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The association of abdominal muscle with outcomes after scheduled abdominal aortic aneurysm repair*

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Summary

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Frailty is associated with an increased incidence of adverse peri-operative outcomes; its accurate identification is complex and quantification of its impact on outcomes consequently fraught with difficulty. Sarcopenia, the degenerative loss of core muscle mass, is an indicator of frailty and its radiological quantitation has shown promise in providing an objective morphometric measure that may facilitate risk stratification. Patients presenting for elective abdominal aortic aneurysm surgery routinely undergo pre-operative computed tomography (CT) imaging, permitting diagnosis of sarcopenia by measurement of Psoas Area (PA) with derivatives such as the L4-Psoas Muscle Index (L4-PMI (mm^2/m^2), psoas muscle cross-sectional area at the fourth lumbar vertebra, corrected for height). We studied the impact of sarcopenia on, and its independent association with, post-operative outcomes following elective abdominal aortic aneurysm surgery. Psoas area and derivative indices were calculated retrospectively for 137 patients and its association with survival and other outcomes including post-operative complications, length of intensive care and hospital stay analysed. This study found an association between reduced post-operative survival and abdominal muscle mass, with left PA and patient age as independent predictors of survival and length of hospital stay. Our results strengthen the case for inclusion of muscle mass indices during pre-operative evaluation and risk-stratification in patients presenting for elective aortic aneurysm repair

Introduction

Elective surgery for abdominal aortic aneurysms (AAA) aims to prevent death or serious morbidity from rupture. This is a preventative operation in often asymptomatic patients and the decision to proceed with elective AAA repair must balance the risk of rupture with that of perioperative complications.

The widespread use of endovascular techniques, now accounting for the majority of AAA repairs carried out, has led to surgery being offered to a broader group of patients, who are increasingly elderly and have significant co-morbidities [1]. While outcomes, particularly in the short-term, are improving, the risk of perioperative complications remains significant. Research into outcomes and pre-operative prognostication has largely focused on cardiopulmonary fitness, but much less on the role of frailty.

Sarcopenia is the degenerative loss of core muscle mass and function. It is a component of a multi-factorial process that leads to frailty with advancing age. Its prevalence is believed to be substantial in adults aged over 65 years [2,3] and increases with age, institutionalisation and acute illness.

Sarcopenia is known to exist even in patients who are otherwise healthy and in the obese, as it is independent of total body mass [4]. It may therefore go undetected in patients not appearing frail on visual assessment. Objective quantification of core muscle loss, as assessed by psoas muscle area, is a simple and robust [5] means of identifying frailty. It can be carried out with little additional impact on resources using CT images that form part of the routine pre-operative work-up for patients undergoing AAA surgery.

It is recognised that sarcopenia is associated with higher levels of disability and unfavourable outcomes in patients with chronic conditions such as heart failure or neurological disease [6,7]. Furthermore, post-operative outcome data from numerous studies including colorectal and hepatobiliary cancer surgery indicates that sarcopenia may be an independent predictor of poorer surgical outcomes [8-11]. This includes significantly higher rates of infective complications, length of hospital stay and death.

Lee *et al*'s study of outcomes after open AAA repair in 262 patients concluded that reduced core muscle size correlates strongly with increased mortality [12]. However, the evidence base for the role of sarcopenia on morbidity in the vascular surgery population, particularly for patients undergoing endovascular aneurysm repair (EVAR) remains small.

Currently, most risk stratification models for AAA repair have limited predictive ability [13] and do not account for frailty. Inclusion of an objective, morphometric measure of sarcopenia as a marker of frailty may also allow targeted modification of perioperative risk, or

‘prehabilitation’, using nutritional, exercise and pharmacological interventions which have shown some promise in reversing the effects of sarcopenia [14,15].

The aim of this study was to assess the impact of sarcopenia on post-operative outcomes in patients undergoing elective AAA surgery and its potential as an independent factor to aid risk-prediction in this population.

Methods

We did not seek ethical approval for this retrospective analysis of data that were routinely collected for patients scheduled for abdominal aortic aneurysm repair at the Royal Free Hospital, London, UK, between February 2012 and December 2014.

We analysed the associations of independent variables with postoperative outcomes. The independent variables were muscle areas on CT and patient sex, age at operation, height, weight and body mass index, renal function (eGFR) and history of myocardial infarction, angina, stroke, transient cerebral ischaemia and hypercholesterolaemia. The CT images were recorded within 12 pre-operative months, or within 3 postoperative months if pre-operative scans were unavailable or of insufficient quality. The primary postoperative outcome was survival; secondary postoperative outcomes were: complications; length of intensive care unit (ICU) and hospital stays; and discharge destination (home or further care). We used the Clavien-Dindo Classification to grade postoperative complications.

Two radiologists unaware of patient outcomes measured two muscle areas: total abdominal muscle area (TAMA); and total psoas area (TPA). We used software that semi-automatically derived muscle area at the level of the fourth lumbar vertebra: the radiologists then traced the area of each psoas by hand, which when summed gave a combined psoas area (mm^2) [10,12,16]. We standardised muscle areas to patient: height ($mm^2.m^{-2}$); weight ($mm^2.kg^{-1}$); and body size ($mm.kg^{-0.83}$) [ref]. In addition, superficial, visceral and total abdominal fat areas (SFA, VFA and TFA, respectively) were also measured [17].

We included all patients recorded in our database at the time of analysis. A sample size calculation was therefore not carried out. We used the chi-squared test to compare categorical variables and Student's t-test or Mann-Whitney U test to compare continuous variables, as appropriate. Univariable Cox regression analyses were performed individually to assess the association of independent variables with survival and secondary outcomes using the Efron method for tied failures. Variables with p values <0.05 were used to generate multivariable survival and other outcome models. The Akaike Information Criterion was used to select the model with the highest information. We used SPSS Version 24.0 (IBM, Chicago, IL, USA) for analyses.

Results

Demographic information for the study cohort are shown in Table 1. The primary measure of sarcopenia in this study, L4-PMI, had a mean value of 814.5.4 mm^2/m^2 (SD 156.2) in male patients and 639.9mm^2/m^2 (SD 199.0) in female patients.

In 17 patients (12.4%), post-operative CT scans were used for analysis due to suitable pre-operative images being unavailable.

The primary outcome measure, longest median post-operative survival, was 3.8 years (IQR 3.2 – 4.4 [range 3 days – 5.1 years]). One-year mortality was 3.7% (n=5) and twenty-three patients (16.7%) died during the 5-year follow up period. Univariate Cox regression showed patient age (p= 0.010) and left PA (p= 0.049) to be the only covariables independently associated with survival (Table 2). This relationship was more marked when left PA was adjusted for weight (left PA-W, p= 0.027) and body size (left PA-S, p=0.021). Multivariate regression analysis showed no significant reduction in survival associated with a reduced left PA-S (p = 0.080) but a significant association with patient age (p = 0.034) (Table 3). We also fitted our data to a multivariate regression model as used in a validated AAA survival calculator [16], which similarly showed that age (p = 0.029) but not PA-W (p = 0.073) were independently associated with survival. This survival calculator predicted accurately (within 95% CI) the actual survival in our patient cohort (Figure 1).

Analysis of secondary outcomes revealed an incidence of in-hospital post-operative complications of 35.0% (n=48): Eighteen patients (13.1%) suffered from respiratory complications; 16 (11.7%) from cardiovascular complications; Nine (6.6%) from renal complications and 9 (6.6%) from neurological complications. Of these complications, 27% (13/48) were categorised as severe (CDC Grade 3 or higher).

Fifteen patients (10.9%) required a return to the operating theatre during their stay. Fourteen patients (10.2%) could not be discharged home, as they required further care such as rehabilitation or transfer to another hospital for additional interventions.

Median ICU length of stay for the entire cohort was 2 days (IQR 1-3 [Range 0-79]) and median hospital length of stay 5 days (IQR 3-9 [Range 1-105]). Multivariate regression showed that 2 covariables were independently associated with hospital length of stay: left PA-S (PA corrected for body size; Hazard ratio (HR) 1.021, (95% Confidence interval (CI) 1.000 – 1.042), p < 0.0001) and patient age (HR 1.053 (95% CI 1.027-1.080), p = 0.047) (Table 4).

Discussion

This study examines the role of sarcopenia as an independent predictor of post-operative outcomes in patients undergoing abdominal aortic aneurysm repair predominantly performed using an endovascular approach.

Age and left PA-S (psoas area corrected for body size) emerged as the 2 covariables independently predictive of survival. An increase in left PA-S is associated with a higher chance of survival. Our findings are corroborated by other studies that found strong correlations between reduced core muscle mass and increased mortality following open AAA repair [12]. Our results further strengthen the case for consideration of sarcopenia as a predictor for perioperative morbidity following elective AAA repair, which should form part of pre-operative risk assessment. Total abdominal muscle area, TAMA, and measures of abdominal fat area (SFA, VFA and TFA) did not have any association with post-operative outcomes in this study.

Our results also suggest that sarcopenia is independently associated with a longer length of in-hospital stay following AAA surgery. This is an important finding given the conflicting results regarding length of stay after surgery that are reported in the literature [18-20]. Our results are concordant with studies of patients with long-term co-morbid conditions such as colorectal carcinoma or chronic cardiovascular disease. Contradictory results from other studies may be due to more heterogenous study populations or varying definitions of sarcopenia.

The median BMI in this study fell within the overweight range, reinforcing the message that sarcopenia is not restricted to underweight individuals. The term "sarcopenic obesity" was coined to describe this increasingly recognised concept [21]. Our data adds to the body of evidence indicating that even overweight and obese individuals may have a degree of muscle wasting that puts them at risk of worse outcomes after surgery [8,22,23]. A decline in muscle mass in patients with a raised BMI may be more difficult to detect clinically, and evaluation of sarcopenia on CT imaging may prove particularly valuable in this patient group.

The value of accurate pre-operative risk prediction extends beyond improved surgical planning and resource allocation. A key element of the informed consent process, risk calculators have the potential to guide appropriate counselling, promote autonomous decision-making and facilitate the provision of individualised care. The role of frailty on peri-operative outcomes currently plays a limited role in most validated risk calculators used in vascular surgical patients, including NSQIP and GUPTA. This may be, at least in part, attributable to difficulties with objective identification and quantification of frailty [24]. The use of cardiopulmonary exercise testing (CPET) has shown promise in quantifying functional

capacity and predicting post-operative cardiac and pulmonary complications [25] after AAA repair. CPET results, however, are subject to a complex interaction of multiple factors and it is possible that assessment of L4-PMI and PA-S has independent incremental value.

An advantage of L4-PMI and PA-S measurement, therefore, is its utility as an independent, objective morphometric marker of frailty that requires no additional imaging in this population. Furthermore, this extended use of CT measurements, in addition to their primary purpose for assessment of aneurysmal anatomy, increases the yield of these radiological investigations. This study suggests that even a simple measurement of unilateral psoas muscle area could have utility in risk estimation. Inclusion of PA-S in risk calculators, perhaps in combination with functional assessments or CPET variables, could lend additional power to prediction models and should be the subject of future research.

Moreover, the use of sarcopenic indices in vascular surgical patients could have more extensive application than risk stratification alone. Identification of patients who may benefit from pre-operative interventions to improve outcomes, termed 'prehabilitation', may reduce morbidity and mortality. Studies investigating the impact of pre-operative nutritional programmes have demonstrated a significant reduction in post-operative complications, length of hospital stay and mortality in sarcopenic patients that was not replicated in study participants with normal or high skeletal muscle mass [26,27]. This suggests that identification of sarcopenic patients may facilitate targeting of interventions and scarce resources at those most likely to benefit and warrants further exploration.

Limitations of this study include its single centre, retrospective design and modest sample size. The study design may lead to selection bias as only cases with complete medical records and appropriate CT imaging within an acceptable time of the operation were included. This resulted in the exclusion of 219 patients from the initial cohort of 356. While the retrospective nature of the study may carry some advantages such as reducing the risk of confounding by indication, future prospective studies using a larger, multicentre trial design would be valuable in assessing the utility of sarcopenia as independent risk predictor.

There is currently no consensus in the literature regarding a quantitative definition of sarcopenia. While some studies use a predefined cut-off point, other authors utilise a cohort-specific, lowest gender-matched third of patients based on their TPA [28]. We feel the use of an unadjusted cut-off value may be inappropriate for this cohort of patients and have accordingly utilised the latter approach. Our study assessed muscle mass as measured from CT scans and consequently included no measure of muscle function in our analysis, which may bring an additional dimension to the assessment [11].

Future research into sarcopenia should look to larger, multi-centre prospective studies to confirm the findings of this study and assess if sarcopenia can also predict post-operative complications. Measures of sarcopenia could be strengthened by assessing muscle function in addition to muscle mass, or even looking at the wider concept of frailty. Additionally, the role of CPET as part of risk stratification alongside sarcopenia warrants further exploration. Meanwhile, efforts must also be made to study which pre-operative interventions hold the greatest potential for modifying the increased risk posed by sarcopenia by increasing pre-operative muscle mass and nutritional status.

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Table 1 Baseline characteristics for 137 patients before scheduled abdominal aortic aneurysm repair. Values are mean (SD), median (IQR [range]) or number (proportion).

	Total (n = 137)
Sex; male	100 (73%)
Age; y	73.9 (8.5)
Height; m	1.68 (1.63-1.74 [1.40-1.90])
Weight; kg	77.2 (68.0-91.3 [43.5-145.0])
BMI; kg.m^{-2}	27.7 (24.9-31.7 [17.0-48.0])
Albumin; g.l^{-1}	42.2 (4.1)
eGFR; ml.min^{-1}.1.73m^{-2}	66.5 (22.3)
L4 PMI; mm^2.m^{-2}	766.3 (185.6)
Comorbidity	
Hypercholesterolaemia	102 (78%)
Stroke or TIA	13 (10%)
Chronic renal impairment	104 (80%)
Myocardial infarction	25 (18%)
Angina	35 (26%)
Chronic heart failure	3 (2%)
Peripheral arterial disease	9 (7%)
Type of repair	
Endovascular, not complex	67 (49%)
Endovascular, complex	54 (39%)
Endovascular, thoraco-abdominal	11 (8%)
Open	5 (4%)

BMI, body mass index; eGFR, estimated glomerular filtration rate (MDRD method); L4 PMI, combined cross-sectional areas of left and right psoas muscles at L4 per metre height; TIA, transient ischaemic attack

Table 2: Univariate regression for pre-operative variables associated with survival in patients undergoing AAA repair. Variable associated with survival are highlighted in bold. Hazard ratio > 1 indicates increased risk of dying

	Number of patients	Hazard Ratio (95%CI)	Standard Error	z	p value
Age; years	137	1.077 (1.018-1.140)	0.031	2.58	**0.01**
Male sex	137	0.813 (0.335-1.978)	0.369	-0.46	0.649
Weight; kg	137	0.997 (0.973-1.021)	0.012	-0.27	0.787
Height; m	137	0.051 (0.0004-5.961)	0.123	-1.23	0.22
BMI; $kg.m^{-2}$	137	1.010 (0.936-1.090)	0.039	0.25	0.801
Haemoglobin concentration; $g.L^{-1}$	131	0.987 (0.967-1.007)	0.01	-1.26	0.207
Albumin; $g.L^{-1}$	108	0.943 (0.864-1.029)	0.042	-1.32	0.186
Creatinine; $\mu mol.kg^{-1}$	132	0.997 (0.988-1.007)	0.005	-0.54	0.591
eGFR; $ml.min^{-1}.1.73m^{-2}$	137	0.995 (0.979-1.010)	0.008	-0.68	0.496
L3TAMA:	137	0.943 (0.864-1.029)	0.042	-1.32	0.186
L3TAMA; mm^2		1.000 (0.988-1.012)	0.006	0.03	0.979
L3TAMA index; $mm^2.m^{-2}$		1.010 (0.975-1.046)	0.018	0.57	0.572
L4:	134				
SFA; mm^2		1.001 (0.998-1.005)	0.002	0.66	0.509
VFA; mm^2		0.998 (0.994-1.003)	0.002	-0.72	0.469
TFA; mm^2		1.000 (0.998-1.002)	0.001	0.01	0.992
TFA:TAMA ratio		1.019 (0.639-1.626)	0.243	0.08	0.937
TPA:	134				
Right + Left TPA; mm^2		0.999 (0.999-1.000)	0.0004	-1.65	0.099
PMI; $mm^2.m^{-2}$		0.998 (0.996-1.000)	0.0013	-1.61	0.107
RightTPA; mm^2		0.999 (0.998-1.000)	0.001	-1.25	0.211
LeftTPA; mm^2		0.999 (0.997-1.000)	0.001	-1.97	**0.049**
LeftTPA corr for weight; $mm^2.kg^{-1}$		0.854 (0.742-0.983)	0.061	-2.2	**0.027**
LeftTPA corr for body size; $mm.kg^{-0.83}$		0.924 (0.864-0.988)	0.032	-2.31	**0.021**

CI, Confidence Interval; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate; L3TAMA, Total Abdominal Muscle Area at the 3rd lumbar vertebral level; SFA, Superficial Fat Area; VFA, Visceral Fat Area; TFA, Total Fat Area; TPA, Total Psoas Area; PMI, Psoas Muscle Index

Table 3: Multivariate Cox regression for pre-operative variables associated with survival in patients undergoing AAA repair. Hazard ratio > 1 indicates increased risk of dying

	Hazard ratio (95% CI)	**Standard error**	**z**	**p value**
Age; years	1.063 (1.005-1.125)	0.031	2.13	**0.034**
Left TPA / Power(kg,-0.83)	0.941 (0.879-1.007)	0.033	-1.75	0.080

OR, Odds Ratio; CI, Confidence Interval; CVA, Cerebrovascular Accident; eGFR, estimated Glomerular Filtration Rate; L4-PMI, Psoas Muscle Index at 4th lumbar vertebral level

Table 4: Multivariate Cox regression for pre-operative variables associated with Length of Hospital of Stay. Hazard ratio > 1 indicates earlier discharge home.

	Hazard ratio (95% CI)	**Standard error**	**z**	**p value**
Age; years	1.021 (1.000-1.042)	0.011	1.99	**0.047**
Left TPA / Power(kg,-0.83)	1.053 (1.027-1.080)	0.014	3.99	**<0.0001**

OR, Odds ratio; CI, confidence interval; TPA, Total psoas area

Figure 1 Comparison of Kaplan–Meier curves for actual (up to 5 year) survival (—) with 95% Confidence Intervals (—) against predicted survival (—), derived from a survival calculator [16].

[To be supplied as separate document]