

Title: Frailty factors and outcomes in vascular surgery patients: a systematic review and meta-analysis

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Systematic Review

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Abstract

Objective

To describe and critique tools used to assess frailty in vascular surgery patients, and investigate its associations with patient factors and outcomes.

Background

Increasing evidence shows negative impacts of frailty on outcomes in surgical patients, but little investigation of its associations with patient factors has been undertaken.

Methods

Systematic review and meta-analysis of studies reporting frailty in vascular surgery patients (PROSPERO registration: CRD42018116253) searching Medline, Embase, CINAHL, PsycINFO and Scopus. Quality of studies was assessed using Newcastle-Ottawa scores (NOS) and quality of evidence using GRADE criteria. Associations of frailty with patient factors were investigated by difference in means (MD) or expressed as risk ratios (RR), and associations with outcomes expressed as odds ratios (OR) or hazard ratios (HR). Data were pooled using random effects models.

Results

Fifty-three studies were included in the review and only 8 (15%) were both good quality (NOS ≥ 7) and used a well-validated frailty measure. Eighteen studies (62,976 patients) provided data for the meta-analysis. Frailty was associated with increased age (MD 4.05 years; 95% confidence interval [CI] 3.35, 4.75), female sex (RR 1.32; 95%CI 1.14, 1.54), and lower body-mass index (MD -1.81; 95%CI -2.94, -0.68). Frailty was associated with 30-day mortality (adjusted [A]OR 2.77; 95%CI 2.01-3.81),

24 post-operative complications (AOR 2.16; 95%CI 1.55, 3.02) and long-term mortality
25 (HR 1.85; 95%CI 1.31, 2.62). Sarcopenia was not associated with any outcomes.

26 Conclusion

27 Frailty, but not sarcopenia, is associated with worse outcomes in vascular surgery
28 patients. Well-validated frailty assessment tools should be preferred clinically, and in
29 future research.

INTRODUCTION

Frailty is increasingly recognised as an important consideration in the peri-operative management of older adults.¹ Frailty has been described in two broad models: as a phenotype encompassing weight loss, weakness, poor endurance, slowness and low physical activity; and as an accumulation of deficits in different physiological systems that, in combination, are associated with increased risk of institutionalisation and death.^{2, 3} A number of validated tools based upon these definitions have been developed to assess individual patients for frailty.^{4, 5} Additionally, frailty has significant overlap with sarcopenia which is defined as “a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes” and is also the focus of increasing research in older patients undergoing surgery.⁶ Frail patients have reduced physiological reserve to respond to acute stressors and are more likely to suffer adverse health outcomes.⁷ Recent systematic reviews have shown frailty to be associated with worse outcomes, such as post-operative complications, increased length of stay, functional decline, poor quality of life and reduced survival, following cardiac and major non-cardiac surgery.^{1, 8}

Numerous different tools, both validated and unvalidated, have been used to assess frailty in surgical patients and no consensus exists on the optimal assessment.⁹ Additionally, sarcopenia can be assessed using cross-sectional imaging and has been utilised as a proxy measure for frailty.¹⁰ Vascular surgery patients are frequently old, with multiple-comorbidities, and frailty may be highly prevalent among those undergoing major arterial surgery.¹¹

The aims of this systematic review and meta-analysis were to describe and critique the tools used in published studies to assess frailty (including sarcopenia) in vascular surgery patients, the quality of evidence for their use, and investigate patient factors associated with frailty and its association with outcomes in vascular surgery patients.

METHODS

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018116253). The report was prepared in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.¹²

Search strategies

Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and Scopus were searched from inception to September 2018 for articles investigating frailty and sarcopenia in vascular surgery patients. Search strategies for both frailty, and frailty tools, plus vascular surgery were developed in Medline in collaboration with an experienced clinical librarian (CP), then adapted for, and applied to the other databases (Appendix 1 and 2, Supplemental Digital Content). Reference lists of included studies were also hand searched. Search results were combined using Endnote® (version X7 for Windows, Clarivate Analytics, Philadelphia, PA, USA) and duplicate references removed. Searches were re-run on 8th March 2019.

Study selection

Two reviewers (JH and AN) independently screened titles and abstracts against inclusion and exclusion criteria (Table S1, Supplemental Digital Content). Full texts were then screened by two reviewers (JH plus AN, AM or SN) independently.

Disagreements were resolved by discussion. Study selection was based on the following inclusion criteria: studies that included vascular patients assessed using a defined or previously validated measure of frailty or sarcopenia; and reported on either associations of frailty with patient factors and/or outcomes. Studies were excluded if: they included vascular patients with asymptomatic disease or disease below threshold for treatment; frailty was only measured post-intervention; no comparison was made between either frail and non-frail patients (or frailty scores in patients experiencing and not-experiencing the primary endpoint); non-frail patients were not included; studies in which data for vascular patients were not reported separately; and studies that included patients with vascular trauma whose data were not reported separately. Conference abstracts were included in the review to ensure breadth. Authors of included conference abstracts were contacted if eligible for inclusion into the meta-analysis. Non-English language articles were translated into English using Google Translate® (Google, Mountain View, CA, USA) prior to screening. A similar method has been described previously and was felt to be a reasonable methodological compromise to ensure breadth of the review.¹³ No non-English studies were subsequently included in the review.

Data extraction and quality assessment

Data were extracted from the included studies and study quality assessed by two independent reviewers (JH plus AN, AM or SN). Study quality was assessed using the Newcastle-Ottawa scale (NOS) for cohort studies or an adapted version for cross-sectional studies.^{14, 15} Details of whether the tool(s) used to assess frailty were validated in previous research was classified as: not validated, validated in a disease-specific population, or validated in a general population of older adults. Validation of both the tool and cut-off used to define frailty, either by its association

with poor health-related outcome or diagnostic accuracy against an established frailty tool validated in a general older adult population, was required. Study reference lists and original articles reporting the development of the frailty tool were used to assess validation. For tools repurposed to identify frailty (e.g. tools to assess disability), Medline was searched ([assessment tool] AND frail*.af) to assess validation. Studies not using a defined multi-domain tool were deemed not-applicable to validation and treated as not validated. Studies with NOS ≥ 7 and using a frailty measure validated in a general population of older adults were deemed high-quality. Disagreements were again resolved by discussion.

Narrative synthesis

A descriptive narrative of results was undertaken for all studies included in the systematic review. Frailty assessment tools used in the included studies were evaluated by the domains assessed and method of assessment (patient self-report or clinical assessment/health record). Details were recorded of score range and cut-off for defining frailty. A similar process was undertaken for studies investigating sarcopenia as a marker of frailty. A number of studies included patient data from the American College of Surgeons National Surgical Quality Improvement Programme database (ACS-NSQIP). Study designs were compared to ensure results from the same patients were not included more than once in the subsequent meta-analysis.

Meta-analysis

Data from studies which reported patient factors and/or outcomes for frail and non-frail patients separately were eligible to be included in the meta-analysis. Studies that did not define a cut-off value for frailty or sarcopenia, or defined it based on a proportion of the study population (e.g. lowest tertile), and studies with overlapping

patient cohorts were excluded from the meta-analysis (Table S1, Supplemental Digital Content).

Data extracted from included studies were pooled in accordance with methodology detailed in the Cochrane Handbook (version 5.1.0).¹⁶ Data for associations of patient factors with frailty were either continuous or dichotomous. Continuous data comparing patient factors by frailty were expressed as difference of means (MD) and dichotomous data as risk-ratios (RR). Unadjusted data for associations of frailty with short-term outcomes were dichotomous and expressed as odds-ratios (OR) and adjusted data for associations with outcomes reported as OR, or adjusted time-to-event data reported as hazard-ratios (HR). One study reported frailty as low, intermediate or high and was dichotomised by pooling data from the intermediate and high groups.¹⁷ This study reported long-term mortality as adjusted time-to-event data which were pooled using the generic inverse variance method (random effects) before entry into the meta-analysis.

Meta-analyses were performed for factors and outcomes reported by a minimum of three studies, irrespective of frailty tool used. Random-effects models were used to pool data for all outcomes due to expected heterogeneity of included studies. Mean differences were combined using the inverse variance method. The Mantel-Haenszel method was used for RR assessing associations with patient factors, and OR assessing associations with outcomes (unadjusted for confounders). Inverse variance method was used to combine adjusted OR and HR assessing associations with outcomes. Effect estimates were reported with 95% confidence intervals (CI) and presented as forest plots. The χ^2 heterogeneity test was used to assess each outcome for overall heterogeneity and expressed as an I^2 statistic. Subgroup analyses were undertaken for all outcomes, grouping studies into three subgroups

by frailty tool used: validated, unvalidated or sarcopenia. Sensitivity analyses were performed by removing data extracted from data from studies that used only sarcopenia as a measure of frailty. No minimum study number threshold was set for subgroup or sensitivity analyses. All statistical analyses were undertaken using Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Risk of bias for studies included in the meta-analysis was assessed using the Risk of Bias In Non-Randomized Studies – of Exposures (ROBINS-E) tool.¹⁸ Overall quality of the evidence for each patient factor and outcome meta-analysis were rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system using GRADEpro Guideline Development Tool (McMaster University, Hamilton, Ontario, Canada).¹⁹

RESULTS

After de-duplication and inclusion of additional records, 4665 records were identified and screened. A further five records were included after the searches were re-run. A total of 53 studies were identified that met the inclusion and exclusion criteria (Figure 1).^{10, 11, 17, 20-69} Of these, three were conference abstracts.^{43, 48, 66} One study reported patients undergoing different vascular surgery procedures separately (four populations) and two studies reported patients in two separate groups.^{33, 49, 67} These were treated separately in the review, giving a total of 59 included study populations.

Study designs

Four studies using a frailty assessment tool were prospective cohorts,^{11, 17, 43, 61} one was cross-sectional,⁵⁷ and 24 were retrospective cohorts.^{21-24, 26, 30, 31, 33, 36-41, 44, 45, 51, 52, 56, 62, 63, 65, 68, 69} Two studies assessing frailty by sarcopenia were cross-sectional and two were prospective, in both cases one measured sarcopenia clinically and one

using dual energy x-ray absorptiometry (DEXA).^{20, 32, 46, 47} All 21 studies assessing frailty by sarcopenia using cross-sectional imaging (computed tomography [CT]) were retrospective.^{10, 24, 25, 27-29, 34, 35, 42, 48-50, 53-55, 58-60, 64, 66, 67}

Nineteen study populations included only patients with lower extremity arterial disease (LEAD),^{17, 20-22, 29, 30, 33, 36, 40, 41, 43, 45, 50, 52, 55, 59, 63, 66, 68} 18 included abdominal aortic aneurysm (AAA) patients exclusively,^{25, 26, 28, 33-35, 38, 42, 44, 48, 49, 53, 54, 58, 64, 65} four both LEAD and AAA,^{11, 31, 46, 47} three included only those with carotid artery disease,^{33, 56, 60} one study (two populations) investigated thoracic aortic aneurysm,⁶⁷ and six included patients with AAA, LEAD or carotid disease.^{23, 32, 39, 51, 62, 69} Six studies investigated frailty in “all vascular patients” (or similar).^{10, 24, 27, 37, 57, 61} Forty-six study populations included only patients undergoing an intervention,^{11, 17, 21-23, 25, 26, 28-30, 33-36, 38-56, 58-60, 64-69} five included only patients not undergoing an intervention,^{20, 32, 49, 57, 63} whilst seven included patients both undergoing and not undergoing an intervention.^{10, 24, 27, 31, 37, 61, 62}

Frailty assessment tools

Sixteen different tools were utilised to assess patients for frailty (Table 1). Nine broad domains were identified that were tested as part of the assessment tools for frailty. The majority of frailty assessment tools used (11 tools) tested three or more domains, however only seven tools (Clinical Frailty Scale [CFS], Edmonton Frail Scale [EFS], Frail Non-Disabled, Fried criteria, Groningen Frailty Indicator, Katz Index and Multidimensional Prognostic Index) are multi-domain and validated in a general population of older adults.

Sarcopenia was determined either clinically, using grip strength, or radiologically, using CT or DEXA (Table S2, Supplemental Digital Content). Broadly seven different

methods of assessing sarcopenia by CT imaging were reported measuring cross-sectional area or density of either psoas, masseter or total abdominal skeletal muscles. All included studies measuring sarcopenia on abdominal CT imaging did so at the level of the third or fourth lumbar vertebrae (L3 or L4) with one study additionally measuring sarcopenia at L2 and L5.⁵⁴ Two studies assessed sarcopenia using DEXA: measuring either Appendicular Lean Mass/height² or Skeletal Muscle Mass.^{20, 47} A further two studies assessed sarcopenia by grip strength.^{32, 46}

Descriptive results

Results from all included studies that utilised one or more frailty assessment tool are summarised in Table S3 (Supplemental Digital Content) and results from studies that used sarcopenia, either measured radiologically or clinically, as a marker of frailty are summarised in Table S4 (Supplemental Digital Content). The included studies reported results for a total of 416,969 patients however 12 studies used patient data from the ACS-NSQIP, of which there is a significant overlap of patients (Table S5, Supplemental Digital Content).^{21, 22, 26, 33, 36, 38-40, 45, 51, 56, 69} The studies by Mirabelli et al., Donald et al., and Ghaffarian et al. included patients from a single unit during overlapping timeframes,^{23, 24, 57} and a further two pairs of studies also included data from the same cohort of patients.^{29, 55, 62, 68} Excluding possible duplicates, this review included data from a minimum 161,700 individual patients.

The studies with no specific inclusion or exclusion criteria based on vascular surgical diagnosis included a total of 1,606 patients. Of these, 46 had venous disease, 33 were reviewed for haemodialysis access and 110 “miscellaneous” or “other” diagnoses, whilst Ghaffarian et al. did not specify diagnoses in their 415 patients.^{10,}

24, 27, 37, 57, 61 Therefore $\geq 99.5\%$ of the patients included in this review had an arterial vascular surgical pathology.

Short-term outcomes:

There were reported associations of frailty with 30-day (or post-operative) mortality from 21 cohorts. Of these, 15 out of 17 assessing frailty using an assessment tool reported an association of frailty with increased 30-day mortality,^{11, 21, 22, 26, 30, 33, 36, 38, 40, 44, 51, 56, 69} whilst all four sarcopenia studies and one that used an assessment tool reported no relationship.^{28, 45, 46, 67} Nineteen cohorts had associations with either 30-day morbidity or post-operative complications reported. All but one of the 13 study populations who had frailty assessed with an assessment tool reported a relationship between frailty and increased morbidity and complications,^{11, 21, 26, 30, 33, 36, 38-40, 45, 51, 69} whilst only one of the six that used sarcopenia did.^{28, 46, 50, 58, 67} These results should be interpreted with caution as all ten studies using data from the ACS-NSQIP (likely including a significant number of duplicate patients) reported 30 day mortality and morbidity outcomes. Six studies (three assessment tool; three sarcopenia) reported non-home discharge or discharge to a higher level of community care with all but one reporting a relationship between frailty and non-home discharge.^{23, 26, 27, 39, 67} Five studies using assessment tools reported an association between frailty and increased length of stay,^{11, 23, 26, 44, 61} whilst of the six sarcopenia studies reporting length of stay as an outcome, only one found a relationship between sarcopenia and increased length of stay.^{34, 47, 50, 58, 64, 67} Incidence of delirium was reported in four studies of which only one reported an independent association with frailty.^{11, 61, 62, 68}

Long-term outcomes:

Five studies utilising an assessment tool for frailty, 19 assessing sarcopenia, and one utilising both, reported long-term survival (minimum of one year). All five studies that used only an assessment tool found frailty was associated with worse survival.^{17, 31, 37, 52, 65} Whilst 11 sarcopenia studies found a similar association with worse survival,^{25, 28, 29, 34, 42, 48, 50, 53, 58, 60, 67} six reported no relationship,^{10, 27, 35, 49, 67} and two studies (Shah et al. and Lindstrom et al.) used multiple measures of sarcopenia, finding an independent association with survival in 1/14 and 7/35 of them respectively, however neither reported correcting for multiple testing in their methodologies.^{54, 64} The study by Ghaffarian et al. utilised a frailty tool (CFS) in addition to assessing sarcopenia using CT (SMA/height²), finding CFS ≥ 5 +/- sarcopenia, but not sarcopenia alone, to be independently associated with worse survival.²⁴ Two studies using frailty tools reported an association of frailty with worse amputation free survival but the single sarcopenia study investigating it found no association.^{17, 30, 59} One frailty tool study and two sarcopenia studies reported an association of frailty with increased major adverse cardiac events (MACE) or worse cardiac event-free survival.^{55, 63, 66}

Quality assessment

Study quality as measured by the NOS alone was generally good, 47 studies (89%) scored ≥ 7 (Table S6, Supplemental Digital Content). Twenty-five studies used a previously utilised frailty or sarcopenia measure, however only 11 studies (21%) used an assessment method for frailty or sarcopenia validated in a general population of older adults. A total of only six studies (20%) utilising a frailty assessment tool and 2 studies (8%) assessing sarcopenia were of high quality (used a measure validated in a general older adult population and NOS ≥ 7). No studies

assessing sarcopenia using CT imaging used a measure validated in a general population of older adults.

Meta-analysis

Eight studies used the Modified Frailty Index (mFI) which is heavily reliant on comorbidities such that an individual patient can be classified as 'frail' based on comorbidity alone.⁶⁹ Studies using mFI were deemed too unreliable to include in the meta-analysis due to its over-reliance on comorbidity. The study by Endicott et al. had significantly higher numbers of ruptured AAA in the frail cohort and did not report the numbers of EVAR vs open AAA repair undermining the reliability of the results and was also excluded.⁴⁴ The lower extremity bypass and EVAR cohorts from Scarborough et al. were excluded as they overlapped with patient cohorts from Crawford et al. and Harris et al. respectively, as all three studies used patient data exclusively from the ACS-NSQIP database.^{21, 26, 33} Only the 2015 study by Matsubara et al. was included, as the 2017 study only reported a composite outcome of major adverse cardiac events.^{29, 55} The study by Mirabelli et al. was excluded, and only outcome data from the study by Donald et al. was included, as they both recruited patients from the same cohort as Ghaffarian et al. (studies by Donald et al. and Ghaffarian et al. reported different outcome data).^{23, 24, 57} Additionally, outcome data from Ghaffarian et al. was reported in patients undergoing operative and non-operative management separately.²⁴ The authors of Drudi et al. provided an unpublished, peer-reviewed proof manuscript of their study which was not subsequently included in the meta-analysis.⁴³ Data from 11 studies (13 cohorts) that used a frailty assessment tool and eight studies that assessed sarcopenia (62,976 patients) were included in the meta-analysis (Table 2).^{11, 17, 20-35} Risk of bias was

293 moderate (six studies) or serious (12 studies) (Table S7, Supplemental Digital
294 Content).

295 Associations of patient factors with frailty (Table 3)

296 Association with patient age, sex, smoking status and body-mass index (BMI) as well
297 as seven comorbidities were investigated. Studies that used only sarcopenia as a
298 frailty measure were not included in the analysis of association with BMI as this
299 would have significantly biased the findings.

300 Frail patients were older (MD: 4.05 years [95%CI 3.35, 4.75]) (Figure 2), and frailty
301 was also associated with lower BMI, female sex and inversely associated with
302 current smoking. Chronic respiratory disease and cerebrovascular disease were the
303 only comorbidities associated with frailty. There was significant heterogeneity (I^2
304 >75% in six analyses) and the quality of evidence was very low, except for the
305 association with age which was moderate.

306 Associations of frailty with outcomes (Table 4)

307 The unadjusted association of frailty was investigated for seven short-term
308 outcomes. Thirty day-mortality and composite post-operative complications were the
309 only short-term outcomes presented as adjusted ORs. Mortality was the only long-
310 term outcome that could be analysed and used data presented as adjusted HRs.
311 Kays et al. included a small number of patients (6.3%) with both ruptured and non-
312 ruptured AAAs so 30-day mortality and morbidity data were not included in the meta-
313 analysis, however long-term mortality data were included as 30-day mortality was
314 low (2.6%) and not significantly different between frail and non-frail groups.²⁸ Data
315 from Dinga Madou et al. were excluded from the surgical site infection meta-analysis
316 as the non-frail group had a significantly higher proportion of hybrid procedures, and

this study removed patients undergoing hybrid procedures from their adjusted analysis of 30-day mortality.²²

Frailty was associated with increased odds of pneumonia, surgical site infection, composite post-operative complications, non-home discharge and 30-day mortality compared to non-frail patients, however these were unadjusted for confounders. Frailty was not associated with post-operative myocardial infarction/acute coronary syndrome or post-operative stroke/transient ischaemic attack. The association of frailty with both post-operative complications and 30-day mortality remained after adjustment for confounders by included studies and, whilst the effect estimates were reduced compared to the unadjusted associations, frailty conferred an over two-fold increased odds in both outcomes. Additionally, frailty was associated with an increased risk of long-term mortality (HR: 1.85 [95%CI: 1.31, 2.62]) compared to non-frailty, adjusted for potential confounders (Figure 3). There was moderate heterogeneity ($I^2 > 75\%$ in two analyses) and evidence quality was low or very low.

Subgroup and sensitivity analyses

All subgroup analyses are presented as forest plots for each patient factor and outcome investigated (Figures 2-3 and Figures S1-S19, Supplemental Digital Content). The relation of frailty to age and BMI were the only associations maintained in all subgroups. Sarcopenia alone was additionally only associated with chronic respiratory disease and dialysis dependence, and was not associated with any outcome measures. Removing studies using sarcopenia alone to measure frailty did not significantly alter the effect estimates or heterogeneity for associations of patient factors with frailty. It did significantly increase the effect estimate of non-home discharge, increasing the OR from 3.57 (95%CI: 1.29, 9.87) to 6.18 (95% CI: 4.79,

7.97) and reduced heterogeneity from $I^2 = 88\%$ to $I^2 = 0\%$. Removing data from sarcopenia studies also increased the effect estimate of frailty on long-term mortality from HR 1.85 (95%CI: 1.31, 2.62) to 2.46 (95%CI: 1.64, 3.68) and reduced heterogeneity from $I^2 = 74\%$ to $I^2 = 52\%$.

DISCUSSION

Frailty is attracting increasing interest in both the vascular, and wider surgical research literature, with 25 studies (46%) included in this review notably published in 2018-19. The vast majority of studies included in this review are retrospective and predominantly use either unvalidated tools and measures, or ones only validated in a disease-specific population, which is reflective of the surgical literature as a whole. Whilst numerous well-validated tools for assessing frailty have been developed in the general adult or older-adult population, few studies of surgical patients actually utilise them (21% in this review).^{4, 5} One challenge in validating frailty tools is that there is not an identified gold-standard measure with which to compare. However, tools such as the mFI, which have only been validated in surgical patients based on risk of mortality, are frequently utilised as measures of frailty in surgical studies.⁷⁰ The mFI warrants particular mention as it is widely used, and cited, in surgical literature and was the most frequently utilised frailty tool in this review. The mFI comprises only 11 items, despite Searle et al. suggesting 30-40 total deficits for a frailty index and stating “estimates are unstable when the number of deficits is small – about 10 or less”.⁷¹ Nine of the 11 deficits for the mFI are comorbidities and, with a cut-off of ≥ 0.25 for frailty in a frailty index ($\geq 25\%$ of potential deficits present), a patient with hypertension, diabetes and coronary artery disease (common in non-frail patients) would be classified as ‘frail’ using the mFI. The mFI may well be a useful tool to assess risk of poor outcome after surgery but its ability to detect and diagnose frailty

per se is yet to be established. Whilst there were multiple measures of sarcopenia used in the included studies, none that were used to identify sarcopenia via CT imaging have been validated in a general older adult population.

This systematic review and meta-analysis has shown that frailty is associated with worse outcomes by multiple measures in vascular surgery patients, as well as with patient factors such as age, female sex and low BMI. Interestingly, vascular patients who currently smoke had a lower risk of frailty, however this may represent less frail, younger patients presenting with predominantly smoking-related arterial disease. Similarly, comorbidity was shown to have few significant associations with frailty which may reflect the high levels of multi-morbidity across all vascular patients raising further questions as to the utility of frailty tools heavily reliant on comorbidity, although these results may not be generalisable to other surgical cohorts.

Sarcopenia alone was not shown to have significant associations with any measured outcome included in the meta-analysis despite multiple studies investigating sarcopenia included in the systematic review reporting worse outcome, possibly due to only including studies that utilised a pre-defined cut-off for sarcopenia in the meta-analysis. Differences in association of sarcopenia with outcome within the meta-analysis is likely due to heterogeneity in study design. For example, studies by Waduud et al. and Heard et al., that showed no association with long-term mortality, had larger sample sizes and statistical analyses which better take into account confounders, whilst the study by Thurston et al. (which showed a strong association) used the same measure of sarcopenia as Waduud et al. but a lower threshold to define sarcopenia.^{27, 34, 35} Not all individuals with sarcopenia are frail and *vice versa*: indeed frailty and sarcopenia are distinct (but frequently overlapping) health states.⁶ The evidence for using sarcopenia identified by CT as either a tool to identify frailty

or predict risk of poor outcome in vascular surgery patients is equivocal and therefore its clinical utility is questionable. There may be a role for assessing sarcopenia by CT in non-vascular surgical patients, however a meta-analysis of patients undergoing surgery for gastrointestinal malignancy also showed no association of sarcopenia with major post-operative complications in the subgroup of studies using a pre-defined cut-off.⁷² The use of pre-operative functional assessments of sarcopenia (e.g. grip strength, SARC-F questionnaire) may be superior to cross-sectional imaging and warrant further evaluation.⁶

A clear distinction needs to be made between frailty and risk, particularly in the utilisation of frailty assessment tools in surgical patients. Whilst frail patients may well be at increased risk of poor outcome following surgery, not all those at increased risk will be frail. The usefulness of frailty tools which have been validated only by their ability to predict risk of poor outcome following surgical admission or intervention is questionable. The ability of tools such as the Modified Essential Frailty Toolkit, mFI, and Risk Analysis Index (included in this review and widely used in the surgical literature) to detect frailty as distinct from surgical risk is therefore uncertain.^{56, 69, 73} Frailty assessment tools such as the CFS, EFS and Fried criteria, that are well-validated and reliable, should be preferred both in surgical practice and research. Also, whilst there is clearly an association of frailty with increased risk of poor outcome following intervention, the degree to which this risk can be modified is unclear. A randomised controlled trial of comprehensive geriatric assessment and pre-operative optimisation of vascular surgery patients has shown clear benefits in reducing length of stay and post-operative complications, however this trial recruited patients based on age and not frailty status.⁷⁴ No studies were identified during this review that investigated the role in which frailty assessment can be utilised in patient

management, and there was a striking lack of studies that utilised frailty-related outcomes such as post-operative delirium, falls, return to independent living, or quality of life measures, which should be a focus for future research. The current literature does not provide evidence that frail patients should be turned-down for surgical intervention based on frailty alone. The influence of frailty assessment on the management of asymptomatic patients (e.g. AAA repair), where quality of life is risked against a potential mortality benefit, is likely to be different to that in symptomatic patients, such as those with critical limb ischaemia, whose symptoms (which may be reversible) may contribute significantly to their degree of frailty, and intervention may improve frailty status and quality of life.

This review is significantly larger in scope, with a much wider search strategy, than two similar, recently published reviews.^{9, 75} The meta-analysis by Wang et al. included two studies which only used a cognitive or nutrition assessment to identify frailty, and a study that included patients with non-ischaemia related lower limb amputations, all of which were excluded from this review.⁹ Additionally, Wang et al. did not account for overlapping patients in the five studies that used data from the ACS-NSQIP, likely overestimating the size and precision of their effect estimates.^{22,}

26, 33, 36, 40

There are a number of limitations to this review and meta-analysis. The aim of this review was to provide a global view of the published evidence in frailty across the breadth of vascular surgery patients, thus included studies recruited patients with different diagnoses, undergoing different procedures (both emergent and elective) and used different measures to assess frailty. Additionally, event rates for some outcome measures (e.g. 30 day mortality, post-operative pneumonia) were low. As such the pooled analyses should be interpreted with caution as, whilst the direction

441 of effect estimate is likely to be accurate, the magnitude of the effect of frailty on
442 outcome remains uncertain and limits the conclusions that can be drawn from the
443 results (reflected in the large I^2 statistics and low GRADE scores in many analyses).
444 The majority of studies included only patients undergoing procedures limiting its
445 generalisability, and therefore no estimate of the prevalence of frailty in vascular
446 patients was made as it is likely the frailest are not offered intervention. Similarly,
447 there is therefore inherent bias in the associations of patient factors with frailty, as
448 the frailest vascular patients are likely to be underrepresented. The meta-analysis
449 was additionally limited both by the outcome measures and how they were reported,
450 meaning data from relatively few studies could be pooled in each analysis. This also
451 prevented any further investigation of heterogeneity by meta-regression. Similarly,
452 no formal assessment of publication bias could be undertaken as none of the
453 analyses of outcomes included 10 or more studies.¹⁶ It is likely there is a moderate
454 effect of publication bias, particularly of lower quality, smaller studies of sarcopenia
455 which were mostly excluded from the meta-analysis due to their study design.
456 Additionally, it was only possible to determine the unadjusted (univariable)
457 associations of frailty with all of the patient factors and many of the outcomes, so
458 both are likely to be significantly affected by confounders and independent
459 associations with frailty should not be inferred. The HR data pooling for the two frail
460 groups in Takeji et al. was limited by the way data were presented, meaning
461 precision has been overestimated due to double-counting the non-frail group, which
462 should be considered when interpreting the results.¹⁷ Both intermediate and high
463 frailty groups were similarly sized and contributed equally to the meta-analysis
464 (weight was 50.3% and 49.7% respectively) so this is unlikely to significantly impact
465 the conclusions. Finally, the inclusion of studies identifying frailty by sarcopenia

alone is potentially controversial. The decision to include sarcopenia in both the review and meta-analysis reflects the frequent reporting of sarcopenia as a measure of frailty in the vascular surgery literature, and allowed comparisons of frailty defined by an assessment tool with sarcopenia alone. Subgroup and sensitivity analyses were performed to account for any distortion of the effect estimates by the inclusion of sarcopenia studies.

Conclusions

Frailty in vascular surgery patients is associated with age, female sex and lower BMI but has only weak association with comorbidity. Frail vascular patients have poorer outcomes, however no evidence exists to decline surgical intervention based on frailty score alone. There is no clear evidence that sarcopenia alone either identifies frailty or predicts risk in vascular surgery patients. Only frailty tools validated in a general population of older adults should be used in pre-operative frailty assessment. Prospective observational studies or clinical trials are needed to investigate how best to incorporate frailty assessment into peri-operative care.

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