*) analysis of computed tomography (CT) measurements

L3	ICC[a]		ICC[b]		*P* value
Right psoas muscle					
Area	0.674	0.35-0.89	0.640	0.31-0.87	<.001
HU	0.765	0.49-0.92	0.778	0.52-0.93	<.001
Left psoas muscle					
Area	0.720	0.42-0.91	0.676	0.35-0.89	<.001
HU	0.691	0.37-0.89	0.693	0.38-0.89	<.001

HU, Hounsfield unit.
[a]Model: ICC two-way random consistency.
[b]Model: ICC two-way random absolute.

Supplementary Table III (online only). Patient demographics and risk factors between included and excluded endovascular aortic aneurysm repair (*EVAR*) and open treated patients

Features	Sample (N = 122)	Excluded EVAR (n = 98)	*P* value	EVAR (n = 220)	Open treated (n = 81)	*P* value
Demographics						
Age, years	75.1 ± 8.1	75.2 ± 7.9	.946	75.2 ± 8.0	69.0 ± 11.3	<.001
Male	110 (90)	86 (89)	.569	196 (89)	72 (88)	.960
Height, m	1.74 ± 0.07	1.73 ± 0.09	.180	1.74 ± 8.2	1.78 ± 8.2	<.001
BMI	26.9 ± 4.1	27.1 ± 4.9	.797	27.0 ± 4.5	25.4 ± 3.9	.006
BSA, m^2	1.99 ± 0.18	1.97 ± 0.23	.899	1.97 ± 0.22	1.99 ± 0.22	.629
Risk factors						
Previous intervention	7 (5.7)	8 (8.2)	.478	15 (6.8)	5 (6.2)	.842
Smoking	26 (21.3)	18 (18.4)	.587	44 (20.0)	27 (33.3)	.016
CAD	73 (59.8)	57 (58.2)	.802	130 (59.0)	23 (28.4)	<.001
DM	15 (12.3)	19 (19.4)	.148	34 (15.5)	7 (8.6)	.126
Hypertension	76 (62.3)	62 (63.3)	.882	138 (62.7)	54 (66.7)	.528
Dyslipidemia	56 (45.9)	44 (44.9)	.882	100 (45.9)	32 (39.5)	.358
Pulmonary disease	29 (23.8)	26 (26.5)	.638	55 (25.0)	13 (16.0)	.100
Stroke or TIA	10 (8.2)	15 (15.3)	.099	25 (11.4)	9 (11.1)	.951
Creatinine level, μmol/L	99 ± 66	122 ± 116	.082	109 ± 92	89 ± 46	.069
Procedural variables						
rAAA	3 (2.5)	3 (3.1)	.785	6 (2.7)	17 (21.0)	<.001
ASA 2	8 (6.6)	3 (3.1)		11 (5.0)	5 (6.1)	
ASA 3	82 (67.2)	55 (56.1)		137 (62.3)	39 (48.1)	
ASA 4	29 (23.8)	39 (39.8)		68 (30.9)	24 (29.6)	
ASA 5	3 (2.5)	1 (1.0)		4 (1.8)	13 (16.0)	

ASA, American Society for Anesthesiologists classification; *BMI*, body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CT*, computed tomography; *DM*, diabetes mellitus; *rAAA*, ruptured abdominal aortic aneurysm; *TIA*, transient ischaemic attack.
Results are presented as mean ± standard deviation or number (%).
Statistically significant difference ($P < .05$, independent-samples *t*-test or χ^2 test).

Supplementary Table IV (online only). Study patients' (N = 122) medication(s)

Medication	No. (%)
Antiaggregant	63 (51.6)
Anticoagulant	28 (23.0)
Oral antidiabetic	14 (11.5)
Insulin	5 (4.1)
Beta blocker	72 (59.0)
Other antihypertensive	72 (59.0)
Statin	78 (63.9)
Glucocorticoid	7 (5.7)

Supplementary Table V (online only). The effect of age and gender on computed tomography (*CT*) measurements on operation *CT* and difference between operation and follow-up *CT*

	Age					Gender			
	T1	T2	T3						
	67.9	77.7	85.6	DM	*P* value	Male (n = 110)	Female (n = 12)	DM	*P* value
Baseline CT									
PMA, cm^2	18.8 ± 4.4	16.8 ± 4.3	14.9 ± 3.7	3.7	<.001[a]	17.3 ± 4.3	12.8 ± 3.1	5.0	<.001[b]
LPMA, $cm^2 \times$ HU	648.8 ± 276.2	542.6 ± 227.8	421.9 ± 207.9	226.9	<.001[a]	560.0 ± 251.5	337.4 ± 198.0	234.2	.002[b]
Difference between baseline and follow-up CT									
PMA, cm^2	−4.7 ± 5.2	−3.8 ± 2.9	−4.6 ± 2.4	0.1	.448	−4.4 ± 3.8	−4.0 ± 1.7	0.4	.474
LPMA, $cm^2 \times$ HU	173.9 ± 132.8	118.5 ± 168.3	98.8 ± 137.1	75.0	.196	134.4 ± 188.2	94.4 ± 139.2	40.0	.477

DM, Difference of means; *HU*, Hounsfield units; *LPMA*, lean psoas muscle area; *PMA*, (left and right) psoas muscle area; *SD*, standard deviation; *T*, tertile. Values are presented as mean ± SD unless otherwise noted.
[a]Statistically significant difference between the oldest and the youngest tertile ($P < .05$; 1-way analysis of variance).
[b]Statistically significant difference compared with males ($P < .05$; independent samples *t*-test).

Supplementary Table VI (online only). Multivariable Cox regression analysis of overall survival

	Model 1		Model 2	
Variables	HR	95% CI	HR	95% CI
Age	1.08[a]	1.04-1.13	1.10[b]	1.05-1.15
Gender	0.61	0.24-1.56	0.77	0.31-1.89
BSA	0.69	0.10-4.78	0.94	0.14-6.58
CAD	1.12	0.65-1.95	1.11	0.64-1.92
DM	0.66	0.27-1.65	0.64	0.26-1.57
Dyslipidemia	0.92	0.48-1.76	0.80	0.42-1.48
Hypertension	0.98	0.53-1.83	0.91	0.50-1.66
Smoking	1.17	0.57-2.40	1.29	0.64-2.60
Baseline parameter (PMA or LPMA)	0.99	0.91-1.07	1.00	0.92-1.08
L3 ΔPMA/BL	0.94[a]	0.16-0.55	–	
L3 ΔLPMA/BL	–		0.73	0.36-1.44

BL, Baseline CT muscle parameter; *BSA*, body surface area; *CAD*, coronary artery disease; *CI*, confidence interval; *DM*, diabetes mellitus; *HR*, hazard ratio; *LPMA*, lean psoas muscle area, *ΔLPMA/BL*, lean psoas muscle area relative change; *PMA*, psoas muscle area; *ΔPMA/BL*, psoas muscle area relative change.
The HR is estimated from Cox hazard regression model. The CI is of the estimated HR.
[a]$P < .01$.
[b]$P < .001$.

PUBLICATION III

Pre-operative masseter area is an independent predictor of long-term survival after carotid endarterectomy

Oksala, N., Lindström, I., Khan, N., Pihlajamäki, V., Lyytikäinen, L-P., Pienimäki, J-P., Hernesniemi, J.

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Pre-Operative Masseter Area is an Independent Predictor of Long-Term Survival after Carotid Endarterectomy

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WHAT THIS PAPER ADDS

Masseter muscle area (MA) can be measured reliably from pre-operative computed tomography angiography and is a significant predictor of long-term mortality after carotid endarterectomy, independent of other risk factors, anthropometric measures, and dental status. To understand its potential in risk stratification and long-term mortality, the results need to be validated in independent cohorts and studies powered to stratify for different indication categories.

Objective/Background: Sarcopenia is a predictor of mortality in elderly patients. Masseter area (MA) reflects sarcopenia in trauma patients. It was hypothesised that MA and Masseter density (MD) could be evaluated reliably from pre-operative computed tomography angiography (CTA) scans and that they predict post-operative survival in carotid endarterectomy (CEA) patients.

Methods: This was an observational registry study. Patients ($n = 242$) were operated on for asymptomatic stenosis ($n = 32$; 13.2%), amaurosis fugax ($n = 41$; 16.9%), transient ischaemic attack ($n = 85$; 35.1%), or ischaemic stroke ($n = 84$; 34.7%). Internal carotid artery stenoses were graded angiographically. Intraclass correlation coefficient (ICC) was used to analyse measurement reliability by three independent observers. Cox regression analysis was used to study the effect of MA and MD on survival (hazard ratio [HR]).

Results: Median patient age was 71.0 years (interquartile range [IQR] 13.0) and follow up time was 68.5 months (range 3–163 months); at the end of follow up (1 October 2017), 104 (43.0%) patients had died according to the National Population Register. The average MA (MAavg, the mean of left and right MA [median 394.0 mm^2; IQR 110.1 mm^2]) and MD (MDavg, the mean of left and right MD [median 53.5 HU; IQR 16.5 HU]) could be measured with excellent reliability (ICC > 0.865, $p < .001$ for all). In multivariable analyses only body surface area (BSA) ($p < .001$) and dental status were associated with MAavg ($p = .021$). Increased MAavg predicted lower mortality (HR 0.76, 95% confidence interval [CI] 0.61–0.96; $p = .023$) independent of age (HR 1.05, 95% CI 1.02–1.07; $p = 0.001$), female sex, body mass index, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth. MDavg was not associated with mortality. After further adjustment, BSA (the most significant determinant of MAavg) did not alter the association between MAavg and mortality (0.75, 95% CI 0.58–0.97; $p = .031$).

Conclusion: Average MA but not MD measured from the pre-operative CTA scan provides a reliable estimate of post-operative long-term survival in CEA patients independent of other risk factors, anthropometric measurements, and dental status.

Keywords: Carotid endarterectomy, Cerebrovascular disease, Computed tomography angiography, Muscle
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INTRODUCTION

The net benefit from carotid endarterectomy (CEA) is critically dependent on length of post-operative survival,[1] which in turn is influenced by several factors. Such factors include age, cardiovascular risk factors, chronic obstructive

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pulmonary disease, renal disease, body mass index (BMI), absence of statin use, and contralateral carotid occlusive disease.[1–5]

The biological state of reduced physiological reserve and increased vulnerability associated with age, i.e., frailty, reflects subclinical cardiovascular disease and has been found to be better than traditional surgical risk scores in estimating post-operative survival.[6–10] Frailty is an independent predictor of post-operative mortality in cardiovascular patients, doubling the risk of mortality and morbidity in patients with stable cardiovascular disease, acute coronary syndromes, heart failure, and surgical and other interventions.[9] Frailty can be estimated by measuring loss of muscle mass, i.e., sarcopenia, walking speed, and daily activity.[9]

Paraspinal muscle mass evaluated from computed tomography (CT) images predicted survival in patients undergoing elective open and endovascular abdominal aortic aneurysm repair,[11,12] and in general surgery and vascular patients.[13] Similarly, masseter muscle area (MA) measured from CT images predicted mortality and correlated well with psoas muscle area in elderly patients experiencing blunt trauma and traumatic brain injury.[14,15] In line with this, masseter muscle tension, chewing ability, dental status, and physical fitness have been shown previously to be closely associated in elderly care home residents.[16]

Sarcopenia related to stroke differs from that related to ageing in that it is characterised by rapid loss of muscle mass, structural alterations in the muscle, and bilateral difference in physical and functional performance determined by the brain lesion, whereas ageing related sarcopenia occurs slowly without structural alterations or bilateral differences.[17] In stroke patients, imbalanced neurovegetative status may also induce a direct catabolic signal to the muscle.[17] Sarcopenia related to stroke is probably unilateral, while that related to ageing and frailty is reflected bilaterally.

At present, sarcopenia is not evaluated pre-operatively and evaluation is not easy to implement in clinical practice. Furthermore, to the best of the authors' knowledge, no data exist on the effect of sarcopenia on post-operative long-term survival after CEA, which is an important factor when considering the net benefit from carotid surgery. It was hypothesised that sarcopenia could be evaluated easily from routine digital pre-operative CT angiography (CTA) scans by measuring MA and masseter density (MD) and that it is an independent predictor of post-operative survival. The purpose of this study was, firstly, to ascertain the reliability of MA and quality measurements from pre-operative CTA scans of CEA patients. Secondly, the study sought to determine the association between sarcopenia represented by these parameters and long-term post-operative mortality in a cohort of patients treated for carotid stenosis.

MATERIALS AND METHODS

Consecutive patients from the prospective vascular registry of Tampere University Hospital (TAUH) subjected to CEA from 2004 to 2010 ($n = 382$) were retrieved, and those with available digital pre-operative CT and CTA scans ($n = 242$; 63.4%) comprised the final study population. CTA was implemented in the authors' clinical practice in 2004; therefore, the majority of excluded patients were operated on during the early years, from 2004 to 2006 ($n = 93$). The demographics, risk factors, indications, and degrees of carotid stenosis of excluded patients ($n = 140$; 36.7%) did not differ significantly from those that were included (Table S1; see Supplementary Material). As patient data were recorded in the prospective register during the operation and no patients died during the operation, the database comprises all patients operated on. These indications are in line with published guidelines.[18] Cardiovascular risk factors obtained from the vascular registry were defined based on previous diagnoses and current medication as follows: diabetes (diagnosis/insulin or oral hypoglycemic medication), arterial hypertension (diagnosis/antihypertensive medication), cardiac risk factor (diagnosis of myocardial infarction, coronary intervention, angina pectoris, ischaemia on electrocardiography, congestive heart failure), pulmonary risk factor (diagnosis of chronic obstructive pulmonary disease), renal risk factor (diagnosis of renal insufficiency), peripheral arterial disease (diagnosis/peripheral vascular intervention or amputation), and dyslipidaemia (diagnosis/antihyperlipidaemic medication). Smoking was defined as smoking within last five years or current smoking.

Standard protocol approvals

The study was approved by the TAUH ethics committee and was conducted adhering to the principles of the Declaration of Helsinki.

Radiological assessment

All study patients were routinely subjected to brain CT and CTA. Internal carotid artery stenoses were determined (NASCET criteria) and categorised (<50%, 50–69%, 70–99%, and 100%)[19] by a neuro-interventional radiologist (J.P.P.). In a pilot analysis of a random set of 30 patients by three independent observers before and after sagittal and coronal tilt adjustment, head tilt was found to have a significant effect on MA measurements. Therefore, tilt alignment of the CTA sections was made according to a tangent along the lower border of arcus zygomaticus in the sagittal plane and along the lowest point of the orbitae in the coronal plane, and measurements were made 20 ± 2 mm below the arcus by outlining the outer surface of masseter muscle along the fascia, after which the image analysis programme automatically calculated the area (mm^2) and mean density (Hounsfield Unit [HU]) across the region of interest (Fig. 1). Thereafter, 30 CTA scans were first randomly selected and the analysis performed in a random and blinded fashion by three independent observers and reliability was assessed by intraclass correlation coefficient analysis (ICC) for both MA and MD measurements. Consequently, after confirmation of excellent repeatability, a single rater proceeded with the rest of the scans. The presence

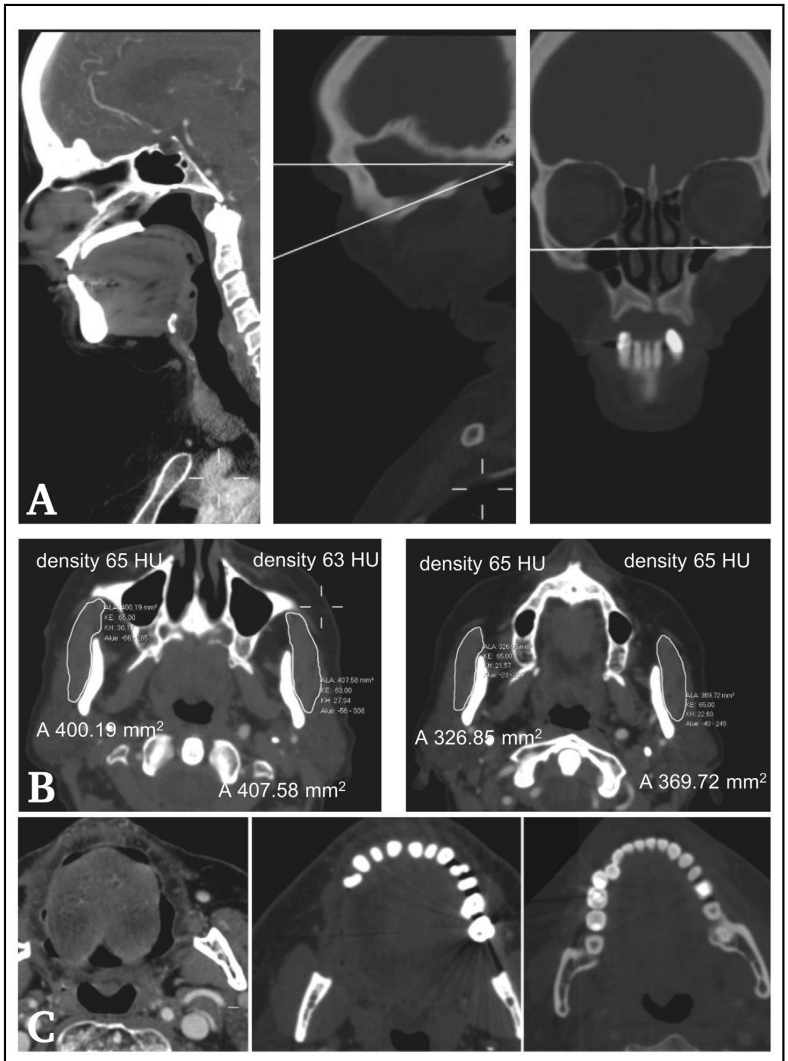

Figure 1. Representative pre-operative images of carotid endarterectomy patients demonstrating (a) the sagittal tilt and coronal tilt measurement, (b) the measurement of masseter area and density before and after tilt correction, where masseter area (A) and density is shown. (c) The grading of presence of teeth: no teeth any missing teeth, and no evidence of missing teeth. *Note.* HU = Hounsfield units.

of teeth was scored in three categories: (i) no teeth; (ii) any missing teeth; and (iii) no evidence of missing teeth (Fig. 1). Average MA (MAavg; mean of left and right MA) and MD (MDavg; mean of left and right MD) were calculated.

Survival and causes of death

Comprehensive long-term survival data on status of the patient (alive/dead) and date of death was obtained from the TAUH patient record database on 1 October 2017; the database is updated in a continuous fashion by the National Population Register. Patients were considered to be alive if there was no date of death available in the register on 1 October 2017, i.e., the last date known to be alive. The potential delay of data transfer from date of death to the National Population Register is between 1 — 3 weeks. Therefore, the register was reviewed on 1 November 2017 to ensure that all delayed information on deaths up to 1 October 2017 was recorded. This database provided full coverage of all the patients included in the study. In Finland, death certificates are mandatory and the data on deaths are without missing cases. The outcome event was all cause

death. The causes of death based on International Statistical Classification of diseases and Related Health Problems (ICD-9 and ICD-10) classifications were obtained and divided further into cardiac (coronary artery disease, valvular heart disease, arrhythmia and congestive heart disease), cerebral (ischaemic or haemorrhagic stroke, cerebral bleeding, vascular dementia), peripheral vascular (peripheral arterial disease, aneurysms) cancer, infection, trauma, and other categories (Statistics Finland).

Statistical analysis

The statistical software used for analyses was SPSS 24 for Mac OS X (IBM, Armonk, NY, U.S.A.). Continuous variables were analysed with the Mann–Whitney *U*-test, and Kruskall–Wallis test for independent samples and the Wilcoxon signed rank test for related samples. Intraclass correlation coefficient (ICC) was utilised to analyse reliability, i.e., intra- and inter-observer variability of the measured parameters (areas, densities) measured by three independent observers. The two way random single measurement model was selected and both consistency and absolute agreement were calculated along with 95% confidence intervals (CIs). ICC was rated as poor (<0.40), fair (0.40–0.59), good (0.60–0.74), and excellent (0.75–1.00). Normal distribution of CT variables was ascertained visually and by Levene's test. The association between clinical characteristics and MA and MD was analysed with adjusted and unadjusted linear regression analysis. Predictors of survival were analysed using Cox regression proportional hazards analysis first as univariable analyses. The effect of age, sex, BMI, body surface area (BSA), and tooth loss on CT variables were examined, and included in the multivariable models owing to their strong a priori association with masseter parameters.[20] Testing of the proportional hazards assumption was based on log–log plots and the correlation of survival rankings with Schoenfeld residuals. All variables except for age fulfilled this assumption. Consequently, all multivariable models using Cox regression were performed with age as a time dependent covariate. Kaplan–Meier survival analysis was used to plot overall survival. Multivariable models testing the independent associations between risk factors and mortality were adjusted with factors associating nominally with mortality ($p < .1$) in univariable analysis. Missing values for ipsilateral stenosis ($n = 32$) and dental status ($n = 33$) were replaced by values calculated by multiple imputation (mice package for R).[21] Patients with a transient event as an indication (amaurosis fugax and transient ischaemic attack [TIA]) were pooled to a single category because the mortality risk attributable to these events was identical. Age, sex, BSA, and dental status were included in the multivariable models owing to their strong a priori association with masseter parameters.[20] For estimation of BSA (and BMI) body weight and height was available only for a subpopulation ($n = 158$; 65.3%). Owing to the large amount of missing data, BSA was included in the analyses separately and without replacing missing values. The reported hazard ratios (HRs) related to the main exposure variables (MAavg and MDavg) correspond to a 1 SD increase in exposure variables. Cox regression models with penalised splines were used to evaluate (plot) the relationship between MA and MD (psplines package for R). According to power analysis based on a pilot study of 100 patients, 242 patients were needed (power of 0.9) to detect a significant difference (alpha = 0.05) in post-operative survival between different MA and MD categories.

RESULTS

Patient characteristics

The median age of the patients was 71.0 years (interquartile range [IQR] 13.0). Less than one third of the patients were women (29.8%) and the majority of patients had hypertension (76.9%), a cardiac risk factor (52.9%), dyslipidaemia (55.8%), ipsilateral stenosis of 70–99% (85.7%), and contralateral stenosis of <50% (55.3%). The main indications for surgery were TIA (35.1%) and ischaemic stroke (34.7%), whereas a minority of the operations were due to asymptomatic stenosis (13.2%). The side of the operation was left in 55.0% and right in 45.0% of cases (Table 1). The majority of patients were on beta blockers (62.2%), statins (87.2%), antiaggregatory medication (73.1%), anticoagulants (37.8%), and

Table 1. Characteristics of carotid endarterectomy patients

Risk factor	$n = 242$	
Median (interquartile range [IQR]) age (y)	71.0	(13.0)
Median (IQR) body mass index (kg/m^2)	26.8	(5.6)
Median (IQR) body surface area	1.9	(0.3)
Female	72	(29.8)
Diabetes mellitus	71	(29.3)
Hypertension	186	(76.9)
Cardiac	128	(52.9)
Dyslipidaemia	135	(55.8)
Renal	5	(2.1)
Peripheral arterial disease	37	(15.3)
Pulmonary	25	(10.3)
Smoking	68	(28.1)
Ipsilateral stenosis (%)		
<50	2	(0.9)
50–69	28	(14.3)
70–99	180	(85.7)
100	0	(0)
Contralateral stenosis (%)		
<50	134	(55.3)
50–69	64	(26.4)
70–99	34	(14.0)
100	10	(4.1)
Indication		
Asymptomatic	32	(13.2)
Amaurosis	41	(16.9)
Transient ischaemic attack	85	(35.1)
Ischaemic stroke	84	(34.7)
Side[a]		
Right	109	(45.0)
Left	133	(55.0)

Note. Data are *n* (%) unless otherwise indicated. IQR = interquartile range.
[a] Side of the index operation.

antihypertensives (75.6%), whereas a smaller group received oral antidiabetic medication (25.6%) or insulin (16.0%).

Determinants of MA

In univariable analyses the strongest factors associated with MAavg were BSA, sex, age, and dental status ($p < .001$ for all; Table 2). In multivariable analyses, the only significant factors linked to MAavg were BSA ($p < .001$) and dental status ($p = .021$). For MDavg, the associating factors were sex, dental status, and age ($p < .01$ for all comparisons in univariable analyses, as well as in multivariable analysis; Table 2). Overall, BSA showed a clearly stronger association with MAavg than BMI. BMI did not correlate significantly with MDavg.

Inter- and intra-observer variability of the CT measurements

MAavg and MDavg demonstrated excellent reliability based on ICC analysis by three independent observers (ICC 0.865—0.971 and $p < .001$ for all) (Table 3).

Association between pre-operative MA and MD and long-term mortality

The median follow up was 68.5 months (range 3—163 months). During the follow up, 104 patients (43.0%) of the study population died. No patients were lost during follow up. A Kaplan—Meier survival plot is presented in Fig. 2.

In univariable analysis, MAavg was significantly associated with mortality with a 1 SD increase corresponding to a lower risk of death (HR 0.72, 95% CI 0.59—0.88; $p = .001$) (Table 4). MDavg was not significantly connected to mortality (HR 0.92, 95% CI 0.76—1.12; $p = .423$) (Table 4).

Factors associated significantly with the measured CT parameters (MAavg and MDavg) and factors nominally connected ($p < .1$) to mortality in univariable analyses (age, BMI, BSA, renal risk factor, ipsilateral stenosis, indication category, teeth) (Table 4) were selected for multivariable analysis. In the resulting multivariable Cox regression analysis, increased MAavg remained a predictor of lower mortality (HR 0.76, 95% CI 0.61—0.96; $p = .023$) independent of age (HR 1.05, 95% CI 1.02—1.07; $p = .001$), female sex, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth (Table 5). In a similar analysis, MDavg was not associated with mortality (HR 1.01, 95% CI 0.81—1.26; $p = .942$). The development of risk of death across the continuum of MAavg shows an inverse linear relationship between MAavg and mortality with a possible tendency for exponential growth in the risk of death when approaching the lowest end of the MAavg range (Fig. 3). The risk of death was linearly associated with age (Fig. S1; see Supplementary Material).

In order to verify that MA is associated with mortality, independently of BSA, which was the most significant determinant of MAavg, the same multivariable analysis was repeated in a subpopulation with available BSA measurement ($n = 182$, representing 63.6% of the entire study population). Despite the lower sample size, the association persisted (0.75, 95% CI 0.59—0.97; $p = .030$).

Table 3. Intraclass correlation coefficient (ICC) analysis of pre-operative computed tomography measurements of masseter muscles of carotid endarterectomy patients

Variable	ICC[a]	*p*	ICC[b]	*p*
Masseter area right side	0.785	<0.001	0.784	<0.001
Masseter density right side	0.940	<0.001	0.942	<0.001
Masseter area left side	0.880	<0.001	0.872	<0.001
Masseter density left side	0.974	<0.001	0.975	<0.001
Average masseter area	0.870	<0.001	0.865	<0.001
Average masseter density	0.970	<0.001	0.971	<0.001

[a] Model: two way random consistency.
[b] Model: two way random absolute.

Causes of death

Of the 104 dead patients, the causes of death were cardiovascular in 29.8%, subclassified further into cerebral (13.5%), cardiac (15.3%), and peripheral vascular (1.0%) causes. The remaining deaths were due to cancer (7.7%), infections (1.0%), trauma (1.0%), and other causes (5.8%).

DISCUSSION

According to the results, MAavg and MDavg can be easily and reliably measured after sagittal and coronal tilt adjustment below the zygomatic arch from routine pre-operative CTA images in CEA patients. The independent factors contributing to MAavg are BSA and dental status, whereas for MDavg these are sex, dental status, and age.

Table 2. Radiological characteristics of carotid endarterectomy patients

	Age					Body surface area				Sex			Teeth category			
	All	T1	T2	T3	*p*	T1	T2	T3	*p*	Male	Female	*p*	1	2	3	*p*
Masseter average area (mm^2)	395.0 (110.1)	423	404	362	<0.001	345	389	446	<0.001	420	349	<0.001	371	394	441	<0.001
Masseter average density (Hounsfield units)	53.5 (16.5)	59	53	49	<0.001	55	58	58	Non-significant	55	49	<0.01	48	57	59	<0.001

Note. Data are median (interquartile range), and as medians and tertiles indicated as T1, T2, and T3 according to age, body surface area and in different teeth categories (1 = no teeth; 2 = any missing teeth; 3 = no evidence of missing teeth according to computed tomography analysis). *P* values calculated for linear trend using linear regression analysis.

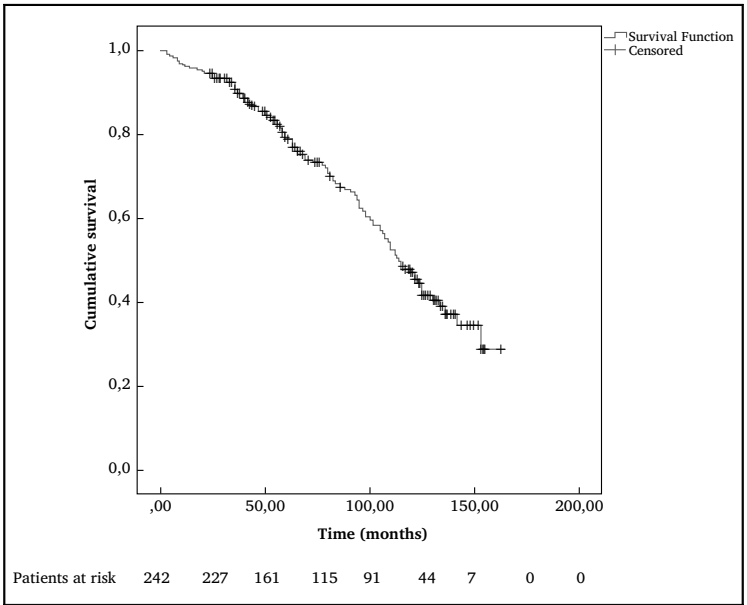

Figure 2. Kaplan–Meier survival plot of carotid endarterectomy patients.

Increased MAavg remains a predictor of lower mortality, independent of age, female sex, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth, whereas MD was not associated with mortality. This effect remains independent of BSA which is the most significant determinant of MA.

The finding of an inverse relationship between MAavg and mortality concurs with previous studies which found that MA predicted mortality in elderly patients suffering blunt trauma[14] or traumatic brain injury,[15] and this in turn suggests that MA could be used as a surrogate for sarcopenia. As in the present study, the association was mostly not influenced by age, suggesting that despite correlating with age, MA provides independent prognostic value when predicting death after trauma or CEA. In the study by Hu et al.,[15] sarcopenia was defined as a decrease in MA of $\geq$1 SD from the sex based mean. The mean MA in these sarcopenic patients was 281 mm^2 in men and 224 mm^2 in women, and they were at increased risk of 30 day mortality (80.0% vs. 50.6%) vs. those with greater MA.[15] This finding is in line with the current analyses, which showed an inverse association between MA and mortality, and suggests that there may be a different threshold for increased mortality according to sex. The present study was not powered to analyse sex differences and the association of MAavg with mortality persisted despite adjustment by sex. In addition to age and sex, other parameters with strong a priori association with masseter parameters (BMI, BSA, tooth loss) were also examined and included in the multivariable models.[20] In the present study, most of the significant risk factors previously associated with perioperative risk and long-term risk among CEA patients in large registry studies and clinical trials were also recorded and considered in the analyses.[22,23] Although some of the previously discovered risk factors were not associated with the risk of long-term mortality (contralateral stenosis and BMI) in the present study, these factors were recorded in the vascular registry online (i.e., at the time of the operation) by treating surgeons and thus with no information of the future outcomes. The smaller sample size in the present study compared with the previous large trials and registry studies most likely explains the lack of power to detect significant associations between these factors and mortality. The previous observation on the effect of age, sex, and dental status on MA and MD[20] was replicated in the present study, which supports the observations and methodology. There were no interactions between age and MA that would suggest the association between MA and mortality would be influenced by age. Age and MA were significantly associated but independent of death in the same model, which confirms that they provide information that is independent regarding survival. This exploratory analysis showed that there is no clear cut off for risk across the continuum of MA, which suggests that categorisation of masseter area would lead to better risk stratification results.

The primary shortcoming of the present study is that it was conducted retrospectively. However, the prospective vascular registry in use is audited annually for data loss and consistency. In addition, all data entries on surgical operations are done in the operation room to ensure all patients operated on are entered. All vascular patients are treated in a single centre, and the patient sample in this study was collected from a cohort comprising all consecutive CEA patients with CTA imaging available. No patients died within

Table 4. Univariable Cox regression analysis of the effect of risk factors and pre-operative masseter area and teeth measured from computed tomography angiography images on long-term survival in carotid endarterectomy patients

Risk factor	Univariable		
	Hazard ratio	95% confidence interval	*p*
Age	1.06	1.03–1.08	<0.001
Female sex	1.01	0.65–1.55	0.978
Body mass index	0.93	0.87–1.01	0.07
Body surface area	0.65	0.24–1.78	0.4
Diabetes mellitus	1.15	0.75–1.75	0.519
Hypertension	0.91	0.57–1.44	0.676
Cardiac[a]	1.32	0.89–1.97	0.17
Dyslipidaemia	0.74	0.50–1.10	0.137
Pulmonary	1.57	0.81–3.04	0.179
Renal[b]	2.60	0.95–7.09	0.063
Peripheral artery disease	1.47	0.89–2.42	0.133
Smoking	0.85	0.54–1.34	0.482
Ipsilateral stenosis	2.32	1.14–4.69	0.02
Contralateral stenosis	1.08	0.86–1.37	0.505
Indication	1.43	1.07–1.92	0.016
Teeth	0.67	0.49–0.92	0.012
Operated side (left/right)	0.70	0.46–1.10	0.1
Average masseter area	0.72	0.59–0.88	<0.001
Average masseter density	0.92	0.76–1.12	0.423

Note. Cox regression proportional hazards analysis. Indication category: (1) asymptomatic, (2) amaurosis fugax, (3) transient ischaemic attack, (4) stroke. The reported hazard ratios for masseter area and density parameters correspond to 1 standard deviation (SD) increase. The presence of teeth was scored in three categories: (1) no teeth, (2) any missing teeth and (3) no evidence of missing teeth.

[a] Diagnosis of myocardial infarction, coronary intervention, angina pectoris or ischaemia on electrocardiography and congestive heart failure.

[b] Diagnosed renal insufficiency.

Table 5. Multivariable Cox regression analysis of the effect of risk factors and pre-operative masseter area and teeth measured from computed tomography angiography images on long-term survival in carotid endarterectomy patients

Risk factor	Hazard ratio	95% confidence interval	*p*
Age	1.05	1.02–1.07	0.001
Sex	0.72	0.45–1.15	0.171
Renal	2.63	0.91–7.59	0.073
Indication	1.24	0.93–1.67	0.150
Ipsilateral stenosis	1.91	0.95–3.84	0.07
Teeth	0.74	0.53–1.05	0.093
Average masseter area	0.76	0.61–0.96	0.023

Note. Cox regression proportional hazards analysis. Indication category: (1) asymptomatic, (2) amaurosis fugax or transient ischaemic attack, (3) stroke. The reported hazard ratio for masseter area parameter corresponds to 1 standard deviation (SD) increase. The presence of teeth was scored in three categories: (1) no teeth, (2) any missing teeth, and (3) no evidence of missing teeth.

30 days of the operation. During the study period, carotid artery stenting was performed only rarely and these cases were excluded from the analysis. The present authors started using CTA for diagnostics in 2004. Therefore, the majority of excluded patients were those treated at the beginning of the study period. No differences were found in demographics, risk factors, or indications or degrees of carotid stenosis between those included and excluded in the study, which makes availability of CTA an unlikely source of bias. In Finland, determination of cause of death has been based on autopsy findings in approximately 30% of all deaths in the past two decades (www.tilastokeskus.fi), which is high compared with other European countries. The death certificates of all deceased, whether or not they underwent autopsy, are reviewed by the district forensic physician and therefore the number of patients with missing date or cause of death is negligible. The potential bias caused by delayed entry of date of death into the National Population Register was eliminated by re-checking the information one month after the end of follow up. The official cause of death has been demonstrated to be an accurate means of evaluating disease specific mortality in Finland.[24] This adds to the reliability of the present study. The patients were of Caucasian origin and with respect to cases of stroke, limited to those with mild to moderate strokes, which restricts the generalisability of the results. Finally, as post-operative CTA imaging was not routinely performed, the effect of the operative procedure itself on MA and MD could not be estimated, although it is an interesting future research topic.

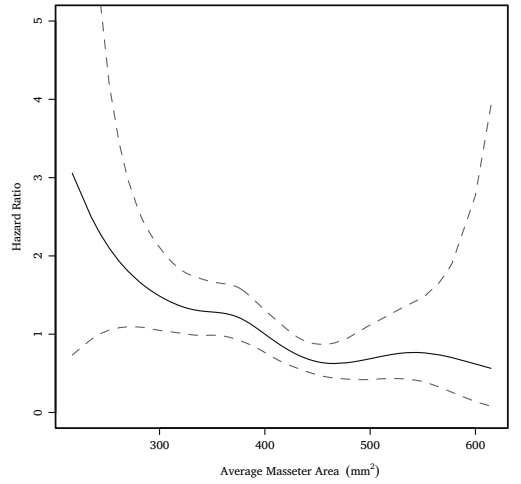

Figure 3. The development of risk of death (hazard rate) across the continuum of average masseter area (mm^2) in carotid endarterectomy patients. The model was adjusted by age, sex, body mass index, renal insufficiency, ipsilateral stenosis, indication category, and dental status.

SUMMARY AND CONCLUSIONS

After sagittal and coronal tilt correction, MA and MD can be reliably measured from pre-operative routine CTA images. MAavg but not MDavg provides long-term predictive value

independently of age, female sex, BMI, renal insufficiency, ipsilateral stenosis, indication category, and presence of teeth, independently of BSA, which is the most significant determinant of MA. The results need to be validated in independent cohorts and studies powered to stratify for different indication categories.

MAavg but not MDavg measured from a pre-operative CTA scan provides a reliable estimate of post-operative long-term survival in CEA patients independently of other risk factors, anthropometric measures, and dental status.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.11.011.

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PUBLICATION IV

Association of masseter area and radiodensity with three-month survival after proximal anterior circulation occlusion

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ASSOCIATION OF MASSETER AREA AND RADIODENSITY WITH THREE-MONTH SURVIVAL AFTER PROXIMAL ANTERIOR CIRCULATION OCCLUSION

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ABSTRACT

BACKGROUND. Masseter area (MA), a surrogate for sarcopenia, appears to be useful when estimating postoperative survival, but there is lack of consensus regarding the potential predictive value of sarcopenia in acute ischemic stroke (AIS) patients. We hypothesized that MA and density (MD) evaluated from pre-interventional computed tomography angiography (CTA) scans predict postinterventional survival in patients undergoing mechanical thrombectomy (MT).

MATERIALS AND METHODS. 312 patients treated with MT for acute occlusions of the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (M1-MCA) between 2013 and 2018. Median follow-up was 27.4 months (range 0-70.4). Binary logistic (alive at 3 months, OR<1) and Cox regression analyses were used to study the effect of MA and MD averages (MAavg and MDavg) on survival.

RESULTS. In Kaplan-Meier analysis, there was a significant inverse relationship with both MDavg and MAavg and mortality (MDavg p<.001, MAavg p=.002). Long-term mortality was 19.6% (n=61) and three-month mortality 12.2% (n=38). In multivariable logistic regression analysis at three months, per 1-SD increase MDavg (OR 0.61, 95% CI 0.41-0.92, p=.018:) and MAavg (OR 0.57, 95% CI 0.35-0.91, p=.019) were the independent predictors associated with lower mortality. In Cox regression analysis, MDavg and MAavg were not associated with long-term survival.

CONCLUSIONS. In acute ischemic stroke patients, MDavg and MAavg are independent predictors of three-month survival after MT of the ICA or M1-MCA. A 1-SD increase in MDavg and MAavg was associated with a 39-43% decrease in the probability of death during the first three months after MT.

INTRODUCTION

Acute ischemic stroke (AIS) continues to be a significant cause of disability and mortality worldwide.[1] Several randomized trials have demonstrated that mechanical thrombectomy (MT) is the treatment of choice in patients with acute proximal anterior circulation ischemic stroke.[2–6] The number of patients receiving MT is increasing as this treatment is recommended by clinical practice guidelines, the time window from symptom onset to treatment has been widened, and the overall stroke treatment chain has been enhanced.[7] Optimising patient selection is crucial in order to efficiently allocate resources and to continue to improve the overall clinical outcome, especially survival, after AIS.

Recognized predictors of survival after a large vessel ischemic stroke include stroke severity, good collateral circulation, age, sex, diabetes, atrial fibrillation, renal insufficiency, frailty, and intracranial hemorrhage. The Alberta stroke program early computed tomography (CT) score (ASPECTS) has also been validated as a risk assessment tool in this cohort.[8–10] Muscle loss, i.e. sarcopenia, is a major component of frailty. In elderly patients, masseter muscle area correlates with psoas muscle area,[11] which has previously been verified to predict mortality in vascular surgical patients.[12–14] Additionally, masseter area measured from CT scans has been used in evaluating sarcopenia in carotid endarterectomy[15] and elderly blunt trauma patients[11] as well as after severe traumatic brain injury.[16,17] In addition to muscle area, radiodensity has also been ascertained as a marker of sarcopenia.[18] Furthermore, masseter muscle tension and chewing ability correlate with physical fitness and quality of life in the elderly.[19] Sarcopenia can be reliably diagnosed from CT scans by a clinician by measuring muscle area and density from a representative slice.[18,20] The advantages of this method include little or no additional costs, as CT imaging is routinely performed in AIS patients, as well as objectivity and reproducibility. Extensive data on the prevalence of sarcopenia

after stroke is available in other studies,[21] but the potential predictive value of sarcopenia in AIS patients treated with MT remains unknown, to the best of our knowledge. We hypothesized that masseter area (MA) and density (MD) measured from standard preoperative CT angiography (CTA) images could predict mortality in a cohort of acute stroke patients undergoing MT.

MATERIALS AND METHODS

Patients

Patients were treated with MT at Tampere University Hospital (TAUH) between January 2013 and February 2018 (n=453). We retrospectively collected the patient data and the times of death from the TAUH patient record database, which is linked to the National Population Register, results of the blood tests from the Fimlab Laboratories Ltd database and CTA images from a picture archiving and communication system (PACS). The initial imaging protocol of stroke patients consisted of non-contrast-enhanced computed tomography (NCCT), CTA, and frequently also CT perfusion (CTP) scanning. The selection of patients as candidates for MT was conducted in a multidisciplinary team consisting of a stroke neurologist and a neurointerventional radiologist, and it was based on the absence of extensive irreversible ischemic changes and hemorrhage in NCCT, a proximal clot position in the internal carotid artery (ICA) or the M1 or M2 segments of the middle cerebral artery, and the amount of salvageable tissue in CTP imaging when available. There were no exclusion criteria for MT based on age, but patients with a history of moderate or severe dementia were treated conservatively. Patients referred to our institution from other hospitals were re-evaluated with at least NCCT and CTA upon arrival before proceeding to the angiographic suite. In line with the results of recent studies, we also treated patients within a longer timeframe, that is, patients presenting after 6 hours from symptom onset or suffering from a wake-up stroke provided that no large infarct could be detected in NCCT and there was still salvageable tissue based on the CTP maps.[22,23] Thrombolysis in cerebral infarction scale (TICI) was used to describe the technical outcome and TICI > 2a was set as a threshold for good outcome.

We included patients presenting with a M1- or ICA-thrombus and available digital preoperative CT and CTA scans (n=312, 68.8%) in the analyses. Position of the clot elsewhere in the cerebral

circulation resulted in exclusion from the study (n=141, 31.1%). The excluded patients did not significantly differ from the study subjects with respect to age, sex, or a history of diabetes, hypertension, coronary artery disease, or atrial fibrillation (Supplementary table 1), an ASPECT-score of ≤7 at 0 and/or 24 hours was less common in the excluded patients. Data on dental status, serum creatinine, hemoglobin (Hb), or serum c-reactive protein (CRP) were not available for the excluded patients. Thrombus locations in the excluded cohort were as follows: M2-segment in 73, M3-segment in 14, basilar artery in 24, P1-segment in 8, A1-segment in 1, A2-segment 1, A3-segment 4, and major venous thrombi in 7 cases. 9 patients with ICA or M1 thrombus were excluded due to the artifacts in CTA caused by metallic dental fillings. Furthermore, 15 patients were excluded due to major space intracranial hemorrhages detected after the procedure: 11 patients had parenchymal hemorrhage (PH2), one patient had parenchymal hemorrhage remote (PHr2) and three patients had combination of both.

Imaging parameters and radiological assessment

CT scans were obtained using a 64-row multidetector CT scanner (General Electric LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA). Brain NCCT was performed using the parameters 120 kV with AUTO mA and SMART mA technic, noise index 3.3, collimation 4x5 mm, 40% adaptive statistical iterative reconstruction (ASIR), and rotation 0.5 s. Images were obtained axially (0.625 mm thick slices) and then contiguous axial slices were reconstructed to the thickness of 5 mm and coronal slices to the thickness of 2 mm. CTA was performed with helical technique using a scanning range from the aortic arch to the vertex of the skull. The imaging parameters were 100 kV, AUTO mA and SMART-mA, noise index 9, 40% ASIR, collimation 40 x 0.625 mm, rotation 0.5 s, pitch factor 0.984. The contrast agent (iomeprol, 350 mg I/ml, IOMERON, Bracco, Milan, Italy) was administered via an antecubital vein with an 18-gauge cannula using a double-piston power injector with a flow rate of 5 ml/s using 70 ml of contrast agent followed by a 50 ml saline flush. Automatic bolus triggering from the aortic arch was used.

CTA images were used to measure the area (mm^2) and mean radiodensity (Hounsfield Unit, HU) across the region of interest of the masseter muscle. The measurements were performed after sagittal and coronal tilt adjustment, since in our previous study head tilt was found to have a significant effect on MA measurements.[15] The area and mean radiodensity were calculated from the CTA sections according to tangents along the lower borders of the zygomatic arches in sagittal planes and along the lowest points of the orbitae in coronal planes. Measurements were then made 20 ± 2 mm below the arches by outlining the outer surface of the masseter muscles along the fasciae. We have demonstrated excellent inter-observer reliability of masseter area and density measurements by three independent observers in our previous article.[15] In order to confirm intra-observer reliability, 30 CT scans in this study population were randomly selected and rated by a independent clinician in a repeated manner. Intraclass correlation coefficient (ICC) was determined for MA and MD measurements. The

presence of teeth was scored in three categories: 1) no teeth, 2) any missing teeth, and 3) no evidence of missing teeth. Average MA (MAavg, mean of left and right MA) and MD (MDavg, mean of left and right MD) were calculated.

Statistical analysis

The statistical analyses were performed with SPSS 25 for Mac OS X. Reliability of radiological measurements was estimated by intraclass correlation coefficient (ICC) using two-way random single measurement with both consistency and absolute agreement. ICC over 0.75 was classified as excellent reproducibility. Normality distributions of parameters were observed using histograms and Levene's test. Means along with standard deviations were reported for normally distributed variables and medians with interquartile ranges for variables with skewed distributions. Based on normality, parametric or non-parametric tests were selected. The Mann-Whitney U-test was selected for non-Gaussian variables for two independent samples and the Kruskal-Wallis test for three or more independent samples. The Pearson correlation coefficient analysis was used to evaluate the pairwise association between the risk factors or other clinical variables and muscle parameters, and statistically significant ($p<.05$) correlations were checked with the multivariable Cox regression analysis using backward selection algorithm. Kaplan-Meier survival analysis was used to evaluate overall survival using tertiles of MAavg and MDavg. When studying three-month mortality in multivariable binary logistic regression analysis patients were classified as being alive or dead at the three-month fixed time-point. Cox regression was first carried out as univariable analyses, and the proportional hazards assumption was tested by log-minus-log plots. This was followed by a multivariable Cox regression analysis that included parameters associated with mortality ($p<0.1$) in univariable analyses as covariates. Both models, Cox and logistic regression, were adjusted for age, diabetes, local intracranial hemorrhage, and hemoglobin (Hb) level and in addition to these, dental status, atrial fibrillation, and serum creatinine level, which were significant in univariable Cox regression, were

included in multivariable analysis. Increased CRP correlated inversely with Hb, but only the highest Hb value was selected for multivariable analysis in order to avoid confounding. Criteria for cerebral edema and local intracranial hemorrhage were determined by The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST). Interactions between covariates and muscle parameters were tested by bivariate correlation. Age, sex, and dental status were examined and included in separate multivariable models because of their strong *a priori* association with masseter parameters.[24] Due to the emergency nature of AIS patients undergoing MT treatment, weight and height data were missing in the majority of the study cohort and NIH stroke scale in 25 patients (8.0%). We were able to calculate BSA only for 39.1% (n=122) of the patients and it was therefore not included in the multivariable analyses. MDavg did not correlate linearly with weight, height, or BSA in this subpopulation. However, in a subpopulation with the 3-month modified rankin scale (mRS) available (n=267, 85.6% of the population), MDavg and MAavg correlated equally with mRS 3-month in Pearson coefficient analysis (p=.002). The association of age with mortality was analyzed as a time-dependent covariate in all the Cox survival analyses. The main muscle parameters (MAavg and MDavg) were z-scored and reported hazard ratios (HRs) or odds ratios (ORs) correspond to a one standard deviation increase in the muscle parameter.

Ethical considerations

The study was conducted adhering to the ethical principles of the Declaration of Helsinki and was approved by the Pirkanmaa Hospital District Science Center.

RESULTS

Patient characteristics

The study included 312 patients (Table 1 shows the demographic data). The median age of the patients was 69.2 years (IQR 15.3) and 61.1% of the patients were male. Among these, 198 (63.5%) patients had an M1-thrombus, 74 patients (23.7%) an ICA-thrombus, and 40 patients (12.8%) had both an M1- and an ICA-thrombus in the preoperative CTA. TICI scale was > 2a in 283 patients (90.7%) indicating a good technical outcome of MT.

Table 1. Characteristics of acute stroke patients subjected to mechanical thrombectomy.

Risk factor	n=312
Age, median (IQR)	69.2 (15.3)
Female (%)	115 (36.9)
DM (%)	45 (14.4)
HT (%)	132 (42.3)
CAD (%)	43 (13.8)
FA (%)	157 (50.3)
M1-thrombus, n (%)	198 (63.5)
ICA-thrombus, n (%)	74 (23.7)
M1- and ICA-thrombus, n (%)	40 (12.8)
Cerebral edema, n (%)	122 (39.1)
Collateral Score, median (IQR)	2 (2)
NIH Stroke Scale, median (IQR)	16 (7)
ASPECTS 0h ≤ 7, n (%)	91 (29.2)
ASPECTS 24h ≤ 7, n (%)	99 (31.7)
TICI ≥ 2b (%)	283 (90.7)
Arrival Hb (g/l), median (IQR)	133 (22)
Arrival CRP(mg/l), median (IQR)	3 (7)

Creatinine level (µmol/l), median (IQR)	77 (29)
Teeth, n (%)	
No teeth	55 (17.6)
Any missing teeth	184 (59.0)
No evidence of missing teeth	73 (23.4)
MDavg (HU), (SD)	63.7 (12.4)
MAavg (cm^2), (SD)	4.3 (1.16)

DM, Diabetes mellitus; HT, hypertension; CAD, Coronary artery disease; FA, atrial fibrillation; M1, M1 segment of the middle cerebral artery; ICA, internal carotid artery; Hb, hemoglobin; CRP, c-reactive protein; ASPECTS, the Alberta stroke program early CT score; TICI, Thrombolysis in cerebral infarction scale; MDavg, Masseter density average; MAavg, Masseter area average.

Determinants of masseter area

Table 2 presents the MAavg and MDavg values of the cohort. Age, dental status, and sex were strongly associated with MAavg and MDavg ($p<.001$ for all). More specifically, advanced age, female sex, and poor dental status were linked to decreased MAavg and MDavg.

Table 2. Radiological parameters of acute stroke patients subjected to mechanical thrombectomy.

		Age tertiles				Teeth category				Gender		
	All (IQR)	T1	T2	T3	p	1	2	3	p	M	F	p
MAavg	4.1 (1.6)	4.7	3.9	3.6	<.001[a]	3.3	4.1	4.8	<.001[a]	4.5	3.6	<.001[b]
MDavg	63.8 (15.9)	70.3	63.5	59.0	<.001[a]	55.5	62.5	72.5	<.001[a]	65.5	61.0	<.001[b]

Masseter average area (MAavg, cm^2) and masseter average density (MDavg, Hounsfield Units) are presented as medians (interquartile range) in all patients and as medians and tertiles indicated as T1, T2 and T3 according to age, in different teeth categories (1=no teeth, 2=any missing teeth and 3=no evidence of missing teeth according to computed tomography analysis) and in male (M) and female (F) genders. [a] Statistically significant difference between the oldest and the youngest tertile and teeth categories ($P<.05$, Kruskal-Wallis test). [b] Statistically significant difference compared to males ($P<.05$, Mann-Whitney-U test).

Reproducibility of the CT measurement

Intraobserver variability of the MDavg and MAavg were excellent as tested by ICC analysis (ICC .839-.981, p< 0.001) (Supplementary table 2).

Association of preoperative masseter area and density with mortality

The follow-up lasted until December 31th, 2018 with the median duration being 27.4 months (IQR 30.2, range 0-70.4 months). According to the Kaplan-Meier survival analysis, most of the deaths occurred within the first 3 months (n=38, 62.3% of all deaths, 3-month mortality 12.2%) and, in line with this, the tertiles of MDavg and MAavg were almost parallel after three months of follow-up. Overall, there was an inverse relationship between both MDavg and MAavg and mortality in the log-rank test (p<.001 to p=.002) (figure 1). Long-term mortality was 19.6% (n=61) and no patients were lost to follow-up. The risk of death across the full range of MDavg showed an inverse linear relationship between standardized MDavg and mortality with a tendency for growth in the risk of mortality when approaching the lowest end of the MDavg range (Supplementary figure 1).

Univariable and multivariable binary logistic regression analyses were used to study the association of risk factors with three-month survival (Tables 3). MDavg and MAavg (OR 0.61, 95% CI 0.41-0.92, p=.018 and OR 0.57, 95% CI 0.35-0.91, p=.019; per 1-SD increase, respectively) as well as the Hb level (OR 0.98, 95% CI 0.96-1.00, p=.018 -.020) were independently associated with lower mortality. Furthermore, despite adding *a priori* risk factors (age, teeth, gender) strongly associated with MAavg and MDavg (Table 2) in multivariable analyses, increased MDavg and MAavg persisted as predictors of lower mortality (MDavg OR 0.58, 95% CI 0.39-0.86, p=.007; MAavg OR 0.52, 95% CI 0.32- 0.85, p=.009) (Supplementary table 3).

In multivariable Cox regression analyses of long-term survival, increased MDavg (HR 0.69, 95% CI 0.51-0.94, p=.017, per 1-SD increase) was independently associated with a 31% decrease in the probability of death, whereas MAavg was not statistically associated with long-term mortality (HR 0.74, 95% CI 0.53-1.03, p=.075) (Supplementary table 4). When multivariable Cox regression was performed only on patients surviving past the first three months after the intervention (n=274), MDavg and MAavg no longer showed a statistically significant association with survival (Supplementary table 5). Patients who died within the first three months postoperatively had smaller MAavg (4.33 vs. 3.68 cm^2, p=.001) and MDavg (64.6 vs. 57.3 HU, p=.001) compared to those alive after three months.

Table 3. Univariable and multivariable binary logistic regression on the association with 3-month postoperative mortality.

	Unadjusted		Adjusted with MDavg		Adjusted with MAavg	
Risk factor	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.0 (1.0-1.1)	.08*	1.00 (0.96-1.04)	.92	1.00 (0.97-1.04)	.97
Gender	1.5 (0.7-2.9)	.29	-		-	
DM	1.9 (0.9-4.7)	.09*	1.49 (0.60-3.07)	.39	1.74 (0.70-4.33)	.23
HT	1.0 (0.5-2.0)	.98	-		-	
CAD	2.2 (1.0-5.0)	.06*	1.77 (0.70-4.46)	.23	1.46 (0.58-3.64)	.42
AF	1.5 (0.7-2.9)	.28	-		-	
Cerebral edema	1.5 (0.7-2.9)	.27	-		-	
Unfavorable CS (0-1)	0.6 (0.3-1.3)	.19	-		-	
NIH Stroke Scale	1.0 (1.0-1.1)	.21	-		-	
ASPECTS 0h ≤ 7	1.0 (0.5-2.1)	.98	-		-	
ASPECTS 24h ≤ 7	0.9 (0.4-1.8)	.69	-		-	
Arrival Hb (per unit)	1.0 (0.9-1.0)	.001*	0.98 (0.96-1.00)	.020*	0.98 (0.96-1.00)	.018*
Arrival CRP (per unit)	1.0 (1.0-1.0)	.002*	-		-	
Creatinine (per unit)	1.0 (1.0-1.0)	.29	-		-	
Dental status (per category)	0.6 (0.4-1.1)	.10	-		-	

MDavg	0.5 (0.4-0.8)	.001*	0.61 (0.41-0.92)	.018*	-	
MAavg	0.5 (0.3-0.8)	.002*	-		0.57 (0.35-0.91)	.019*

Binary logistic regression analysis. A Multivariable model including parameters with P<.1 in univariable analysis. OR, Odds ratio; CI, Confidence interval; DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease; AF, atrial fibrillation; CS, collateral score; ASPECTS, the Alberta stroke program early CT score; Hb, hemoglobin (g/l); CRP, c-reactive protein (mg/l); MAavg, Masseter area average; MDavg, Masseter density average. Odds ratio (OR) estimated from binary logistic regression model with 3 months mortality after operation (cut-off 3 months). Odds ratios for MAavg and MDavg correspond to 1 standard deviation increase. * = statistical significance.

DISCUSSION

We found that MDavg and MAavg measured from preinterventional CTA scans are independent predictors of three-month mortality after MT of ICA or M1-MCA occlusions in patients with AIS and with a good initial technical outcome. During the first three months after the intervention, increases of 1SD in MDavg and MAavg were associated with a 39% and a 43% decrease in the probability of death, respectively. However, when analyzing only patients surviving past the initial three months no association of MDavg and MAavg with mortality could be demonstrated. We have previously reported the excellent feasibility and reliability of MDavg and MAavg measurements from routine CT images in clinical work.[15] This study demonstrates MAavg and MDavg to be independent predictors of three-month mortality in AIS patients treated with MT.

Wallace et al. and Hu et al. studied elderly trauma patients and found that MA correlates with survival.[11,16] Short- and long-term mortality were not analyzed separately in either study but similar to the present study, the majority of deaths occurred during the first months of follow-up. Our results may not be directly comparable to the findings in these earlier studies[11,16] due to differences in age and sex distributions, which according to our results can affect MA. In addition, the studies did not adjust for dental status, which has been demonstrated to be associated with MA in the present study and also in our previous study.[15] The association of dental status with the masseter muscle parameters has been proposed to be stronger than that of aging or skeletal muscle index in the elderly.[15,25,26] Dental status is also highly correlated with chewing ability, which, in turn, is associated with overall functional status.[27] In the study by Wallace et al., the patients were markedly older than in our study (mean age 80.0 years vs. median 69.2 years) and consequently the MA values were also smaller.[11] In the study by Hu et al. the proportion of males was higher than in our study (73.1% vs. 63.1%) and correspondingly the mean MA was larger.[16]

Muscle area and density are closely related, and in addition to muscle area, radiodensity has been demonstrated to be a marker of sarcopenia.[18] However, previous brain trauma studies[11,16] did not address MD which, like MA, is correlated to age, gender, and dental status.[15] Interestingly, we found that high mean MD value was the muscle parameter that best predicts survival. It is possible that fat infiltration in the masseter muscle is the first phase in the development of sarcopenia and signals frailty even before MA decreases, but further research is required to verify this.

The strong association between MAavg and MDavg with short-term mortality in AIS patients who received MT differs from our previous findings in patients treated with carotid endarterectomy for (mostly symptomatic) ICA stenoses in that the association with improved survival in the earlier study was evident only in long-term.[15] This may be due to differences in patient selection in the studies, since AIS patients eligible for MT are treated immediately, whereas those treated with carotid endarterectomy are operated mainly within 2 weeks from symptom onset. Additionally, patients with asymptomatic carotid stenoses or suffering from severe stroke are either denied operation or operated on a delayed schedule. Another notable difference between our studies was the lower mean/median MD in carotid endarterectomy patients compared to the MT patients (53.5 ± 16.5 vs. 63.7 ± 12.4 HU) despite comparable age and a higher proportion of males in the endarterectomy cohort. It is possible that this difference could be due to the common occurrence of stenosis also in the external carotid artery and the potential effect this has on the perfusion of the masseter muscles. The fact that in AIS patients the association of MAavg and MDavg with mortality was seen only in short-term follow-up can be correlated with the timing of significant changes in neuronal plasticity which might have its' most significant influence on recovery during the first 3 months after stroke.[28] Our results on the effect of Hb and creatinine values are in line with previous research.[29,30]

This was a single-center study focusing on AIS patients undergoing MT due to ICA or M1-MCA occlusions, which may limit the generalizability of the results. A further limitation is the retrospective nature of part of the data collection and measurements, which may introduce biases. Additionally, high quality data on the functional (as a rule the patients had pre-stroke mRS ≤2 to be eligible to MT) and nutritional status, or all relevant previous medications of the study subjects at the time of the MT was not available. However, our findings on the effect of advanced age, sex, and dental status on MA and MD are compatible with previous reports.[15,25,26] We consider our method of MA and MD measurement reliable according to excellent ICC values in the present and our previous study.[15]

SUMMARY AND CONCLUSIONS

MDavg and MAavg determined from routine pre-interventional CTA scans predict three-month survival in AIS patients suffering from ICA or M1-MCA occlusions treated with MT with a 1-SD increase in MDavg and MAavg corresponding to a 39-43 % decrease in short-term mortality.

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CONFLICTS OF INTEREST STATEMENT

The authors report no conflicts of interest.

AUTHOR STATEMENTS

I.L.: Participated in research conception and design, data collection, wrote the statistical analysis plan, analyzed data and wrote and revised the manuscript.

S.P.: Participated in research conception and design, data collection and wrote and revised the manuscript.

N.K.: Participated in research conception and design and wrote and revised the manuscript.

J.H.: Participated in research conception and design, data collection, statistical analysis and interpretation and wrote and revised the manuscript.

N.S.: Participated in research conception and design, data collection, statistical analysis and interpretation and wrote and revised the manuscript.

N.O.: Participated in research conception and design, data collection, analysis and interpretation and wrote and revised the manuscript. As professor, he is guarantor.

All authors agree to be accountable for all aspects of the work.

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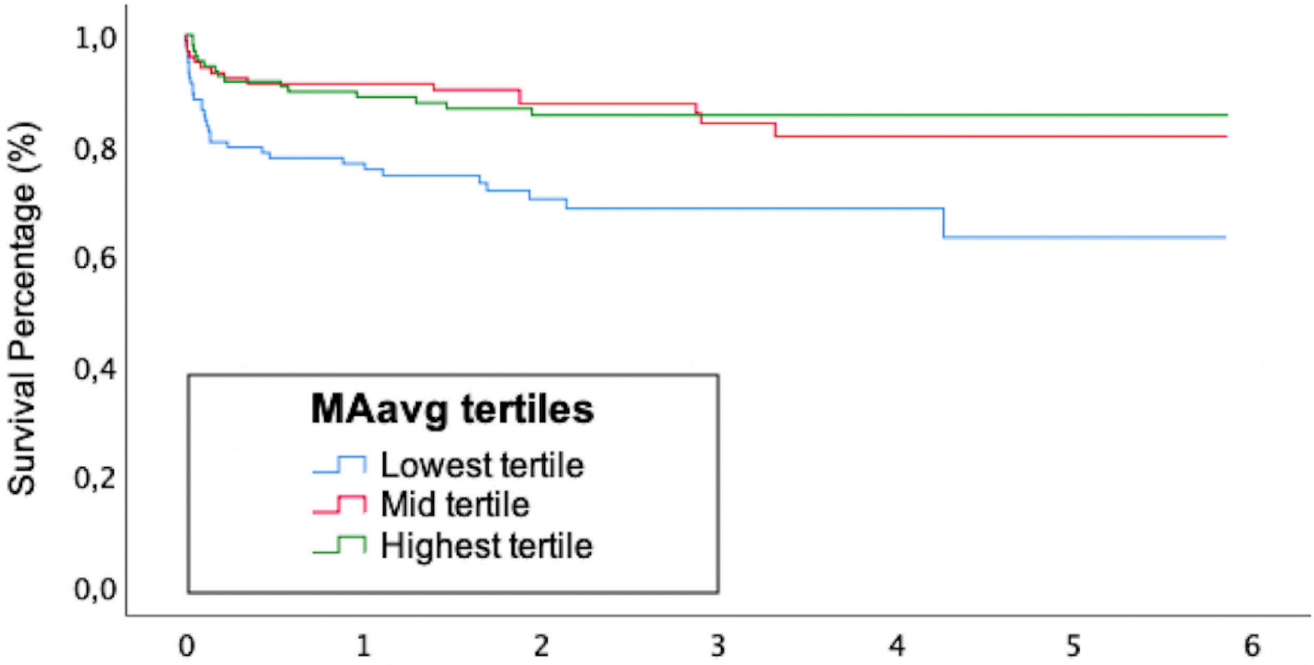
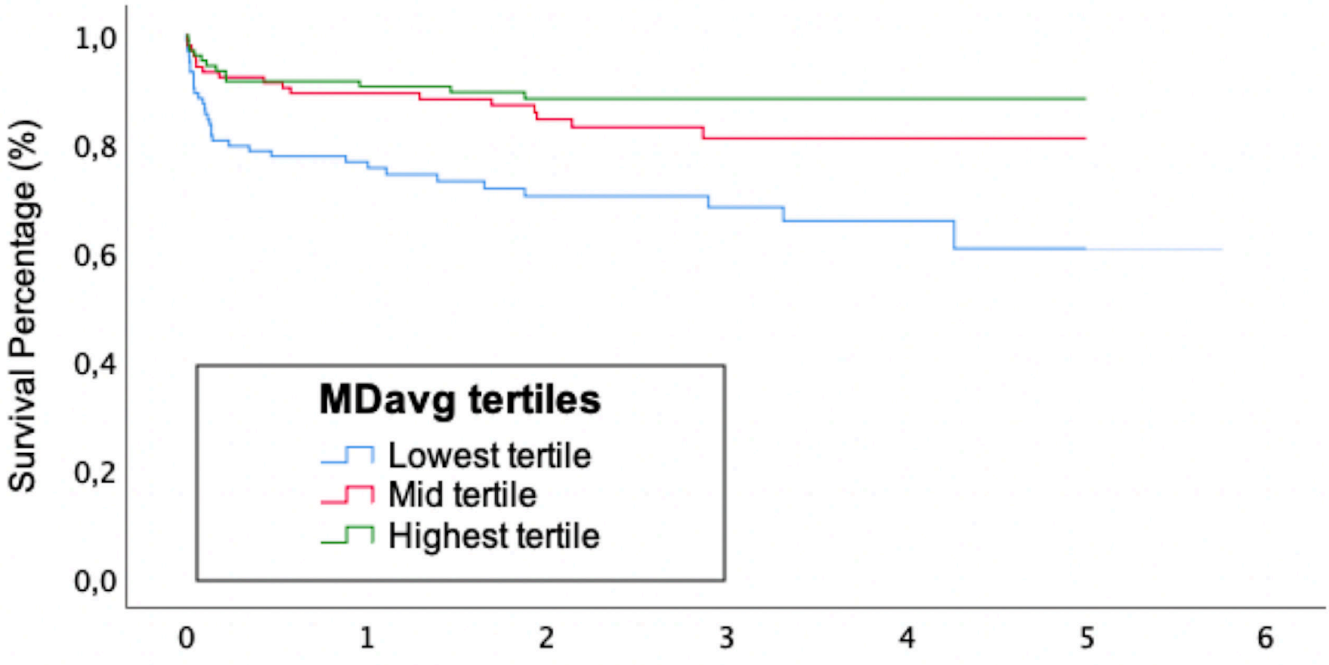
FIGURE LEGENDS

Figure 1. Kaplan-Meier survival plots. Kaplan-Meier survival curve comparing patients in different MDavg and MAavg tertiles in acute stroke patients subjected to mechanical thrombectomy. Patients in the lowest tertile had a significantly worse survival according to the log-rank test ($p<.001$).



Number at risk							
Lowest tertile	104	80	74	73	72	71	71
Mid tertile	104	93	89	87	87	87	87
Highest tertile	104	94	92	92	92	92	92



Number at risk							
Lowest tertile	104	80	75	74	73	72	72
Mid tertile	104	93	89	87	87	87	87
Highest tertile	104	93	91	91	91	91	91