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SYSTEMATIC REVIEW

Effect of Low Skeletal Muscle Mass on Post-operative Survival of Patients With Abdominal Aortic Aneurysm: A Prognostic Factor Review and Meta-Analysis of Time-to-Event Data

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WHAT THIS PAPER ADDS

Patients with abdominal aortic aneurysm (AAA) often present with a significant burden of comorbidities and are likely to be frail. Low skeletal muscle mass, a surrogate of sarcopenia and indicator of frailty, has been associated with increased mortality and morbidity after surgery. The prognostic role of low skeletal muscle mass in the survival of patients with AAA undergoing open or endovascular repair was investigated by conducting a meta-analysis of bibliographic data. Patients with low skeletal muscle mass had a significantly higher risk of mortality. Further research is required to validate the use of body composition for risk prediction after aortic surgery.

Objective/Background: Low psoas muscle mass is associated with increased mortality and morbidity after surgery. Recent evidence has linked low psoas muscle mass with survival after abdominal aortic aneurysm (AAA) repair. The aim of this study was to investigate the prognostic role of low skeletal muscle mass in survival of patients with AAA undergoing open or endovascular aneurysm repair (EVAR).
Methods: A review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PROSPERO registration number: CRD42018107793). The prognostic factor of interest was degenerative loss of skeletal muscle. A time-to-event data meta-analysis was performed for all cause mortality using the inverse variance method and the results were reported as summary hazard ratio (HR) and 95% confidence interval (CI). Pooled estimates of peri-operative outcome data were calculated using the odds ratio (OR) or risk difference (RD) and 95% CI. Random-effects models of meta-analysis were applied.
Results: Seven observational cohort studies reporting a total of 1,440 patients were eligible for quantitative synthesis. Patients with low skeletal muscle mass had a significantly higher hazard of mortality than those without low skeletal muscle mass (HR 1.66, 95% CI 1.15—2.40; $p = .007$). Subgroup analysis including only patients who underwent EVAR showed a marginal survival benefit for patients without low skeletal muscle mass (HR 1.86, 95% CI 1.00—3.43; $p = .05$). Meta-analysis of two studies found no significant difference in peri-operative mortality (RD 0.04, 95% CI −0.13 to 0.21) and morbidity (OR 1.58, 95% CI 0.90—2.76; $p = .11$) between patients with and without low skeletal muscle mass.
Conclusion: There is a significant link between low skeletal muscle mass and mortality in patients undergoing AAA repair. Prospective studies validating the use of body composition for risk prediction after aortic surgery are required before this tool can be used to support decision making and patient selection.

Keywords: Aortic aneurysm, Frailty, Psoas muscle mass, Sarcopenia, Survival
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INTRODUCTION

Patients with abdominal aortic aneurysms (AAAs) often present with a significant burden of comorbidities and are likely to be frail.[1—3] Despite this, the peri-operative morbidity and mortality in this group of patients has significantly improved in the last two decades as a result of the wide adoption of endovascular aneurysm repair (EVAR) and pre-operative risk stratification and modification.[4]

Current predictive models and assessment methods have limited value since they use only a snapshot of clinical information and can rarely predict outcomes beyond the peri-operative period.[5–7] A search for a better way of stratifying patients resulted in attempts to adopt more comprehensive assessment strategies that include frailty assessment and analysis of body composition, also known as morphometry.[1–3,8] Some morphometric parameters (morphomarkers), such as low psoas muscle mass, have been associated with mortality and major complications after vascular,[2,9] trauma,[10,11] cancer,[12] and transplant surgery.[13] Recent research linked low muscle mass with medium-term outcomes after AAA surgery.[2,14–19] However, these studies were retrospective, based on very modest sample sizes, and differed in methodology.

A systematic review was conducted with the aim of analysing the available evidence on the prognostic value of low core muscle mass in patients undergoing surgery for AAA and to help define future research objectives. The specific objective was to investigate whether patients undergoing surgical treatment for AAA who have low skeletal muscle mass have a lower survival than patients with AAA without low skeletal muscle mass.

METHODS

Review design

The objectives and methodology of the review were pre-specified in a protocol, which was registered (registration number: CRD42018107793) at the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO), developed and maintained by the Centre for Reviews and Dissemination of the University of York, UK.[20] The review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Criteria for considering studies

Types of studies. All types of studies investigating the role of low skeletal muscle mass as a prognostic factor for survival in patients undergoing interventional treatment for AAA were considered.

Types of participants. Eligible participants were patients with a confirmed diagnosis of AAA who underwent elective endovascular or open surgical repair. Only patients who had been worked up with computed tomography (CT) within a maximum of 12 months prior to surgical treatment for AAA were considered.

Type of prognostic factor. The prognostic factor of interest was degenerative loss of skeletal muscle (low skeletal muscle mass). Eligible studies would have commonly used psoas muscle area as the surrogate for skeletal muscle loss. Psoas muscle area would have been measured on axial CT imaging at the level of the third or fourth lumbar vertebra. Any method (semi-automated contour detection algorithm or manual segmentation of muscle groups) used to define the cross sectional area of the right and left psoas muscles applying any threshold (in Hounsfield units) to identify muscle tissue was considered.

Types of outcome measures. *Primary outcome* Primary outcome was defined as all cause mortality during follow up after surgical treatment for AAA.

Secondary outcomes Secondary outcome endpoints were peri-operative (in hospital or 30 day) mortality and morbidity. The definition of peri-operative morbidity set by the individual studies was accepted.

Search methods for identification of studies

The literature search strategy was developed by the review author team in collaboration with clinical information specialists. Studies related to the subject were identified by searching electronic information sources and scanning bibliographic lists of relevant articles. The Healthcare Databases Advanced Search (HDAS) interface developed by the National Institute for Heath and Care Excellence (NICE) was used. The following electronic bibliographic databases were interrogated: the National Library of Medicine's database (MEDLINE), Excerpta Medica Database (Embase), and the Cochrane Register of Studies (CRS) (CENTRAL). A combination of controlled vocabulary and free text terms was used to search the databases. No language constraints were applied. The literature search was run in September 2018 and an additional limited literature search was conducted in February 2019. The search strategy is presented in Appendix S1 (Supplementary Material).

Selection of studies and data management

Two review authors (G.A., J.R.) conducted the pre-specified literature searches and evaluated the eligibility of studies independently. When disagreement arose, a third review author (SA) acted as an arbitrator.

One review author (G.A.) extracted data from selected studies. The collected data were then cross checked by a second review author (S.A.). Retrieved data were entered into a spreadsheet. Only published data were considered. The following information was extracted: (i) study related data (year and journal of publication; country of the corresponding author; single or multicentre study; prospective or retrospective study design; time period over which patients were recruited; inclusion and exclusion criteria for patient enrolment; definition/stratification of low skeletal muscle mass; low skeletal muscle mass stratification method; total number of patients in the entire cohort; number of patients with and without low skeletal muscle mass; duration of follow up); (ii) data related to risk of bias assessment (see next section); (iii) clinical characteristics of the study populations (sex; age; body mass index [BMI]; smoking history; co-morbidities including diabetes mellitus, coronary artery disease, hypertension, chronic obstructive pulmonary disease and chronic kidney disease; type of surgery [endovascular or open repair]); (iv) outcome data, as outlined in the “Criteria for considering studies” section.

Assessment of risk of bias of included studies

The Quality in Prognosis Studies (QIPS) tool was used to evaluate the validity and bias in selected studies.[22] The tool consists of six domains that can inform judgements of risk of bias in prognostic research: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. Each domain consists of items for which the adequacy of reporting can be judged as yes, no, or unsure. The potential risk of bias in each of the six domains is rated as high, moderate, or low considering all relevant issues. The risk of bias assessment was performed by two review authors independently (G.A., M.J.) and discrepancies were resolved by discussion.

Data synthesis

Measures of treatment effect. When the authors of selected studies stratified the psoas muscle area in tertiles (low, medium, and high psoas muscle area) with or without normalisation for patient sex and/or height, the lowest tertile was considered as the working definition for low skeletal muscle mass and outcomes between the low and medium/high tertile group were compared. When authors defined low skeletal muscle mass using a (commonly arbitrary) cut-off value of psoas (or any other abdominal or pelvic skeletal muscle) muscle area (with or without normalisation for sex and/or height), outcomes were compared in patients with and without low skeletal muscle mass based on the definition set by the study authors.

Pooled estimates of dichotomous peri-operative (in hospital or 30 day) outcome data (e.g., in hospital mortality) were calculated using the odds ratio (OR) or risk difference (RD) and associated 95% confidence interval (CI). For continuous outcome variables (e.g., length of hospital stay), the plan was to calculate the weighted mean differences using mean $\pm$ standard deviation (SD).

For late outcomes (e.g., all cause mortality during follow up), a time-to-event data meta-analysis was conducted using the inverse variance method and the results were as summary hazard ratio (HR) and associated 95% CI. A mixture of direct (e.g., from Cox regression models or from reported HRs with CI) or indirect methods (e.g., when the *p* value from log rank test and total events were provided, or from survival curves incorporating numbers at risk) was applied to calculate the individual study HR and standard error (SE) for specific outcome measures.[23] Data extracted from published Kaplan—Meier curves were digitised using the open source software Plot Digitizer (http://plotdigitizer.sourceforge.net).

A further meta-analysis of key clinical characteristics was performed to evaluate whether there was variability in the demographics of patients with and without low skeletal muscle mass.

Assessment of heterogeneity. Inter-study heterogeneity was assessed visually using a forest plot. The I^2 statistic was also calculated to measure the amount of inter-study heterogeneity. I^2 values $< 50\%$ were considered as indicative of low heterogeneity, I^2 values of 50—75% as indicative of moderate heterogeneity, and I^2 values $> 75\%$ as indicative of significant heterogeneity.

Missing data. No attempt was made to contact the authors of included studies to enquire about missing or incomplete data.

Data synthesis. In view of the anticipated variability in the cut-off threshold to define low skeletal muscle mass and the clinical or methodological diversity among the selected studies, summary estimates were calculated using the random-effects models of DerSimonian and Laird.[24] A forest plot for each treatment effect was created.

Sensitivity and subgroup analysis. Studies of low methodological quality in two or more domains of the QIPS tool were sequentially excluded and a pooled sensitivity analysis was performed in order to assess whether the included studies, deemed to be biased, affected the final analysis. A subgroup analysis for the type of surgery for AAA (endovascular or open repair) was conducted.

Statistical software

For data synthesis, RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen) was used.

RESULTS

Results of the literature search

The literature search revealed seven eligible studies that investigated the prognostic role of low skeletal muscle mass in survival of patients undergoing surgery for AAA.[2,14—19] One study assessed the association between cross sectional areas of abdominal muscles, including psoas muscle, with survival, but provided no comparative data and performed no comparative analysis of outcomes in patients with and without low skeletal muscle mass and was therefore excluded from quantitative synthesis.[16] Two additional relevant studies were identified through regular interrogation of contemporary vascular literature: one was deemed suitable for inclusion in the meta-analysis;[25] the other was excluded because it did not stratify patients into groups of low and no low skeletal muscle mass, and included patients with ruptured AAA.[26] The results of the literature search are presented in Fig. 1.

Description of studies

All but one study were single centre studies,[2,14,15,17,18,25] usually of a retrospective design, published between 2011

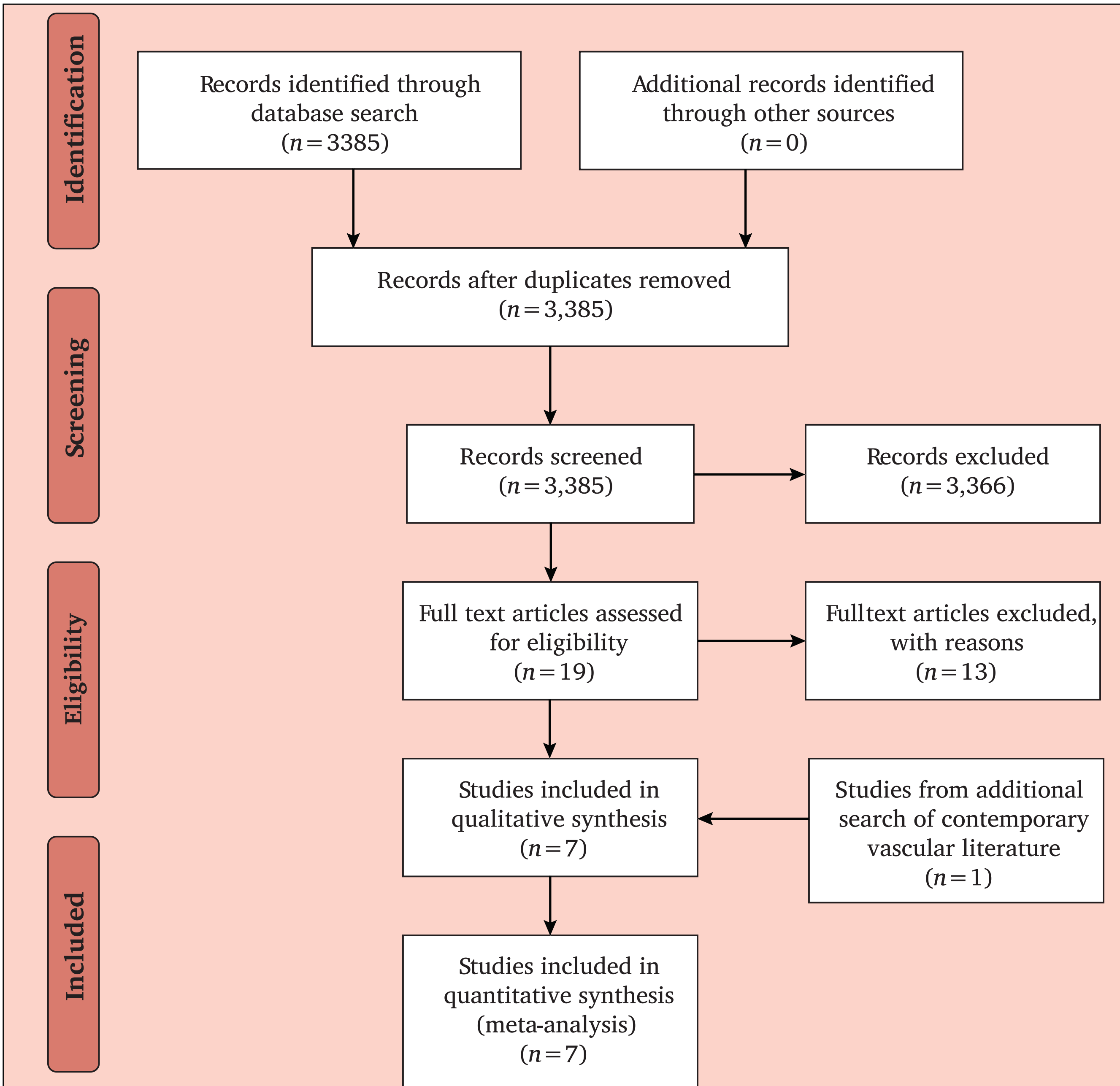

Figure 1. Study flow diagram.

and 2019, with a recruitment period extending from 1999 to 2016. Three studies were conducted in the USA,[2,15,18] and the remaining four in Canada,[14] Australia,[19] the Netherlands,[17] and the UK.[25] Three studies included only patients that underwent EVAR,[15,18,19] and another study recruited only patients who had open repair of AAA.[2] Drudi et al.[14] and Waduud et al.[25] reported a mixture of cases of EVAR and open aneurysm repair, with the former including 29 patients (19%) with complex endovascular procedures. The study characteristics are summarised in Table 1 and the inclusion/exclusion criteria for patient recruitment in the individual studies are presented in Table S1 (see Supplementary Material).

The seven studies included in the meta-analysis reported a total of 1,440 patients. Four studies stratified their patient cohort into low, medium, and high tertiles based on the total psoas muscle area and compared outcomes in patients with low vs. medium/high total psoas area.[2,14,17,18] The remaining three studies set a cut-off point for total psoas or other abdominal/pelvic skeletal (abdominal wall, paraspinal, psoas) muscle area, defined low skeletal muscle mass as the muscle area below that point, and compared outcomes in patients with and without low skeletal muscle mass.[15,19,25] The low skeletal muscle mass group of the meta-analysis population comprised a total of 374 patients; the remaining 1,066 patients did not have low skeletal muscle mass

Table 1. Study characteristics

Study	Study type	Study design	Recruitment period	Total no. of patients (low skeletal muscle mass/no low skeletal muscle mass)	Low skeletal muscle mass stratification method	Muscle area cut-off value for definition of low skeletal muscle mass	Level of psoas muscle area measurement	Method of measurement (manual or automated tracing)	Duration of follow up
Waduud et al.[25]	Single centre	Prospective[a]	January 2010–December 2016	380 (110/270)	Low vs. no low skeletal muscle mass according to set definition (corrected for sex)	5.5 cm^2 per m^2 in men, 4.0 cm^2 per m^2 in women	L3	Not reported (NR)	Mean 2.7 years (SD 2.7)
Indrakusuma et al.[17]	Single centre	Retrospective	January 2007–December 2013	124 (31/93)	Low/medium/high tertile (not corrected for sex or height)	14.6 cm^2	Central level of L3	NR	NR
Newton et al.[18]	Single centre	NR	December 2010–March 2016	134 (45/89)	Low/medium/high tertile (not mentioned whether corrected for sex or height)	240.6 cm^2 [b]	Immediately inferior to L4 superior endplate	Manual outline tool	Median 27 months (IQR 18–40)
Thurston et al.[19]	Multi centre	Retrospective	January 2008–May 2013	191 (30/161)	Low vs. no low skeletal muscle mass according to set definition (corrected for height)	50 cm^2/m^2 [b, c]	Most caudal aspect of L3	Manual tracing	NR
Drudi et al.[14]	Single centre	Retrospective	January 2010–July 2015	149 (49/100)	Low/medium/high tertile (corrected for sex)	21.7 cm^2 in men, 13.5 cm^2 in women	Top of L4	Semi-automated contour detection algorithm	Mean 22.4 months
Hale et al.[15]	Single centre	Retrospective	February 1999–December 2007	200 (25/175)	Low vs. no low skeletal muscle mass according to set definition (not mentioned whether corrected for sex or height)	114.0 cm^2 in men, 89.8 cm^2 in women (abdominal wall, spinal and psoas muscle)	Central level of L3	Manual segmentation of muscle groups	Median 8.4 years (IQR 5.3–11.7)
Lee et al.[2]	Single centre	NR	January 2000–December 2008	262 (84/178)	Low/medium/high tertile (not mentioned whether corrected for sex or height)	NR	Superior aspect of L4	Semi-automated contour detection algorithm	2.3 years

Note. IQR = interquartile range; NR = not reported; SD = standard deviation.
[a] The authors state prospective but it is probably a retrospective study.
[b] Total psoas muscle area.
[c] Normalised for patient height.

according to the definitions described above. All studies measured the skeletal muscle area at the level of the third or fourth lumbar vertebra using a manual or semi-automated tracing tool.

The baseline demographics and clinical characteristics of the study populations are presented in Table S2 (Supplementary Material). Meta-analysis of these variables showed no significant difference between patients with and without low skeletal muscle mass except for age; patients with low skeletal muscle mass were significantly older.

Risk of bias in included studies

The risk of bias graph and summary are presented in Figs. S1 and S2, respectively (Supplementary Material), and the rating of risk of bias for each domain of the QIPS tool in each study is summarised in Table 2. The risk of bias for "Study Participation" was judged to be moderate or high mainly because of inadequate participation in the studies by eligible individuals, as CT for skeletal muscle area measurement was not available for a considerable proportion of patients. Risk of bias for "Study Attrition" was high in most studies because there was no information on patients that were lost to follow up or dropped out of the studies. For the "Prognostic Factor Measurement" item of the QIPS tool, the risk of bias was moderate because the definition of low skeletal muscle mass was data dependent and the skeletal muscle area was not normalised for sex or height in most studies. No sufficient information was reported on the method of outcome of interest (i.e., survival) measurement (e.g., hospital or community records), and therefore the risk of bias for "Outcome Measurement" was judged to be moderate or high in most studies. Important potential confounders, including age, were appropriately accounted for in most studies, limiting potential bias with respect to the relationship between low skeletal muscle mass and outcome, and the statistical analysis was appropriate resulting in moderate or low risk of bias in the "Study Confounding" and "Statistical Analysis and Reporting" items of the QIPS tool. The supports for judgement of each item are summarised in Appendix S2 (Supplementary Material).

Table 2. **Assessment of risk of bias of included studies using the Quality in Prognosis Studies (QIPS) tool**

Biases	Lee et al. (2011)[2]	Hale et al. (2016)[15]	Drudi et al. (2016)[14]	Thurston et al. (2017)[19]	Newton et al. (2017)[18]	Indrakusuma et al. (2018)[17]	Waduud et al. (2019)[25]
Study Participation	High	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Study Attrition	High	High	High	High	High	Low	High
Prognostic Factor Measurement	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Outcome Measurement	High	Low	High	Moderate	Low	Moderate	Low
Study Confounding	Moderate	Low	Moderate	Moderate	Moderate	High	Moderate
Statistical Analysis and Reporting	Low	Low	Low	Low	Low	Moderate	Low

Note. Potential risk of bias for each of the six domains rated as high, moderate, or low, considering all relevant issues.

Effects of interventions

Primary outcome. All seven included studies reported time-to-event data for meta-analysis for the primary outcome (374 patients with low skeletal muscle mass and 1,066 patients without low skeletal muscle mass).[2,14,15,17–19,25] Patients with low skeletal muscle mass had a significantly higher hazard of mortality than those without low skeletal muscle mass (HR 1.66, 95% CI 1.15–2.40; $p = .007$). Statistical heterogeneity was moderate ($I^2 = 55\%$, $p = .04$) (Fig. 2).

Secondary outcomes. Two studies reported data on peri-operative mortality (529 patients).[14,25] Data on the proportion of patients who underwent EVAR were provided in one of these studies,[14] in which more patients in the low skeletal muscle mass group underwent EVAR than open aneurysm repair (94% vs. 80%; $p = .08$). Patients with low skeletal muscle mass were not found to have a higher risk of peri-operative mortality than those without low skeletal muscle mass (RD 0.04, 95% CI −0.13 to 0.21; $p = .66$). The statistical heterogeneity was significant ($I^2 = 93\%$, $p < .001$).

Two studies reported data on peri-operative complications (529 patients).[18,19] Both included only patients who underwent EVAR. Meta-analysis showed no significant difference in the peri-operative morbidity risk between patients with and without low skeletal muscle mass (OR 1.58, 95% CI 0.90–2.76; $p = .11$). The between study statistical heterogeneity was low ($I^2 = 0\%$; $p = .73$).

Sensitivity and subgroup analysis. Removing one study at a time did not change the pooled estimate for any of the outcomes. Removing the two studies that scored a high risk of bias in two or more domains of the QIPS tool did not alter the results of the meta-analysis either.[2,14]

Subgroup analysis including only patients who underwent EVAR showed a marginal survival benefit for patients without low skeletal muscle mass (HR 1.86, 95% CI 1.00–3.43; $p = .05$). The statistical heterogeneity was moderate ($I^2 = 67\%$, $p = .003$).

DISCUSSION

Summary of main results

Meta-analysis of time-to-event data found that patients with low skeletal muscle mass who underwent surgery for AAA had a significantly higher risk of death during follow up. Subgroup analysis of patients that underwent EVAR showed a marginal survival benefit in favour of patients without low skeletal muscle mass. Pooled analysis of the two studies that reported data on peri-operative morbidity in patients who underwent EVAR found no significant difference between patients with and without low skeletal muscle mass.

Overall completeness and applicability of evidence

The decision to repair an AAA relies on the balanced risk between rupture if the aneurysm is left untreated and the peri-operative mortality and morbidity of elective surgery. Several risk stratification models have primarily focused on peri-operative outcomes.[5–7] Recently, low skeletal muscle mass has been introduced as a surrogate of frailty and physiological reserve and as an indicator of sarcopenia. It has been linked to increased risk of peri-operative adverse events and mortality and reduced medium-term survival after surgery for AAA. The European Working Group on Sarcopenia in Older People and International Working Group on Sarcopenia have proposed a definition of sarcopenia that includes both reduced muscle mass and muscle function.[27] The methods by which sarcopenia is diagnosed varies across the literature; most studies have included direct measures of muscle strength assessed by clinical evaluation and/or indirect measures of skeletal muscle mass (area or volume) or consistency using cross sectional imaging (e.g., CT).[28] As CT is an essential part of the pre-operative work up in elective AAA treatment that allows examination of aneurysm morphology and EVAR planning, it is readily available for assessment of skeletal muscle mass and an indirect measurement of sarcopenia. It can therefore be used as a tool for risk stratification and assessment of long-term prognosis in patients with AAA.

All studies included in this review represent real world clinical practice including relatively homogenous cohorts of patients with degenerative AAA and treatments. Two studies explicitly reported inclusion of patients with aortic anatomy suitable for EVAR.[15,18] Therefore, it remains unknown whether the results of this review can be extrapolated to the entire AAA population undergoing surgical treatment or to patients with aneurysm morphology amenable to EVAR, as there has been no research

Study or Subgroup	log [Hazard Ratio]	SE	Low core muscle mass Total	No low core muscle mass Total	Weight	Hazard Ratio IV, Random, 95%CI	Year
Lee	0.28	0.29	84	178	16.5%	1.31 [0.75, 2.34]	2011
Hale	0.75	0.3	25	175	16.1%	2.05 [1.14, 3.70]	2016
Drudi	0.79	0.38	49	100	12.9%	2.20 [1.05, 4.64]	2016
Thurston	0.9708	0.3384	30	161	14.4%	2.64 [1.36, 5.12]	2017
Newton	1.28	0.62	45	89	6.9%	3.60[1.07, 12.12]	2017
Indrakusuma	0.35	0.34	31	93	14.4%	1.42 [0.73, 2.76]	2018
Waduud	−0.1863	0.2386	110	270	18.9%	0.83 [0.52, 1.32]	2019
Total (95% CI)			**374**	**1066**	**100.0%**	**1.66 [1.15, 2.40]**	

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 13.25$, $df = 6$ ($P = 0.04$); $I^2 = 55\%$
Test for overall effect: $Z = 2.70$ ($P = 0.007$)

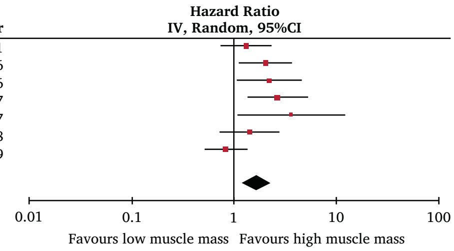

Figure 2. Forest plot of survival in patients with vs. without low skeletal muscle area. *Note.* CI = confidence interval; IV = inverse variance; SE = standard error.

investigating potential association between morphological features of AAA and skeletal muscle mass.

The selected studies investigated the impact of low skeletal muscle mass on survival of patients that underwent surgery. It is uncertain whether low muscle mass is associated with reduced survival in patients with AAA that undergo no treatment because they are considered unfit for surgery. Indrakusuma et al.[17] found that patients with AAA managed conservatively had a lower psoas muscle area and were older than patients receiving surgery, but there was no survival difference between patients with and without low skeletal muscle mass in this conservative patient cohort. It remains to be investigated whether low skeletal muscle mass may constitute a prognostic factor for all patients diagnosed with AAA that are considered for treatment or only for the subgroup of AAA patients that undergo surgical intervention.

The external validity of the present findings and the use of skeletal muscle mass as a universal tool for risk stratification is also limited by the lack of a clear definition of low skeletal muscle mass. Four of the studies included in the meta-analysis divided their patient cohorts into tertiles according to the total skeletal muscle area, and the lowest tertile was used as the working definition of low skeletal muscle mass.[2,14,17,18] Two studies corrected muscle area cut-off values for sex,[14,25] and one for height,[19] with the remaining studies either not making any corrections for sex or height or not reporting this information at all. The definition of low skeletal muscle mass was therefore data dependent, which makes it difficult (if not impossible) to transfer findings of this meta-analysis into clinical practice and translate research data into a morphometric stratification system. Furthermore, the level of skeletal muscle measurement ranged from the central level of L3 to inferior to L4 superior endplate, and the method of measurement varied across the studies with some researchers having used manual tracing and some others semi-automated muscle contour detection methods. Standardisation of measurement of skeletal muscle area, probably through an international consortium consensus, may enhance the applicability of morphometric parameters in survival prediction models.

Quality of the evidence

Seven studies were identified that compared clinical outcomes in a total of 1,440 patients with and without low skeletal muscle mass.[2,14,15,17–19,25] All patients underwent surgery for AAA (either EVAR or open repair) and were followed up for a period ranging from 22 months to eight years. The quality of the available evidence is downgraded by the retrospective design of most studies included in the review. However, the results of most studies were consistent, demonstrating a survival benefit in patients who were found not to have low skeletal muscle mass on cross sectional imaging. The statistical heterogeneity was moderate, reflecting a fairly homogenous meta-analysis population (the majority had degenerative infrarenal aortic aneurysm and were suitable for treatment by either open or endovascular repair). Heterogeneity also reflects different definitions of low skeletal muscle mass and methodological diversity across the studies. Solid conclusions cannot be drawn on the impact of low skeletal muscle mass on peri-operative mortality as only two studies with a limited number of patients and events reported this outcome.[14,25] Even though clinical characteristics were similar between patients with and without low skeletal muscle mass, there was a significant difference in age, which is a major confounder and prognostic factor for survival. Age specific reference values may be more advantageous in identifying skeletal muscle mass depletion and defining the role of reduced psoas muscle area in risk prediction in the AAA population.[29]

Even though most studies were judged to be of low to moderate risk of bias in most domains of the QIPS tool, six studies were found to have high risk of attrition bias,[2,14,15,18,19,25] which is a major deficiency in survival studies. Insufficient information was provided on the proportion of baseline sample available for analysis and on whether and how many patients dropped out of those studies. However, most studies measured important confounders, including age, and applied an appropriate statistical analytical strategy. Furthermore, the possibility of publication bias was not assessed because of the insufficient number of studies.[30]

Potential biases in the review process

An exhaustive literature search was performed to identify all studies investigating the prognostic role of low skeletal muscle mass in patients with AAA; however, the "grey literature" was not interrogated, i.e. work that is either unpublished or has been published in non-commercial form, resulting in the possibility of an amount of research data having escaped consideration. Furthermore, no attempt was made to contact authors of the primary studies enquiring about missing data related to baseline demographics (e.g., BMI), clinical characteristics (e.g., presence of diabetes or chronic kidney disease), or outcomes (e.g., peri-operative mortality). The methods of statistical analysis may have introduced bias, as two studies only directly reported unadjusted values of HR from Cox regression models,[19,25] whereas in the remaining studies the HR was calculated indirectly from curve data with numbers at risk or total number of deaths and log rank *p* value.

Agreements and disagreements with other studies or reviews

Even though there is no previous review on the role of low skeletal muscle mass in patients undergoing vascular surgery, there is ample evidence investigating the prognostic role of low skeletal muscle mass as an indicator of sarcopenia in other surgical disciplines, including abdominal surgery,[31] spinal surgery,[32] oncological surgery,[33,34] and trauma.[35] A recent systematic review and meta-analysis of 24 cohort studies that enrolled a total of 5,267 patients who had any type of abdominal surgery found sarcopenia to be associated with a significant risk of major post-operative complications and 30-day mortality and to be a predictor of survival at one, two, and three years.[31] The largest volume of research in this topic is in oncological surgical populations, in whom the prevalence of sarcopenia has been shown to be high. In a systematic review and meta-analysis, sarcopenia identified before surgery by CT was found to be associated with reduced overall survival in patients having surgery for gastrointestinal and hepatopancreatobiliary malignancies.[33] Sarcopenia has also been found to be an increased mortality risk in patients undergoing amputation for diabetic foot sepsis.[36] However, one would speculate that other patient groups, such as those of patients with cancer or diabetes mellitus, may have different morphometric characteristics; therefore, extrapolating the results of those studies in the AAA population would probably be inappropriate.

The role of muscle strength, which constitutes the other aspect of the definition of sarcopenia, has been inadequately investigated. Such research would provide further insight into the prognostic significance of sarcopenia in surgical patients and add to the evidence base for incorporating sarcopenia in surgical risk stratification tools.

In addition to its potential prognostic role and risk stratification in surgical patients, sarcopenia may be a modifiable frailty parameter, which underlines the potential role of prehabilitation and targeted interventions to optimise patient health and fitness prior to major surgery. A systematic review and meta-analysis of seven randomised controlled trials found that exercise interventions, nutritional interventions, and the combination of the two may be effective in improving muscle mass and function parameters.[37] Sarcopenic vascular, general surgery, and transplant patients that participated in a pre-operative training and support programme aimed at optimising sarcopenia had reduced length of stay and reduced costs compared with sarcopenic patients that did not take part in this programme.[38]

CONCLUSIONS

Implications for practice

There is a significant and clinically relevant link between low core muscle mass and mortality in patients undergoing AAA repair. As cross sectional imaging is an essential part of the pre-operative work up for patients with AAA, measurements of skeletal muscle cross section is possible in most cases. Defining and validating universally accepted thresholds for psoas muscle area would be helpful in the use of low skeletal muscle mass as (or within) a risk stratification tool and decision making in cases of uncertainty in survival advantage of AAA treatment.

Implications for research

A universally accepted definition and measurement method for low skeletal muscle mass is required. Prospective studies validating the use of body composition for risk prediction after aortic surgery are required before this tool can be widely used to support decision making and patient selection. The impact of modifying sarcopenia and improvement in core muscle mass and function within prehabilitation programmes on outcomes after AAA surgery is a virgin and potentially promising research field.

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.2019.03.020.

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