

The impact of computed tomography-assessed sarcopenia on outcomes for trauma patients – a systematic review and meta-analysis

Weisi Xia^{a,*}, Ahmed W.H. Barazanchi^a, Wiremu S. MacFater^a, Andrew G. Hill^b

^a Department of Surgery, South Auckland Clinical Campus, The University of Auckland, New Zealand

^b Department of Surgery, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand

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ABSTRACT

Introduction: Sarcopenia is the progressive loss of skeletal muscle mass, strength and general decline in function associated with age, and has previously been shown to be a predictor of poor outcomes following surgery. Computed tomography (CT)-assessed sarcopenia has been proposed to be an independent predictor of outcomes for trauma patients. This systematic review aims to determine the impact of CT-assessed sarcopenia on patient mortality following trauma.

Materials and Methods: A systematic review and meta-analysis of the literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. EMBASE, MEDLINE and CENTRAL databases were searched from database inception to 26 November 2018. Bibliographies of included articles were hand searched for potential articles. All observational studies which included trauma patients who had skeletal muscle mass or density assessed by CT were included in the review. Two authors independently performed the search with decisions reached by consensus. Meta-analysis was performed using Review Manager v5.3 using a random effects model. The primary outcome was all cause mortality, as established *a priori*.

Results: Following an initial search of 1984 records, a total of 20 retrospective observational studies were included for qualitative analysis. Ten of these studies consisting of a pooled, partly-overlapping, 2867 patients were included in the meta-analysis. There was a wide variation in the reported prevalence of sarcopenia (25.0–71.1%). Sarcopenia patients were at a significantly increased risk of mortality during inpatient stay (RR 1.96 [95%CI 1.30–2.94], $p = 0.001$), at 30 days (RR 1.60 [95%CI 1.21–2.13], $p = 0.001$) and at 1-year (RR 3.11 [95%CI 1.94–4.96], $p < 0.00001$). There was no significant difference in total complications encountered, ICU duration or total inpatient stay.

Conclusion: Sarcopenia identified by CT is associated with increased risk of inpatient, 30-day, and 1-year mortality in trauma patients.

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Introduction

Sarcopenia is the progressive and general loss of skeletal muscle mass and strength and decline in function associated with age. [1] Sarcopenia is closely linked to the biological concept of frailty [2], which is a multisystem impairment that results in decreased physiological reserve [3]. The concept of frailty as part of an individualised risk assessment has become increasingly popular amongst clinicians looking after surgical patients [4–6]. The involuntary loss of skeletal muscle mass is closely related, but

remains distinct, to frailty; with sarcopenia serving as an indicator and key component of frailty (7).

Sarcopenia alone has been proposed to function as part of perioperative risk assessment for surgical patients [8] with studies indicating it is an independent risk factor for mortality and morbidity outcomes in a range of elective gastro-intestinal [9], oncological [10] and transplant [11] surgical procedures. The concept is not new as protein depletion was initially shown by Hill et al. to be associated with increased rates of sepsis [12] and pneumonia [13] following surgery. The measurement of this required sophisticated techniques not available outside specialised units but there has been a recent resurgence of interest given the accessibility and availability of computed tomography (CT) assessment of sarcopenia.

While surgery results in planned iatrogenic shock to patients, trauma itself results in a significant insult to patients. Recent

* Corresponding author at: South Auckland Clinical Campus, Middlemore Hospital, Private Bag 93311, Otahuhu, Auckland, New Zealand.
E-mail address: w.xia@auckland.ac.nz (W. Xia).

studies have suggested that sarcopenic patients have a worse recovery after trauma, given their decreased resilience and physiological reserve [14]. While there has been an increase in the medical literature in sarcopenia and elective surgery, there lacks a systematic review of outcomes following specifically trauma patients with sarcopenia.

A wide variety of measurement modalities to define sarcopenia have been proposed [15]. The management of trauma patients frequently occurs under time constraints and these modalities may be yet to be accepted in routine clinical care. CT-assessment of skeletal muscle mass has been described as a way to quantify muscle loss in sarcopenia [1]. Given that CT scanning of the head, abdomen and pelvis is routine and widely available in clinical practice following trauma, it may provide an opportunistic assessment tool for assessment of sarcopenia for clinicians.

This study aimed to review the literature on the effect of low skeletal muscle mass or sarcopenia, assessed by CT Scan, on mortality in trauma patients.

Materials and methods

This study is a systematic review and meta-analysis reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16].

Eligibility criteria

The eligibility criteria were established *a priori*. We included all observational studies. Participants of all ages with all types of trauma were included. Studies which evaluated CT-assessed sarcopenia, skeletal muscle index, psoas or masseter mass or density on outcomes were included. All CT-assessed definitions of sarcopenia were included in our study. Other methods of

sarcopenia assessment were excluded. Primary outcome measures were all cause mortality during inpatient stay, 30-days and 1-year.

Information sources

Studies were identified by searching electronic databases and hand-searching reference lists of all included articles. The search terms were applied from each database inception with the last search performed on 26 November 2018 for MEDLINE (1946 – present); EMBASE (1980 – present) and Cochrane Controlled Register of Trials (CENTRAL).

Search

We used the following search terms to query MEDLINE (using OvidSP): (exp Sarcopenia/ OR sarcopeni*.mp. OR “muscle index”.mp. OR L3.mp. OR exp Psoas Muscles/ OR psoas.mp. OR exp Masseter Muscle/ OR masseter.mp.) AND (exp “Wounds and Injuries”/ OR Trauma.mp.). Similar queries constructed for EMBASE and CENTRAL. Only published articles in peer-reviewed journals in English were included. We excluded case reports, opinion articles and review articles. Identified electronic database citation results were collected in EndNote X7 (Clarivate Analytics, Philadelphia, PA, United States).

Study selection

After duplicate removal, all articles were initially screened by title and abstract by two authors (WX and AB). Full-text articles were assessed by the same authors. Disagreements were resolved by consensus. The first author, WX, hand-searched the reference lists of all included studies for additional studies that fulfil the eligibility criteria. A third author WM examined and agreed with the final inclusion of studies.

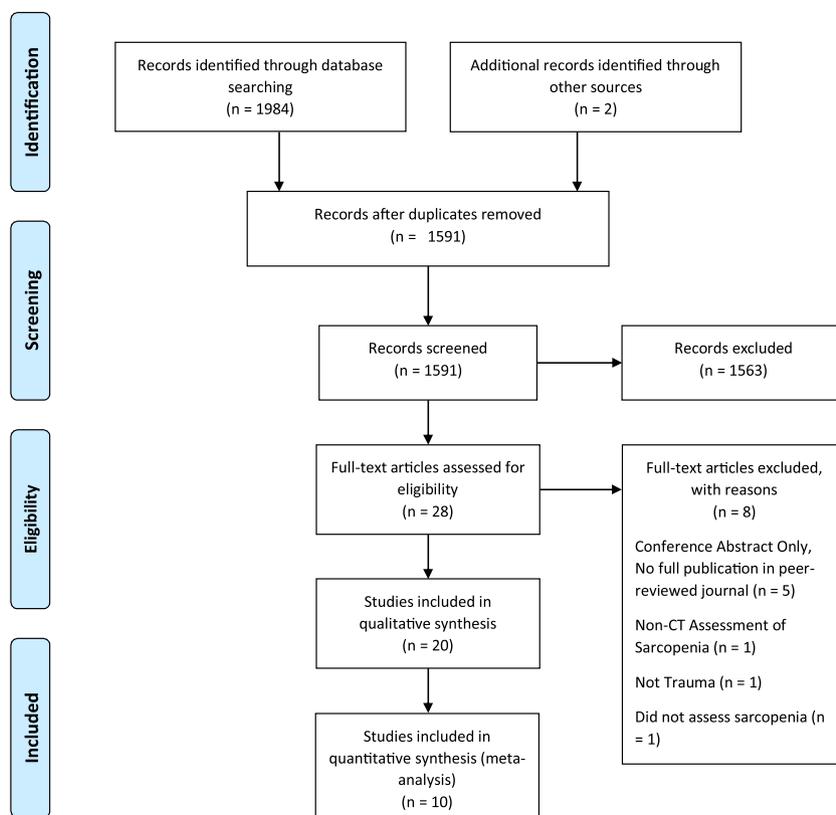


Fig. 1. – PRISMA Flow Chart.

Table 1
Study Characteristics and Demographics. A) Characteristics of Meta-Analysis Studies.

| Study | Country | Study Interval | Patient Selection | Mechanism of Injury | Sample Size n Sarcopenia No Sarco | Age Years | Sex M/F | BMI Kg/m ² | ISS |
|--------------------------|---------|--------------------|---|--|--|--|---|---|---|
| Akahoshi 2016 | Japan | Apr 2012 –Dec 2014 | >20 years old admitted to ICU, high-energy blunt trauma <i>Exclusion:</i> Dead on arrival | Traffic accident (75); Fall from height (9) | 84 25 59 | – 56.7 ± 18.4 43.2 ± 14.2 | – 13/12 34/25 | – 22.2 ± 3.6 21.6 ± 3.2 | – 30.4 ± 22.4 22.9 ± 15.4 |
| Deren 2017 | USA | 2005–2014 | ≥60 years old with closed acetabular fracture <i>Exclusion:</i> lumbar spine fracture, previous lumbar spine instrumentation, major thoracic or head trauma, lack of height/weight/BMI | Not Stated | 99 42 57 | – 76.5 72.7 | – 32/10 29/28 | – 23.6 23.7 | – 10.7 12 |
| Ebbeling 2014 | USA | 2005–2010 | ≥55 years old, ISS > 15, ICU length of stay >48 hours <i>Exclusion:</i> Head/Neck AIS ≥ 5; L4 fracture/metalware; L4 retroperitoneal haematoma | Fall (92); MVC (48); Pedestrian (21); MCC (4); Gunshot (4); Other (10) | 180 90 90 | 74 (63-82) 79 (72-85) 70 (60-77) | 103/77 39/51 64/26 | – – – | 24 (19-29) 25 (18-29) 24 (19-29) |
| Hu 2018 | USA | 2011-2016 | ≥55 years old with traumatic brain injury <i>Exclusion:</i> mortality due to exsanguinating haemorrhage <24 hours | Blunt (101); Penetrating (7) | 108 25 83 | 67.4 ± 10.6 74.4 ± 11.1 65.4 ± 9.6 | 79/29 16/9 63/20 | – – – | – 26 (20-36) 26 (24-34) |
| ^a Kaplan 2017 | USA | Jan 2011 –May 2014 | ≥65 years old admitted to ICU with CT < 48 hours of admission <i>Exclusion:</i> Head AIS ≥ 3; death <24 hours | Fall (221); Blunt other than fall (215); Penetrating (4); Other (10) | 450 241 209 | – – – | – 163/78 106/103 | – – – | – – – |
| Malekpour 2017 | USA | 2010-2014 | >64 years old with blunt trauma <i>Exclusion:</i> Unknown height, unknown GCS, dead on arrival | Fall (710); MVC (337); Pedestrian (40); MCC (32); Other (56) | 1175 294 884 | – 80.5 ± 7.7 77.4 ± 8.2 | – 149/145 448/443 | – 25.0 ± 5.2 28.9 ± 6.4 | – 12 (9-20) 12 (9-17) |
| McCusker 2018 | USA | 2013-2016 | ≥65 years old <i>Exclusion:</i> Unknown weight/height, psoas haematoma | Fall (191); MVC (116) | 325 81 244 | 74.4 ± 7 – – | 417/234 – – | – – – | 11 (9-17) – – |
| Mitchell 2018 | USA | 2003-2014 | >60 years old with acetabular fracture | MVC (78); Pedestrian (7); MCC (5); Fall from height (27); Fall from ground (21); Other (8) | 146 37 109 | 70.1 ± 7.4 74.4 ± 8.2 68.7 ± 6.5 | 107/39 14/23 93/16 | 27.9 ± 6.5 26.9 ± 8.4 28.4 ± 5.6 | – – – |
| Moisey 2013 | USA | 2009-2010 | ≥65 years old admitted to ICU | MVC (51); Pedestrian (4); Fall (37); Other (8) | 149 106 43 | 79 (72-85) 80 (73-86) 76 (68-83) | 85/64 71/35 14/29 | 25.6 (22.7-28.2) 24.4 (21.7-27.3) 27.6 (25.5-30.4) | 19 (24-26) 20 (14-29) 17 (13-24) |
| ^b Yoo 2017 | USA | 2008 | ≥45 years old with blunt trauma | Not Stated | 151 A 38 A 113 B 38 B 113 | 58.5 ± 11.2 65.6 ± 13.2 56.5 ± 9.5 52.2 ± 11.7 57.6 ± 10.8 | 92/59 20/18 72/41 23/15 69/44 | 28.3 ± 6.9 30.4 ± 10.8 27.6 ± 4.7 26.0 ± 5.3 29.1 ± 7.1 | 10.4 ± 7.6 11.4 ± 8.9 10.0 ± 7.1 8.6 ± 7.8 10.9 ± 7.5 |

B) Characteristics of Qualitative Studies

| Study | Country | Study Interval | Patient Selection | Mechanism of Injury | Sample Size n | Age years | Gender M/F | BMI Kg/m ² | ISS |
|----------------|-----------|---------------------|--|---------------------|------------------|--------------|---------------|--------------------------|------------|
| Boutin 2017 | USA | 2005 - 2015 | ≥65 years old with low-energy injury with first-time hip fractures treated with surgery <i>Exclusion:</i> vulnerable population or postoperative changes at the region of interest | Not Stated | 274 | 81.3 ± 8.3 | 81/193 | 24.3 ± 5.3 | – |
| Chang 2018 | USA | Jan 2000 – Aug 2016 | ≥50 years old with isolated proximal femur fracture following acute trauma <i>Exclusion:</i> conditions predisposing to sarcopenia, concurrent major trauma, proximal femur fracture not treated operatively, pathological femur fracture | Not Stated | 91 | 81.1 ± 12.2 | 24/67 | 23.1 ± 4.7 | – |
| Couch 2018 | Australia | Apr 2011 – Nov 2014 | >65 years old with ISS>12 | Not Stated | 225 | 76.9 ± 7.7 | 123/102 | – | 20.5 ± 8.6 |
| DeAndrade 2018 | USA | 2012-2014 | Patients presenting as trauma alert | Not Stated | 778 – | – 63 | – – | – 31.1 | – – |

Table 1 (Continued)

B) Characteristics of Qualitative Studies

| Study | Country | Study Interval | Patient Selection | Mechanism of Injury | Sample Size n | Age years | Gender M/F | BMI Kg/m ² | ISS |
|---------------------------|---------|-----------------------|---|---|------------------|----------------------|-----------------|--------------------------|---------------|
| Fairchild 2015 | USA | Jan 2008 – April 2011 | ≥65 years old admitted to a Level I trauma center <i>Exclusion:</i> traumatic brain injury, spinal cord injury | Not Stated | 252 | 42 76 | – 123/129 | 28.2 – | – 9 (8-17) |
| ^c Leeper 2016 | USA | 2010-2014 | ≥65 years old trauma from fall | All falls (445) | 445 | – | 189/256 | – | – |
| | | | | | 256 | – | 137/119 | – | – |
| | | | | | 189 | – | 52/137 | – | – |
| ^d Oskutis 2016 | USA | 2002-2012 | ≥40 years old post motor vehicle crash with a single injury with a maximum AIS ≥ 3 or two injuries in different AIS ≥ 2 | All MVC (202) | 202 | – | 83/119 | – | – |
| Shibahashi 2017 | Japan | Sep 2013 – Sep 2015 | ≥60 years old with traumatic brain injury admitted to ICU <i>Exclusion:</i> CT scan after day of admission, patients dependent on others prior to injury | MVC (24); Free fall (8); Fall on stairs (17); Fall (12); Unknown (13) | 74 40 34 | 74 (66-79) – – | 53/21 – – | – – – | – – – |
| Touban 2018 | USA | 2007-2014 | ≥65 years old with ICD-9-CM codes for extremity and/or pelvic fractures from all injuries <i>Exclusion:</i> artefact obscuring CT, pathologic fractures | Fall (255); Non-fall (303) | 558 | 76.65 ± 8.12 | 254/304 | 27.45 ± 5.90 | 16.8 ± 10.74 |
| ^e Wallace 2017 | USA | 2010 | ≥65 years old with blunt-injured trauma with hospital length of stay >6 hours | ^f | 487 | – | – | – | – |
| | | | | | M 357 | 80.0 ± 8.6 | 192/165 | – | 10.3 ± 9.0 |
| | | | | | P 226 | 80.0 ± 8.7 | 113/113 | – | 10.2 ± 8.0 |

Abbreviations: AIS Abbreviated Injury Scale; BMI Body Mass Index; CT Computed Tomography; GCS Glasgow Coma Scale; ICD-9-CM International Classification of Diseases, 9th Revision, Clinical Modification; ICU Intensive Care Unit; ISS Injury Severity Score; MVC Motor Vehicle Collision; MCC Motorcycle Collision.

^fWallace 2017 discussed the mechanisms of injury for each group which resulted in different numbers depending on which group is assessed.

Values for age, BMI and ISS are given as mean ± standard deviation or *median (interquartile range)*; Deren 2017 and DeAndrade 2018 provided only the mean without standard deviation. “–” indicates data was not supplied in the published study.

^a Kaplan 2016 investigated 4 groups – A) patients with sarcopenia and osteopenia, B) sarcopenia only, C) osteopenia only, D) no sarcopenia or osteopenia. For the purposes of the meta-analysis, we combined groups A + B as the sarcopenia group and C + D as the no sarcopenia group.

^b Yoo 2017 investigated two measurements of sarcopenia in the same population group; Group A using psoas muscle density and Group B using psoas muscle area. We present both with their sarcopenia and non-sarcopenia data sets, respectively.

^c Leeper 2016 investigated a total of 23,622 patients in their original study with the original inclusion criteria of ≥ 18 years old with Level 1 or 2 trauma and 6 months of follow-up data. We include in our table only the subgroup in their dataset which looked at sarcopenia in older trauma patients.

^d Oskutis 2016 data obtained from the Baltimore Crash Injury Research and Engineering Network (CIREN) database.

^e Wallace 2017 compared two groups - masseter (M) and psoas (P) areas for sarcopenia measurement as predictors of outcomes. We include in this table the characteristics of each subgroup.

Data collection process and data items

An Office Excel 2016 (Microsoft, Redmond, WA, United States) form was established for data collection. WX extracted the data results and AB independently checked the results. Disagreements were solved by consensus. The authors elected to use only published results and did not contact study authors for unpublished data.

Extracted data included: 1) the study characteristics consisting of the country of study, study interval, patient selection, the mechanism of injury, total sample size as well as those with sarcopenia, age, sex, body mass index (BMI) as well as Injury Severity Score (ISS); 2) the CT assessment of sarcopenia consisting of the muscle measured, level of muscle measured, software used, study definition of sarcopenia and associated formulae and the prevalence of sarcopenia; 3) the outcome measures which included all mortality, complications, length of intensive care unit (ICU) stay and total length of hospital stay. Regression analyses were included for mortality data. If univariable and multivariable analyses for mortality were performed, only the latter were included in our study.

Quality assessment and risk of Bias

Methodological quality of the included studies was performed using the Newcastle-Ottawa quality assessment scale for cohort studies [17]. A score of 5 or below was considered low quality; a score of 6 or 7 was considered medium quality; and a score of 8 or 9 was considered high quality.

Summary measures, data synthesis and analysis

For each study included in the meta-analysis we calculated risk ratios and 95% confidence intervals for inpatient mortality, 30-day mortality and 1-year mortality in sarcopenic patients compared with nonsarcopenic patients. We calculated the mean difference with standard deviation between these two groups for length of ICU stay and hospital length of stay. For dichotomous outcomes we employed a Mantel-Haenszel random effects model; for continuous outcomes we employed an inverse variance random effects model. Random effects models were used due to the significant variation in population, trauma and definition of sarcopenia. A p-value of <0.05 was considered significant.

Meta-analysis, forest plots and heterogeneity assessment was performed using Cochrane Review Manager version 5.3.5 (The Cochrane Collaboration, Copenhagen, Denmark) [18]. Heterogeneity was assessed using the I^2 statistics [19]. An I^2 score of 25%, 50% and 75% represents low, moderate and high heterogeneity, respectively.

Estimating missing data

Studies [20–23] that reported ICU length of stay and hospital length of stay in median and interquartile ranges were transformed into mean and standard deviation using the validated statistical methods proposed by Luo et al. [24], and Wan et al. [25], respectively. One study's [26] regression analyses of mortality data required p-values to be derived from odds or hazard ratios and their respective 95% confidence intervals [27].

Additional analyses

Sensitivity analyses were planned for the meta-analyses for dichotomous and continuous variables. Dichotomous variables were tested using both risk ratios and odds ratios. Continuous

variables were tested using both mean difference and standard mean difference.

Results

Study selection

A PRISMA flow chart of the selection of articles is shown in Fig. 1. An initial database search yielded 1984 citations, with an additional two studies [14,26] identified by reference screening. A final 20 studies [14,20–23,26,28–41] consisting of 6253 patients fulfilled the criteria for qualitative inclusion. Of these, ten studies [14,20–23,28,32,34,36,41] consisting of a pooled, partly-overlapping, 2867 patients were included in the meta-analysis. All included studies were retrospective cohort studies.

Study characteristics

Table 1 presents the study characteristics of those included in the meta-analysis group, and those included in the qualitative analysis, respectively. Thirteen studies [14,21–23,26,30,32,33,35,36,38–40] examined trauma in an older population (≥ 60 years old) only. Two studies [34,38] examined patients admitted with traumatic brain injuries only. Five studies [14,20,21,28,38] examined only patients admitted to the ICU. Twelve studies [14,20,22,23,28,30,32–34,39–41] provided ISS to assess trauma severity.

There was a wide variety in the mechanism of injury; for studies which provided data on breakdown of the mechanism of injury, all-cause falls (n=2045) was the most common mechanism followed by all-cause motor vehicle injuries (amalgamating motor

Table 2
Newcastle-Ottawa Risk of Bias for Observational Studies.

| Study | 1 | 2 | 3 | 4 | 5A | 5B | 6 | 7 | 8 | Total |
|-----------------|---|---|---|---|----|----|---|---|---|-------|
| Akahoshi 2016 | – | + | + | + | + | + | – | + | + | 7 |
| Boutin 2017 | + | + | + | + | + | + | + | + | + | 9 |
| Chang 2018 | + | + | + | + | + | + | + | + | – | 8 |
| Couch 2018 | + | + | + | + | + | + | – | + | + | 8 |
| DeAndrade 2018 | – | + | + | + | + | + | – | + | – | 6 |
| Deren 2017 | + | + | + | + | – | – | + | + | + | 7 |
| Ebbeling 2014 | + | + | + | + | + | + | + | + | + | 9 |
| Fairchild 2015 | + | + | + | + | – | – | + | + | + | 7 |
| Hu 2018 | + | + | + | + | + | + | + | + | + | 9 |
| Kaplan 2017 | + | + | + | + | + | + | + | + | + | 9 |
| Leeper 2016 | + | + | + | + | – | – | + | + | – | 6 |
| Malekpour 2017 | + | + | + | + | + | + | + | + | + | 9 |
| McCusker 2018 | + | + | + | + | – | – | + | + | + | 7 |
| Mitchell 2018 | + | + | + | + | + | + | + | + | + | 9 |
| Moisey 2013 | + | + | + | + | + | + | + | + | + | 9 |
| Oskutis 2016 | + | + | + | + | + | – | + | + | – | 7 |
| Shibahashi 2017 | + | + | + | + | – | – | + | + | + | 9 |
| Touban 2018 | + | + | + | + | + | + | + | + | + | 9 |
| Wallace 2017 | + | + | + | + | + | + | + | + | + | 9 |
| Yoo 2017 | + | + | + | + | + | + | + | + | + | 9 |

¹ – Representativeness of the exposed cohort – consecutive series of patients with >90% available CT scans, or all included patients.

² – Selection of the non-exposed cohort – taken from the same cohort.

³ – Ascertainment of exposure – measurement of skeletal muscle, either as area or density, at L3/4 or masseters using CT.

⁴ – Demonstration that outcome of interest was not present at start of study – trauma occurs prior to CT scan.

5A – Comparability of cohorts on the basis of the design or analysis adjusted for age.
5B – Comparability of cohorts on the basis of the design or analysis adjusted for sex or comorbidities or Injury Severity Score or type of trauma.

⁶ – Assessment of outcome – independent blind assessment or record linkage.

⁷ – Was follow-up long enough for outcomes to occur – follow up until at least either inpatient mortality or for 30 days.

⁸ – Adequacy of follow up for cohorts – all patients accounted for or <10% lost to follow up.

Table 3
Computed Tomography Assessment of Sarcopenia.

| Study | Muscles Measured | Level | Software | Cut-Off Value/Definition | Formulae Given | Prevalence, % |
|-----------------|--|--------------------------------------|--|---|--|---------------|
| Akahoshi 2016 | Skeletal Muscle CSA | L3 caudal end | Synapse Vincent volume analyser (Fujifilm, Tokyo, Japan) | Measured SMA < 80% estimated SMA | Estimated SMA (cm ²) = Males: 126.9 x BSA – 66.2 Females: 125.6 x BSA – 81.1 BSA = $\sqrt{(\text{body weight (kg)} \times \text{height (cm)})/3,600}$ TMI = left + right paravertebral muscle areas (cm ²) / height ² (m ²) TMD = average attenuation left + right paravertebral muscles (HU) PMI = total psoas muscle area (cm ²) / height ² (m ²) PMD = average attenuation left + right psoas muscle (HU) SMI = CSA of lean muscle (cm ²) / height ² (m ²) | 29.70 |
| Boutin 2017 | Thoracic Muscle Index Thoracic Muscle Density Psoas Muscle Index Psoas Muscle Density | T12 Pedicle L4 Pedicle | iSite version 3.6 (Koninklijke Philips N. V., Amsterdam, the Netherlands) | No definition of sarcopenia | | – |
| Chang 2018 | Skeletal Muscle Density Skeletal Muscle Index | L4 inferior endplate | OsiriX version 8.0.2 (Pixmeo, Geneva, Switzerland) | No definition of sarcopenia | | – |
| Couch 2018 | Lean Psoas Area | L4 vertebral body inferior margin | Vitrea Advanced (Vital Images, Minnetonka, MN, USA) | No definition of sarcopenia | Lean Psoas Area = ((Mean HU + 85)/170 x CSA) | – |
| DeAndrade 2018 | Psoas Muscle Density | L3 | Not Stated | Lowest sex-specific 25 th percentile of Mean HUAC | HUAC = (Left + Right Hounsfield Unit Calculation (HUC))/2 HUC = (HU x Left/Right Psoas Area) / Total Psoas Area | – |
| Deren 2017 | Skeletal Muscle Index | L3 | Not Stated | Male SMI < 55.4 cm ² /m ² Female SMI < 38.5 cm ² /m ² | SMI = Average skeletal CSA at L3 / Height ² | 42.4 |
| Ebbeling 2014 | Psoas : L4 Vertebral Index | L4 inferior body | Not Stated | <50 th percentile of PLVI (≤ 0.83) | PLVI = ((right + left psoas CSA) (mm ²)/2) / L4 vertebral CSA (mm ²) | 50 |
| Fairchild 2015 | Bilateral Psoas CSA | L4 – L5 intervertebral disk space | Slice-O-Matic (Tomovision, Montreal, QC, Canada) | No definition of sarcopenia | – | – |
| Hu 2018 | Bilateral Masseter CSA | 2cm below zygomatic arch | IntelliSpace PACS version 4.4 (Koninklijke Philips N.V., Amsterdam, the Netherlands) | <1 standard deviation from sex-based mean of the study population Male <3.30 cm ² Female <2.34 cm ² | – | 23.15 |
| Kaplan 2017 | Skeletal Muscle Index | L3 superior vertebral body | Slice-O-Matic version 5.0 (Tomovision, Montreal, QC, Canada) | Male <52.4 cm ² /m ² Female <38.5 cm ² /m ² | SMI = Total skeletal CSA (cm ²) / height ² (m ²) | 53.60 |
| Leeper 2016 | Psoas Muscle Index | L3 | iSite (Koninklijke Philips N.V., Amsterdam, the Netherlands) | <5 th percentile for PMI or <2 standard deviations below health adult population (Males <524 mm ² /m ² ; Females <385 mm ² /m ²) | PMI = area normalised for stature using BSA BSA = (Weight (kg) x Height (cm)) / 3600 / 2 | 57.52 |
| Malekpour 2017 | Left Psoas Muscle Index | L3 | Not Stated | Lowest sex-specific quartile (Male <242.6 mm ² /m ² Females <187.8 mm ² /m ²) | Left PMI = left psoas area normalised for height using body composition measurements (mm ² /m ²) | 25 |
| McCusker 2018 | Psoas Muscle Index | L3 superior vertebral body | IntelliSpace PACS (Koninklijke Philips N.V., Amsterdam, the Netherlands) | Lowest sex-specific quartile (Male <3.51 cm ² /m ² Female <2.42 cm ² /m ²) | PMI = total psoas area/height ² (cm ² /m ²) | 24.9 |
| Mitchell 2018 | Psoas : L4 Lumbar Vertebral Index | L4 superior endplate | Not Stated | Lowest quartile of PLVI (≤ 0.64) | PLVI = ((right + left psoas CSA) (mm ²)/2) / L4 vertebral CSA (mm ²) | 25.3 |
| Moisey 2013 | Skeletal Muscle Index | L3 | Slice-O-Matic version 4.3 (TomoVision, Montreal, QC, Canada) | Males <55.4 cm ² /m ² Females <38.9 cm ² /m ² | SMI = Skeletal Muscle CSA / height ² (cm ² /m ²) | 71.14 |
| Oskutis 2016 | Psoas Muscle Index | L3 | TeraRecon Aquarius version 4.4 (TeraRecon, Foster City, CA, USA) | PMI <4 cm ² /m ² | PMI = Bilateral Psoas Muscle normalised for height | 17.30 |
| Shibahashi 2017 | Skeletal Muscle CSA | L3 | SYNAPSE (Fujifilm Medical, Tokyo, Japan) | No definition of sarcopenia | – | 52.60 |
| Touban 2018 | Total Lean Psoas CSA | L3 – 4 superior aspect of disk space | Slice-O-Matic (Tomovision, Montreal, QC, Canada) | No definition of sarcopenia | – | – |

| Wallace 2017 | Bilateral Masseter CSA Total Psoas CSA | 2cm below zygomatic arch L4 L3 | Systems Web Ambassador version 8.2 (Chicago, IL, USA) | No definition of sarcopenia | - | - |
|--------------|--|---|--|--|--|-------|
| Yoo 2017 | Psoas Muscle Index Psoas Muscle Density | | EasyViz PACS (Karos Health, Waterloo, ON, USA) | Lowest sex-specific 25 th percentile (PMI Male $\leq 7.77 \text{ cm}^2/\text{m}^2$ PMI Female $\leq 4.75 \text{ cm}^2/\text{m}^2$ HUAC $< 38.5 \text{ HU}$) | PMI = $(R + I \text{ psoas area}) / \text{height}^2 \text{ (cm}^2/\text{)}^2$ PMD (HUAC) = (Left + Right HUC) / 2 HUC = $(\text{HU} \times \text{Left/Right Psoas Area}) / \text{Total Psoas Area}$ | 25.16 |

Abbreviations: BSA body surface area; CSA cross-sectional area; HU Hounsfield units; HUAC Hounsfield Unit Average Calculation; HUC Hounsfield Unit Calculation; PACS Picture Archiving and Communications System; PLVI Psoas L4 Vertebral Index; PMI psoas muscle index; PMD psoas muscle density; PMI thoracic muscle index; TMD thoracic muscle density; SMA skeletal muscle area.
 "Index" indicates that the skeletal or psoas muscle area has been standardised to a variable, typically height, body-surface area or vertebral size.
 "-": indicates data not available or not relevant.

vehicle collisions, pedestrians struck, motorcycle injuries, traffic accidents) (n = 1044).

Quality assessment and risk of Bias

Table 2 presents the Newcastle-Ottawa Score for the quality of studies included in the review. The quality was medium to high across the studies.

Sarcopenia definition, CT-Assessment methods and prevalence

There was a wide variety of skeletal muscle measurement methods as well as definitions used to define sarcopenia (Table 3). All studies, except two [34,40] which examined the association of masseter muscle and mortality, investigated skeletal muscle or psoas muscle cross-sectional area, muscle index or muscle density at lumbar vertebral levels three or four. Four studies [30,33,39,40] measured the psoas muscle cross-sectional area. Two studies [28,38] measured the skeletal muscle cross-sectional area. Eight studies [20,22,23,26,35–37,41] measured the psoas muscle index (psoas muscle cross-sectional area normalised to height), while four studies [14,21,29,32] measured the skeletal muscle index. Psoas muscle density was measured in three studies [26,31,41], and one study [29] measured skeletal muscle density. One study [26] also measured paravertebral muscle index and density at the thoracic 12th vertebral level. Four studies [26,29,40,41] compared two or more different measurements and their association with outcomes.

Thirteen studies provided a definition of sarcopenia [14,20–23, 28,31,32,34–37,41]. Thirteen studies [14,20–23,28,32,34–38,41] reported the prevalence of sarcopenia in their study population. The prevalence varied greatly, depending on the definition used, and ranged from 23.15 to 71.14%.

Meta-analysis of primary outcomes

The primary outcomes are shown as forest plots in Fig. 2.

In-hospital mortality

Based on six studies with 2077 patients, sarcopenia was associated with nearly a doubled relative risk of in-hospital mortality (RR 1.96 [95%CI 1.30–2.94] $p = 0.001$, $I^2 = 42\%$).

30-Day mortality

Based on three studies with 642 patients, sarcopenia was associated with an increased risk of 30-day mortality (RR 1.60 [95% CI 1.21–2.13] $p = 0.001$, $I^2 = 0\%$).

1-Year mortality

Based on three studies with 695 patients, sarcopenia was associated with a greater than three times increase in 1-year mortality relative risk (RR 3.11 [1.94–4.96] $p = 0.00001$, $I^2 = 0\%$).

Meta-analysis of secondary outcomes

The secondary outcomes are shown as forest plots in Fig. 3.

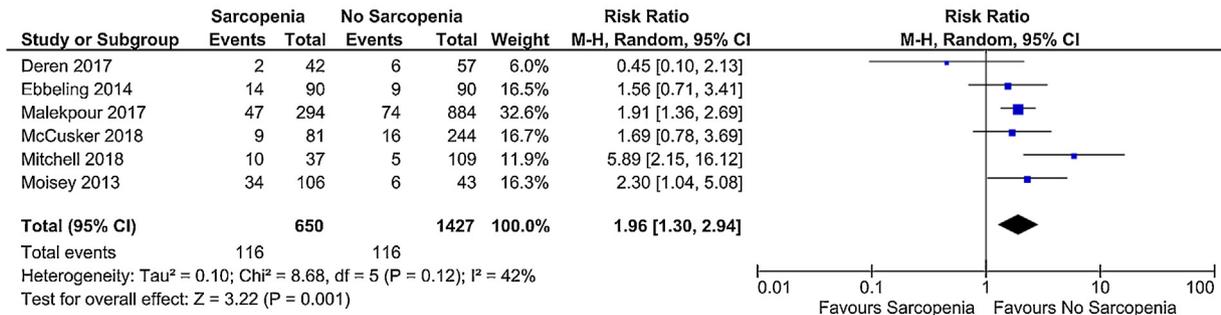
Any inpatient complication

Meta-analysis of six studies with 2383 patients showed sarcopenia was not significantly associated with increased risk of developing any inpatient complication ($p = 0.21$).

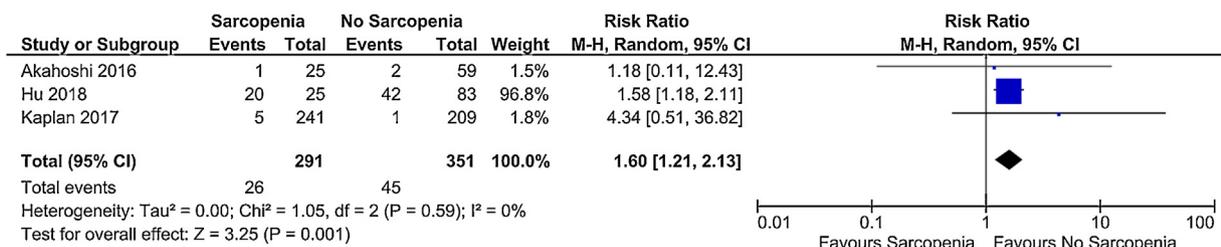
Length of ICU stay

Meta-analysis of six studies with 2325 patients showed sarcopenia was not significantly associated with increased length of ICU stay ($p = 0.94$).

A) In-Hospital Mortality



B) 30-Day Mortality



C) 1-Year Mortality

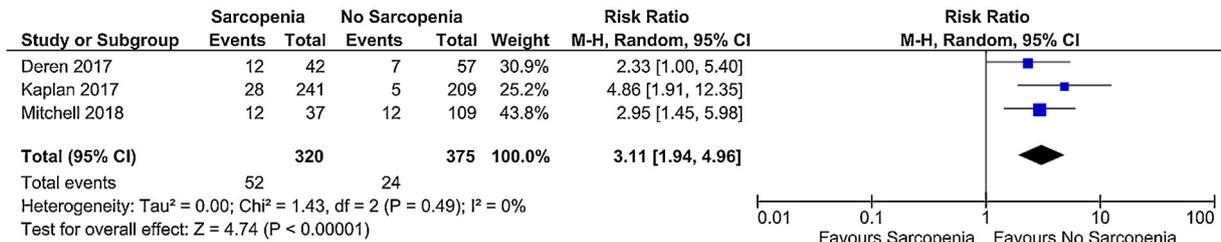


Fig. 2. – Primary Outcomes of Mortality Comparing Sarcopenia and No Sarcopenia Groups.

Length of hospital stay

Meta-analysis of eight studies with 2622 patients showed that sarcopenia was not significantly associated with increased length of hospital stay ($p = 0.80$).

Review of regression analyses for predicting mortality

Twelve studies utilised regression analyses to investigate the relationship between sarcopenia and mortality (Table 4). There were variable reports of significant associations.

Multivariate logistic regression

Nine studies [14,20,22,23,26,30,31,34,36] performed multivariate logistic regression analyses. Malekpour et al. [22] showed a significant relationship between sarcopenia and in-hospital mortality (OR 1.608 [95%CI 1.009–2.564], $p = 0.045$). Moisey et al. [14] showed that an increase in skeletal muscle index was associated with an increased chance of survival (OR 0.93 [95%CI 0.875–0.997] $p = 0.025$). Three other studies [20,23,30] which examined sarcopenia or skeletal muscle mass on in-hospital mortality demonstrated no significant relationship.

Three other studies that examined 30-day, [34] 90-day, [31] and 1-year [36] mortality demonstrated significant increased risk of mortality associated with sarcopenic patients or low skeletal muscle mass.

Cox proportional logistic regression

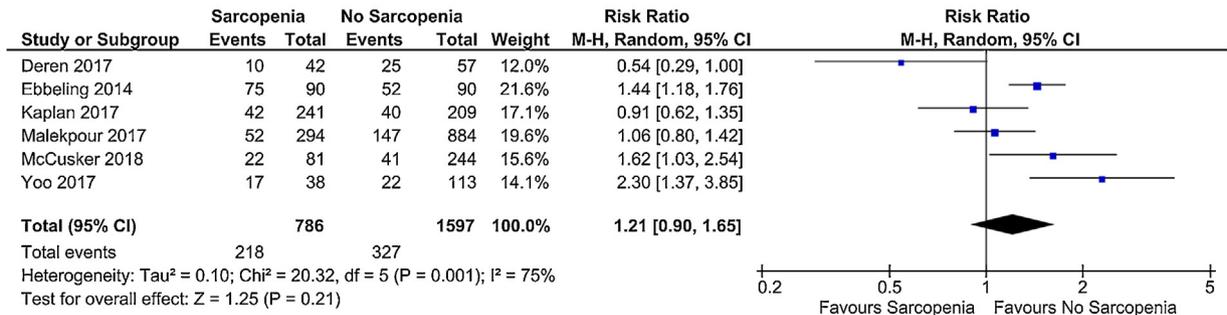
Six studies [21,26,34,35,39,40] performed Cox proportional hazard regression analyses investigating sarcopenia and mortality. One study [35] showed a significant increase in risk of mortality at 6-months (HR 4.77 [95%CI 2.71–8.40] $p < 0.001$). Two studies investigating 1-year mortality showed it was associated with sarcopenia [21] (HR 10.3 [95%CI 1.3–78.8] $p = 0.03$) and low psoas muscle mass [39] (HR 0.93 [95%CI 0.9–0.96] $p < 0.0001$).

One study [34] determined no significant change at 30-days, while two other studies [26,40] demonstrated variable significance depending on the method to measure skeletal muscle mass or sarcopenia.

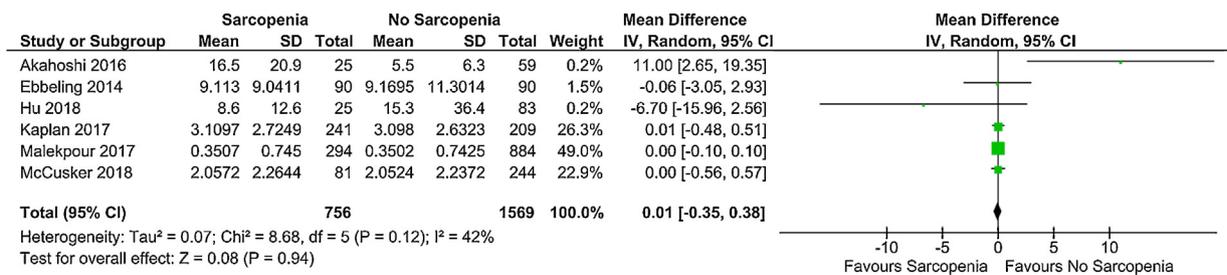
Discharge disposition

Significant heterogeneity prevented meta-analysis of the change in or unfavourable discharge disposition for sarcopenic

A) Any Inpatient Complication



B) ICU Length of Stay



C) Hospital Length of Stay

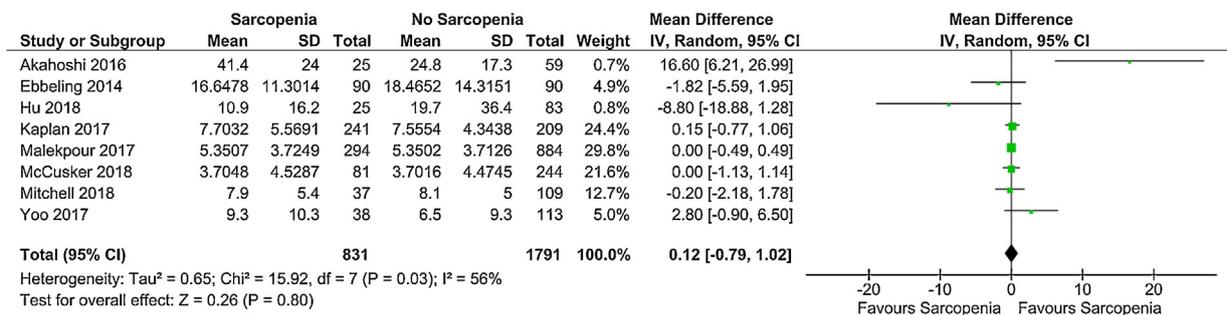


Fig. 3. – Secondary Outcomes Comparing Sarcopenia and No Sarcopenia Groups.

patients. The definition of unfavourable discharge disposition varied slightly depending on the study, with discharge to a skilled nursing facility or nursing home usually the definition. 10 studies [14,21–23,31–34,36,41] commented on the change in discharge disposition with mixed results.

Five studies [22,31–34] reported significantly elevated risk of sarcopenia or association with worse discharge disposition. One study [31] performed univariate logistic regression analysis (OR 1.04 [95%CI 1.015–1.068] $p = 0.0018$) and two studies performed multivariate logistic regression analysis (Fairchild et al. [33] OR 0.836 [95%CI 0.772–0.905] $p < 0.0001$; Malekpour et al. [22] OR 0.704 [95%CI 0.519–0.954] $p = 0.02$) which demonstrated association with less favourable discharge disposition with sarcopenia or decreasing skeletal muscle mass. Two other studies [32,34] commented on a significant higher risk of unfavourable discharge destination.

Four studies reported non-significant results, with two studies [14,21] showing non-significant outcomes and two multivariate logistic regression studies [23,36] demonstrating non-significant association with an unfavourable discharge disposition. Yoo et al. [41] which examined PMI and PMD as measures of sarcopenia provided mixed results, sarcopenic patients defined using PMD was significant for dependent discharge (RR 2.14 [95%CI 1.18–3.88] $p = 0.015$), but sarcopenic patients defined using PMI was non-significant ($p = 0.102$).

Sensitivity analysis

Yoo et al.'s [41] study investigated both psoas muscle index and psoas muscle density as a measure of sarcopenia on the same group of patients. We used psoas muscle density in our meta-analyses for any inpatient complication and total hospital length of

Table 4
Regression Analyses. Multivariate Logistic Regression Studies Reporting Impact of Skeletal Muscle Cross-Sectional Area or Density or Sarcopenia Impacting Mortality.

| Study | Mortality | Reference | Adjusted For | Odds Ratio | 95% Confidence Interval | P-value | |
|-----------------------------|----------------------|--|--|------------|-------------------------|-----------|-------|
| ^a Boutin 2017 | Overall | Per Sex-specific standard deviation increase in each muscle metric (2cm ² /m ² or 8.1 HU for women, 7.1 HU for men) for: | Age, sex, ethnicity, baseline BMI, ASA, Charlson Comorbidity Index | | | | |
| | | | | TMI | 0.72 | 0.52-1.00 | 0.049 |
| | | | | TMD | 0.72 | 0.53-0.99 | 0.039 |
| | | | | LMI | 1.00 | 0.71-1.39 | 1 |
| Couch 2018 | In-hospital | Lean Psoas Area per mm ² | Not Stated | | | | |
| | | | | LMD | 0.94 | 0.70-1.26 | 0.69 |
| ^b DeAndrade 2018 | 90-day | No Sarcopenia (Reference OR = 1) | – | 1.11 | 1.026-1.206 | 0.0094 | |
| Ebbeling 2014 | In-hospital | No Sarcopenia (Reference OR = 1) | Univariate variables with p < 0.10 included in adjustment (age, comorbidities, AIS head) | 1.2 | 0.44-3.26 | 0.72 | |
| Hu 2018 | 30-day | No Sarcopenia (Reference OR = 1) | Univariate variables with p ≤ 0.2 (age) | 2.95 | 1.03-8.49 | 0.045 | |
| Malekpour 2017 | In-hospital | No Sarcopenia (Reference OR = 1) | Univariate variables p < 0.20 (Ventilation days, length of stay, discharge to home/rehab) | 1.608 | 1.009-2.564 | 0.046 | |
| McCusker 2018 | In-hospital | No Sarcopenia (Reference OR = 1) | Univariate variables p < 0.20 (demographics, admission vitals, injury parameters, comorbidities, frailty status) | 1.12 | 0.87-1.35 | 0.73 | |
| ^c Mitchell 2018 | 1-year | Continuous variable measurement of PLVI | Age, gender, smoking, Charlson Comorbidity Index, ISS, associated pelvic ring injury | – | – | 0.046 | |
| Moisey 2013 | In-hospital survival | Continuous variable measurement of skeletal muscle index (per unit increase) | Clinically sound a priori which was placed sequentially into stepwise regression (age, sex, ISS) | 0.93 | 0.875-0.997 | 0.025 | |

| Study | Mortality | Reference | Adjusted For | Hazard Ratio | 95% Confidence Interval | P-value | |
|---------------------------|-------------------------------|--|---|-------------------------------|-------------------------|-----------|---------|
| ^a Boutin 2017 | Overall | Per sex-specific standard deviation increase in each muscle metric (2cm ² /m ² or 8.1 HU for women, 7.1 HU for men) for: | Age, sex, ethnicity, baseline BMI, ASA, Charlson Comorbidity Index | | | | |
| | | | | TMI | 0.86 | 0.70-1.00 | 0.097 |
| | | | | TMD | 0.82 | 0.67-1.00 | 0.052 |
| | | | | PMI | 1.01 | 0.80-1.29 | 0.94 |
| | | | | PMD | 0.84 | 0.69-1.02 | 0.08 |
| Hu 2018 | 30-day | No Sarcopenia (Reference HR = 1) | ISS, race, gender, mechanism of injury | 1.54 | 0.88-2.68 | 0.14 | |
| ^d Kaplan 2017 | 1-Year | No Sarcopenia or Osteopenia (HR = 1) | Clinically significant variables + univariate variables p ≤ 0.2 (Age, sex, comorbidities) | 10.3 | 1.3-78.8 | 0.03 | |
| Leeper 2016 | Post-discharge until 6 months | No Sarcopenia (Reference HR = 1) | Important predictors and univariate variables p ≤ 0.2 (Age, ICU admission, discharge to skilled nursing facility, female sex, fall) | 4.77 | 2.71-8.40 | <0.001 | |
| ^e Touban 2018 | 1-year | Continuous variable for lean psoas cross-sectional area (per unit increase) | – ^c | | | | |
| | | | | Male | 0.93 | 0.9-0.96 | <0.0001 |
| | | | | Female | 0.89 | 0.84-0.96 | 0.0019 |
| ^f Wallace 2017 | 2-year all-cause mortality | Continuous variable (per unit increase) for: | Age, sex, ISS, pre-existing conditions | | | | |
| | | | | Masseter cross-sectional area | 0.76 | 0.60-0.96 | 0.023 |
| | | Psoas cross-sectional area | | 0.67 | 0.46-1.00 | 0.051 | |

Cox Proportional Hazards Regression Studies Reporting Impact of Skeletal Muscle Cross-Sectional Area or Density or Sarcopenia Impacting Mortality.

^a Boutin 2017. No p-values were given, we have calculated the p-value from the odds ratio and confidence interval using the method from Altman DG et al.(27).^b DeAndrade 2018. Looked at univariate logistic regression only without adjusting for other variables.^c Mitchell 2018. Placed PLVI into multivariable logistic regression as a continuous variable, when it was found to be significant then divided PLVI values into quartiles with the lowest quartile defined as sarcopenic. Lower PLVI evidently results in increased 1-year mortality. No odds ratios were given.^d Kaplan 2017. This study originally examined 4 groups, combining a mixture of sarcopenia and osteopenia, see Table 1. We included the sarcopenia group ONLY, as we cannot account for osteopenia.^e Touban 2018. Univariate analysis given. When total population and stratified by male gender are adjusted for BMI, ISS, comorbidities and discharge destinations, the hazard ratios remain significant, but loses significance when age is assessed. Female gender remains non-significant.^f Wallace 2017. Compared multiple models. M-area when adjusted for all co-variables remained significant. For P-value only when adjusted for sex, age, ISS remained significant.

stay. When we change to psoas muscle index, non-significance of the meta-analysis results of the secondary outcomes remained.

For dichotomous variables in our meta-analysis, we employed risk ratios as the outcome measure. The results were

unchanged when odds ratios were used. For continuous variables, we employed the mean difference between groups. The results were unchanged when we substituted with standard mean difference.

Discussion

This is the first systematic review that has investigated the outcomes of CT-assessed sarcopenic trauma patients. A total of 20 studies were included in the qualitative analysis. The evidence from this study suggests that sarcopenia results in a significantly increased risk of in-hospital, 30-day and 1-year mortality. There was no significant difference in complications encountered, length of ICU stay or length of hospital stay. There was mixed evidence for the association between low skeletal muscle mass and a change in discharge disposition.

This study suggests that the effect of trauma on sarcopenic patients is not limited to the initial insult. Recent studies on the mechanisms of recovery in frail patients after emergency surgery have proposed that vulnerable population groups take longer to, or never, recover to their pre-injury state. [42] The result is much poorer functional outcomes in the long-term, especially if a second insult occurs, even if patients manage to overcome the initial injury. Our meta-analysis indicated that the relative risk of mortality at 1-year is much greater, compared with mortality at 30-days and during inpatient admission.

These findings concur with recent meta-analyses on vulnerable population groups such as patients undergoing emergency laparotomy [43], gastrointestinal cancer surgery [10] and liver transplant surgery [11]. This study adds to the growing body of evidence that low skeletal muscle mass appears to be an independent risk factor for mortality across a wide variety of population groups, and could function as part of a perioperative risk assessment [44–46]. Several studies [14,26,30,36,39,40] in our review suggested that a linear relationship between skeletal muscle mass and mortality exists. That is, a dichotomous assessment of sarcopenia on mortality based on a specific cut-off level in area or Hounsfield units may not be appropriate. Trauma not uncommonly occurs in diverse populations. Sarcopenia working groups have previously commented on the effect of different population groups have on the definition of sarcopenia [47]. For risk assessment to accurately be used in the trauma setting, further studies are required investigating the effect of increasing age on sarcopenia, as well as possible risk stratification of gender and ethnicity.

This systematic review also highlights the significant problem of the current lack of consensus on CT-assessed cut-off definitions of sarcopenia [48]. Multiple methods to measure skeletal muscle mass (either area or density) existed in our review, with total central skeletal muscle area or density, psoas muscle area or density only as well more recently the use of masseter muscles all present. Several studies [20,22,23,28,31,34–36,41] employed arbitrary cut-off values in their differing population groups to establish sarcopenia, rather than predefined cut-off values. This is especially problematic in studies with older patients as they may under-estimate the higher prevalence that comes with age. Additionally, recent efforts to define and establish sarcopenia as both physical skeletal muscle decline and functional decline [1,15,49] prevents universal acceptance that skeletal muscle mass alone assessment is sufficient for diagnosis. Previous work has shown that measures of physiologic impairment may also be of use in predicting surgical outcomes [50]. Thus further studies are required to assess the degree of correlation between CT-assessment and studies that incorporate both anthropometric and functional analyses.

Several important limitations in this review and of the included studies should be noted. Firstly, the included studies were all retrospective observational studies with the inherent biases and missing data accorded to retrospective studies. Secondly, only a limited number of studies could be meta-analysed together for our primary outcomes. Thirdly, significant heterogeneity exists

amongst the included study population in terms of their level of trauma, the type of trauma sustained or if operative management took place. Finally, the lack of a unified definition of sarcopenia and skeletal muscle mass measurements, along with arbitrary cut-offs applied without external validation poses a dilemma for applicability of the meta-analysis.

Sarcopenia results in increased overall mortality during inpatient, at 30-days and 1-year. The lack of consensus on specific values to define CT-assessed sarcopenia hampers clinical uptake on what otherwise serves as a promising and practical tool to help in prediction of trauma patient outcomes.

Conflict of interest

None.

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