Sarcopenia as A Predictor of Mortality Among the Critically Ill in an Intensive Care Unit: A Systematic Review and Meta-Analysis

Xiao-Ming Zhang

Peking Union Medical College Hospital Eastern Branch: Peking Union Medical College Hospital

Denghong Chen

The Third affiliated hospital of guangdong medical university

Xiao-Hua Xie

Shenzhen Second People's Hospital

Jun-E Zhang (✉ zhangmuxi0828@163.com)

Sun Yat-sen university

Yingchun Zeng

Third Affiliated Hospital of Guangzhou Medical College

Andy SK Cheng

hongkong Polytechnic University

Research article

Keywords: Sarcopenia, Mortality, Critically ill, intensive care unit, Meta-analysis

Posted Date: November 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-107337/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: The evidence of sarcopenia based on CT-scan as an important prognostic factor for critically ill patients has not seen consistent results.

Objective: To determine the impact of sarcopenia on mortality in critically ill patients, we performed a systematic review and meta-analysis to quantify the association between sarcopenia and mortality.

Methods: We searched studies from the literature of PubMed, EMBASE, and Cochrane Library from database inception to June 15, 2020. All observational studies exploring the relationship between sarcopenia based on CT-scan and mortality in critically ill patients were included. The search and data analysis were independently conducted by two investigators. A meta-analysis was performed using STATA Version 14.0 software using a fixed effects mode.

Results: Fourteen studies with a total of 3,249 participants were included in our meta-analysis. The pooled prevalence of sarcopenia among critically ill patients was 38% (95% CI:36%-39%). Critically ill patients with sarcopenia in intensive care unit have an increased risk of mortality, compared to critically ill patients without sarcopenia (HR=2.22, 95%CI: 1.79-2.75; $P<0.001$; $I^2=0.0\%$). In addition, a subgroup analysis found a significant difference in the association between sarcopenia and mortality when using total psoas muscle area (TPA), skeletal muscle index (SMI), and skeletal muscle area (SMA) to define sarcopenia (HR=2.96,95%CI:1.72-5.11, $P<0.001$; HR = 2.11,95%CI:1.59-2.80, $P<0.01$; HR=2.11, 95%CI:1.33-3.33, $P=0.001$, respectively), whereas the results were not significant when measuring the masseter muscle to define sarcopenia (HR=2.00, 95%CI:0.82-4.90, $P=0.129$).

Conclusion: Sarcopenia increases the risk of mortality in critical illness. Identifying the risk factors of sarcopenia should be routine in clinical assessments, offering corresponding interventions may help medical staff achieve good patient outcomes in ICU departments.

Background

Critically ill patients in intensive care units suffer from multiple organ dysfunction. Mortality rates - especially among oncology and hematology patients - have steadily decreased over time, thanks to dramatic progress in medical care¹. However, mortality among critically illness are still the most important issue that healthcare medical staff need to deal with, especially for older patients with more comorbidities than decades. There are several reasons that account for patient mortality, such as malnutrition², sepsis³, immobility, and multiple organ dysfunction syndrome⁴. Therefore, it is important to predict mortality and stratify the risk of death. For decades, numerous scoring systems have been developed to predict clinical outcomes in critical illness, such as SOFA⁵, systemic inflammatory response syndrome⁶, and Acute Physiology and Chronic Health Evaluation APACHE-II⁷. However, these scoring systems have shown relatively poor predictable performance. Therefore, further studies are required to investigate more precise parameters in order to better predict poor clinical outcomes.

Sarcopenia is characterised by declining loss muscle mass, strength, and physical function⁸. There is an increasing number of studies that show critically ill patients usually suffer from sarcopenia, due to factors such as nutritional status, inflammation, coexistence of disease, and inactivity⁹. It is estimated that the prevalence of sarcopenia is approximately 30%-70% in intensive care units^{10, 11}. Sarcopenia has been confirmed to have an association with negative clinical outcomes, such as falls, fractures, poor quality of life, mortality, and cognitive dysfunction among older adults in the community, nursing homes, or ICU¹²⁻¹⁵. Recently, Xia and colleagues published a meta-analysis concluding that injured patients with sarcopenia are at increased risk of mortality, with a two-fold increased risk compared to patient groups without sarcopenia¹⁶. Only four studies were conducted in ICU departments. Additionally, a number of recent studies have explored the relationship between sarcopenia and mortality in critically ill patients in the ICU. Some have shown that sarcopenia significantly increases mortality risk^{10, 17-21}, while others found no such an association^{11, 22-25}. Given the inconsistent results, it is necessary to synthesise the evidence to explore the role sarcopenia may play in mortality in critically ill patients in the ICU. Therefore, we conducted a systematic review and meta-analysis to confirm whether critically ill patients with sarcopenia are at increased risk of mortality in ICU departments, which could inform prognostication on critically ill patients.

Methods

This study was conducted and reported according to the Observational Studies in Epidemiology guidelines (MOOSE)²⁶, with a detailed checklist shown in supplementary Table1 The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used to categorise the level of evidence.

Search strategy

Two authors (XMZ, DHC) independently searched the electronic database, including PubMed, Embase, and Cochrane CENTRAL Library, from database inception until June 15, 2020. The search strategy includes keywords and medical subject headings (Mesh), including sarcopenia, critically ill (critical illness), or intensive care. The detailed search methods are shown in Supplemental File1. We conducted a manual search of additional references from the selected articles. In addition, we searched grey or unpublished studies from Google or relevant authors. The search results were discussed and confirmed by our team.

Study selection

All of the articles identified from the electronic database were independently evaluated by two authors (Y CZ and DHC). To start with, title and abstract were screened to confirm whether an article was potentially relevant. After that, the two authors checked the full text to identify whether it met the priority eligibility criteria. Any disagreements were addressed through team discussion and consensus.

Inclusion and exclusion criteria

We established a priori inclusion criteria as follows: (i) The study design included observational studies; (ii) We included participants 18 years of age and over from ICU departments; (iii) The study includes a clear definition of sarcopenia using a consensual method; and (iv) The study has shown the relationship between sarcopenia and mortality (30-day mortality, in-hospital mortality, 1-year mortality).

The exclusion criteria are as follows: (i) Article type: Conference, review articles, letters and laboratory research, case report; (ii) Using the sarcopenia index calculated as [(serum creatinine/serum cystatin C) × 100] to report the association between SI (sarcopenia and index) and mortality; (iii) LMM (low muscle mass) was used as a continuous variable to report the association, but did not provide the results of association, between sarcopenia and mortality; (iv) Duplicate publication of articles; and (v) Languages other than English.

Data extraction

The two authors (ASKC and XHX) independently used Microsoft® Excel 2016 to collect all data. The variables of the studies that were included were extracted as follows: Country, year of publication, time of CT scan, male/female ratio, age, prevalence of sarcopenia, sample size, definition of sarcopenia, cause of admission, and outcome. If the study reported more than two terms of mortality, such as 30-day mortality, 1-year mortality, the latter term was included. If mortality was shown in a multivariate analysis, we adopted the adjusted model, otherwise we calculated it. All data were checked by the two authors to achieve the final results.

Quality assessment and risk of bias.

Study quality assessment was evaluated by both authors using the Newcastle-Ottawa Scale (NOS). It included six aspects, with the scale's total score, nine points²⁷. The following NOS information included (i) Representativeness of the exposed cohort, (ii) comparability of the group, (iii) blinding of the investigators who measured the outcomes, (iv) time and completeness of follow-up, (v) contamination bias, and (vi) other potential sources of bias.

Statistical analysis

Both authors (XMZ and ASKC) independently used STATA Version 14.0 software to calculate pooled data and heterogeneity. The studies that were included reported hazard ratio (HR), and 95% confidence intervals (95% CI) were extracted for future meta-analysis. We converted the effect of HR to $\ln(HR)$ for ratios in a meta-analysis, and subgroup analyses were conducted on different types of participants and outcomes. We performed Cochran's Q test to examine statistical heterogeneity by using chi-square and I^2 statistics. According to the GRADE recommendation, heterogeneity was defined as low, moderate, and high, with the I^2 value of 25%, 50%, and 75% as the cutoff. If the $I^2 > 50\%$ or $p < 0.10$, we defined these studies as having significant heterogeneity and used the random-effects model. Otherwise, the fixed-effects model was used. Furthermore, Begg's and Egger's tests were used to identify whether any publication bias existed, and sensitivity analysis was conducted to assess the stability of the results. We also used trial sequential analysis (TSA) to assess whether the results were robust and reliable²⁸.

Assessment of evidence quality.

We displayed the evidence for each outcome using the methods recommended by GRADE. We rated the overall quality of evidence according to four categories: "high", "moderate", "low or very low". These criteria were based on the evaluation of identified risks of bias, indirectness, imprecision, inconsistency, and publication bias.

Results

Study selection

Our team initially searched 594 articles from three Internet databases. After removing the duplicates, 497 articles remained. YCZ and DHC then screened the titles and abstracts, deleting 469 irrelevant studies. A further 28 articles were screened for full-text assessment: six studies were reviews or case studies and four studies were conference papers. In addition, four studies were excluded for not reporting the association between sarcopenia and mortality, as they only provided the association between skeletal muscle index (SMI) as a continuous variable and mortality²⁹⁻³². Therefore, 14 publications were finalised for analysis. (Shown in FigureS1).

Study summary

There were 14 studies with a total of 3,249 patients included in our meta-analysis. All of the studies that were included were retrospective cohort studies, with the exception of one³⁴, which was a prospective cohort study. A total of five studies was conducted in the U.S.^{10,23,24,33,34}, while China^{21,22}, Japan^{17,35}, and the Netherlands^{11,18} each had two studies, and Korea²⁰, Australia²⁵, and Brazil¹⁹ each had one study respectively. All studies used CT to detect sarcopenia. There were several outcomes reported in our meta-analysis. Seven studies used in-hospital mortality^{10,11,18,17,21,23,34}, four studies used 30-day mortality^{19,22,25,35}, and three studies used 1-year mortality^{20,24,33}. The proportion of males among the studies that were included ranged from 51.40% to 61.40% (Table 1). TableS2 showed the result of each study with adjusted covariates. The pooled prevalence of sarcopenia among critically ill patients was 38% (95% CI: 36% -39%; $p=0.000$; $I^2=95.5\%$) (Figure 1).

Study quality

None of the studies was a randomised controlled study, and study quality was relatively moderate, ranging from 5 to 8 points NOS (TableS3)

Mortality

All studies that were included used mortality as the primary outcome. Our study showed that critically ill patients with sarcopenia have an increased risk of mortality when compared to those without sarcopenia (HR=2.22, 95%CI: 1.79-2.75; $P<0.001$; $I^2=0.0\%$) (Figure2). In addition, pooled data showed a significantly high risk of in-hospital mortality in critically ill patients with sarcopenia, compared to non-sarcopenic patients (HR=1.97, 95%CI:1.47-2.64; $P<0.001$; $I^2=0.0\%$), 30-day mortality (HR=2.08, 95%CI:1.36-3.19; $P=0.001$; $I^2=0.0\%$), and 1-year mortality (HR=3.24, 95%CI:2.03-5.16; $P<0.001$; $I^2=0.0\%$) (shown in Figure3). Meanwhile, we examined the minimum sample size required by trial sequential analysis for meta-analysis and found that 1,105 participants were required. There were 3,249 participants included from these 14 studies. In addition, as we can see the Z line has crossed both information size and conventional boundaries, indicating that the association between sarcopenia and all-cause mortality in our analysis was reliable and robust. (Figure S2).

Subgroup analyses

Reasons for ICU admission

Six studies clearly reported that the reason for admission to ICU was trauma^{10,23,33-35}, while three studies indicated sepsis as the reason for admission^{11,17,22}. The patients in the other studies showed complex reasons for ICU department admittance^{18-21,25}. Therefore, we performed a subgroup analysis of the reasons for admission, and found that patients with both sepsis and sarcopenia had an increased mortality risk when compared to patients without sarcopenia (HR=2.20, 95% CI:1.53-3.18; $p<0.001$; $I^2=0.0\%$). The results were similar among trauma patients (HR=1.89, 95%CI:1.33-2.69; $p<0.001$; $I^2=0.0\%$) and patients admitted for other mixed reasons (HR=2.75, 95% CI:1.84-4.10; $p<0.001$; $I^2=21.7\%$) (Figure4).

Different definitions of sarcopenia

There are several methods to measure skeletal muscle mass, including total skeletal muscle area or psoas muscle area, as well as masseter cross-sectional area. Detailed information, including muscle measurement and cutoff values, are shown in Table2. Therefore, we performed a subgroup analysis based on different measures to detect whether there was a difference. Our results showed that critically ill patients with sarcopenia had an increased risk of mortality, compared with non-sarcopenic patients, when using SMI to define sarcopenia (HR=2.11, 95%CI:1.59-2.80; $P<0.001$; $I^2=0.0\%$). In addition, we found similar results when using TPA (HR=2.96, 95% CI: 1.72-5.11; $P<0.001$; $I^2=59.7\%$) or SMA (HR=2.11, 95%CI:1.33-3.33; $P=0.001$; $I^2=0.0\%$) to define sarcopenia. However, the association between sarcopenia, based on masseter cross-sectional area, and mortality was not significantly different (HR=2.00, 95%CI:0.82-4.90; $P=0.129$). (Figure5)

Subgroup analyses according to region

Five studies were conducted in Asian populations^{17,20-22,35}, and nine studies in Western populations^{10,11,18,19,23-25,33,34}. Therefore, we performed a subgroup analysis based on geographical region. The results showed that critically ill Asian patients with sarcopenia have an increased risk of mortality, compared to critically ill Asian patients without sarcopenia (HR=2.86, 95% CI:1.99-4.11; $P=0.001$; $I^2=0.0\%$). Similar results were found in Western populations (HR=1.93, 95% CI:1.48-2.52; $P=0.001$; $I^2=0.0\%$). Figure6 summarises the results.

Subgroup analysis by age

As age is an important confounding factor, we performed a subgroup analysis based on two age groups (more than or equal to 70 years versus less than 70 years). The results showed that the association between mortality and sarcopenia was observed in both of these age groups (HR =2.25, 95%CI:1.57-3.21; $P<0.001$; $I^2=0.0\%$ versus HR=2.20, 95%CI:1.68-2.88; $P<0.001$; $I^2=24.9\%$, respectively). See FigureS3.

Publication bias and sensitivity analysis

The results of Begg's and Egger's tests show no significant bias ($P=0.760$, $P=0.991$, respectively) (Figure S4). In addition, sensitivity analysis results show that the pooled result did not result in significant change after one study was omitted each time (Figure S5).

Overall evidence quality

Our study indicates the quality of evidence was low due to the risk of bias, indirectness, and imprecision (TableS4).

Discussion

Our study found that critically ill patients with sarcopenia have a 2.22-fold increased risk of mortality compared to patients without sarcopenia, regardless of short- or long-term mortality. To the best of our knowledge, this is the first significant comprehensive study to systematically summarise evidence on the association between sarcopenia and mortality in intensive care units. Our study suggests that intensive care physicians should focus more on screening for sarcopenia and should recommend, early and effective preventive programmes, such as resistance training or nutrition treatments, with the goal of reducing patient mortality rates in ICU departments.

The pooled prevalence of sarcopenia was 38% (95%CI: 36%- 39%), which is higher than among community-dwelling older adults³⁶. In fact, the prevalence of sarcopenia varied among different participants and was also determined by measurements detecting muscle mass with different cutoff points. Yang M³⁷ and colleagues performed a meta-analysis and found the pooled prevalence of sarcopenia was 43% in patients with non-small cell lung cancer (NSCLC) and 52% in patients with small cell lung cancer (SCLC), which is higher than in our study. This is due to the fact that cancer patients often suffer from worse conditions, such as malnutrition³⁸ and severe adverse reactions to treatments such as radiotherapy or chemotherapy³⁹.

The main reasons accounting for patient admission to ICU are sepsis or cancer-related infection or trauma^{40–42}. Our subgroup results found that when considering the reasons for admission, critically ill patients with sarcopenia have an increased risk of mortality, profoundly confirming that sarcopenia could be a prognostic factor in critical illness. Our findings are in line with previous research, which has found that older adults with sarcopenia are at increased risk of mortality in other settings, such as the community³⁶, nursing homes⁴³, or in an oncology setting^{44–46}. According to published studies, the main reason explaining the relationship between sarcopenia and mortality is lower muscle mass, which has been confirmed as a strong predictor for an increased risk of death^{31,47}. Apart from these factors, critically ill patients often experience complications from worsening conditions, such as severe inflammation, malnutrition, and multiple organ failure, which make patients ill in a vicious circle through the interaction of sarcopenia.⁴⁸ Furthermore, being critically ill with sarcopenia may aggravate the possibility of adverse effects resulting from intensive care treatments, including polypharmacy, bed rest, sedation, instrumentation, and mechanical ventilation. All of these multiple factors will increase the risk of mortality in critically ill patients with sarcopenia.

There are several definitions for sarcopenia in the studies we included, based on CT scan and the cutoff for low skeletal muscle mass¹⁶. Therefore, we performed a subgroup analysis based on methods to measure skeletal muscle mass. By using different measurements, including SMI, SMA, and TPA, with the exception of masseter muscle measurement, our subgroup analysis found that critically ill patients with sarcopenia are at increased risk of mortality, compared with non-sarcopenic critically ill patients. It is surprising to find a non-association between sarcopenia and mortality when measuring the masseter muscle. Possible reasons may be a limited number of studies, therefore further studies will be required in future to test these issues. There is no consensus on cutoff for CT scans in defining sarcopenia, leading to differing rates of sarcopenia prevalence and problems in standard clinical practice⁴⁹. According to the latest European Working Group on Sarcopenia in Older People (EWGSOP) update, defining sarcopenia should include an assessment of strength, muscle mass, and detecting sarcopenia severity based on physical performance⁵⁰. However, it is difficult for medical staff to detect strength and physical performance in a critical care setting. The definition of sarcopenia based on a CT scan of muscle mass is currently routine application for critically ill patients, particularly trauma patients, but further studies are required to testify to a standard criteria definition of sarcopenia that can be applicable in clinical practice.

Body composition in people of different ethnicities can vary, given the variety between populations⁵¹. It is obvious that ethnic and environmental factors, such as industrialisation, may lead to varying lifestyles and levels of physical activity, which can affect body composition. Using the same cutoff values for different ethnicities can be problematic. Several academic organisations, such as EWGSOP and The Asian Working Group for Sarcopenia (AWGS)⁵² have formulated different sarcopenia criteria. These two criteria have widely been used in both Asian and Western countries, but with different cutoff values for low skeletal muscle mass. This meta-analysis included many studies from different countries. Our subgroup analysis shows that people who are critically ill with sarcopenia are at increased risk of mortality in both Asian and Western populations, indicating that sarcopenia's impact on critically ill patients is not affected by ethnicity.

Obesity was another important and common condition among critically ill patients, with a prevalence rate of 20% among ICU patients⁵³. The "obesity paradox" is a well-known phenomenon in most chronic wasting diseases. A recent study confirmed the "obesity paradox" (proven in e.g. chronic heart failure or dialysis patients) among hospitalized and ICU patients, indicating a J-shaped association between BMI and mortality. This indicates that moderate obesity was a protective factor for critically ill patients, compared to normal or more severe obesity⁵⁴. Critically ill patients with sarcopenia can coexist with obesity, which is called sarcopenic obesity⁵⁵. A previous review revealed that adults with sarcopenic obesity could be at increased risk for all-cause mortality in different settings⁵⁶. However, the participants in that study were seldom critically ill. Therefore, whether sarcopenic obesity could lead to a worse prognosis for specific critically ill patients needs to be studied further.

Implications For Clinicians, Policy, And Research

A crucial aspect of our study is to confirm whether ICU care processes could be amended to improve clinical outcomes in patients with sarcopenia. Recent studies have determined processes that may exert an important impact on sarcopenic patients, include resistance training programmes⁵⁷, nutritional support, and intensity of rehabilitation⁵⁸. While research is being conducted on how to reduce patient mortality rates in intensive care units, realising sarcopenia as a risk factor in mortality is also significant, and may help in more effective care planning. To date, many conventional scoring systems, including Acute Physiology and Chronic Health Evaluation (APACHE), sequential organ failure assessment (SOFA), and systemic inflammatory response syndrome (SIRS) have been used to assess critically ill patients^{6,59}. However, published studies have shown their performance in predicting mortality is modest and cannot satisfy intensive care physicians⁶⁰. Our study supports the value of sarcopenia screening upon ICU admission. Whether measuring muscle mass using CT can improve mortality prediction by adding to conventional scoring systems is worthy of study, given the convenience and simplicity of CT scans.

Our study has a number of strengths. First, to the best of our knowledge, this is the first meta-analysis to quantify the relationship between sarcopenia and mortality in critically ill patients using comprehensive methods and low heterogeneity. Second, we assessed our study using GRADE and recommend using the level of evidence to help medical staff guide clinical work. Our study may also have some limitations. First, the studies that were included in our meta-analysis were all observational studies. They might contain biases, such as selection and confirmation, and cannot determine causation. Second, five studies reported that sarcopenia detection occurred within several days after ICU department admission, meaning that sarcopenia could be a consequence of disease severity. Therefore, this meta-analysis could intensify sarcopenia's impact on mortality. Third, there are several different measurements of muscle mass with various SMI cutoffs to determine sarcopenia, resulting in a differing prevalence of sarcopenia and which could eventually lead to different results. Various cut-off of SMI, without a universally agreed consensus on cutoff values for low skeletal muscle, can generate a problem that influences the treatment of patients for sarcopenia. According to the study of Yoowannakul, cutoff values for low skeletal muscle should be adjusted according to gender, normative ethnicity, and age values⁶¹. When we conducted a subgroup analysis based on muscle measurement, we found the results were similar across various sarcopenia measures, with the exception of masseter muscle measurement. However, unanswered questions remain as to which is the most appropriate measure in an ICU setting. Third, most studies performed multivariate analysis to investigate the relationship between sarcopenia and mortality in critically ill patients, yet

not all studies adjusted the same confounders, which may have resulted in an underestimation or overestimation of our results. In addition, a number of important confounding factors, such as chronic obstructive pulmonary disease (COPD) and cardiac failure, which would have influenced sarcopenia's impact on mortality, were not reported in the original studies. Therefore, we could not conduct a subgroup analysis based on these parameters. Fourth, the studies that were included were from different countries, with different hospital systems and a variety of medical technologies and healthcare settings, which could have influenced the outcomes. Fifth, there are different types of outcomes, including in-hospital mortality, 30-day mortality, and 1-year mortality, which might have exerted an adverse impact on aggregation.

Conclusions

Our study found that critically ill patients with sarcopenia have an increased 2.22-fold risk of mortality compared to those without sarcopenia. Timely routine assessment for sarcopenia upon ICU admission may provide an important prognostic factor in patient survival. Offering corresponding interventions may help medical staff achieve good patient outcomes. Furthermore, this study also suggests the importance of initiating effective intervention programmes, such as resistance training and appropriate nutritional treatment, which may reduce the risk of mortality.

Abbreviations

CT

computed tomography; Mesh:medical subject headings; NOS:Newcastle Ottawa Scale; HR:Hazard ratios, SMI:skeletal muscle index; SMA:skeletal muscle area; TPA:total psoas muscle area; MCSA:masseter cross-sectional area.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

All the author agrees with the final version

Availability of data and materials

All the data can obtain from internet database

Competing interests

None of the authors has any conflict of interest to declare.

Funding

This research received NO grant from any organization. No sponsors had any role in the design, methods, subject recruitment, data collection, analysis, or preparation of this manuscript.

Authors' Contributions

XMZ and DHC were responsible for producing the initial draft of the manuscript.

XMZ and DHC were responsible for implementing the search strategy.

ASKC and XHX were responsible for the data extraction.

YCZ and DHC were responsible for screening the papers and the quality assessment.

XMZ and ASKC responsible for the statistical analysis.

ZJE, XHX and ASKC were responsible for the manuscript revision.

All authors approved the final version of the manuscript.

Acknowledgements

The authors thank the staff of the Department of nursing at Peking Union Medical College Hospital (Dongdan campus) and the Department of Nursing at Sun Yat-sen University for their guidance and support.

References

1. Darmon M, Bourmaud A, Georges Q, et al. Changes in critically ill cancer patients' short-term outcome over the last decades: results of systematic review with meta-analysis on individual data. *Intensive Care Med.* Jul 2019;45(7):977-987.

2. Ceniccola GD, Holanda TP, Pequeno RSF, et al. Relevance of AND-ASPEN criteria of malnutrition to predict hospital mortality in critically ill patients: A prospective study. *J Crit Care.* Apr 2018;44:398-403.
3. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet.* Jan 18 2020;395(10219):200-211.
4. Mayr VD, Dunser MW, Greil V, et al. Causes of death and determinants of outcome in critically ill patients. *Crit Care.* 2006;10(6):R154.
5. Lee CW, Kou HW, Chou HS, et al. A combination of SOFA score and biomarkers gives a better prediction of septic AKI and in-hospital mortality in critically ill surgical patients: a pilot study. *World J Emerg Surg.* 2018;13:41.
6. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. The systemic inflammatory response syndrome criteria and their differential association with mortality. *J Crit Care.* Aug 2018;46:29-36.
7. Lee H, Lim CW, Hong HP, et al. Efficacy of the APACHE II score at ICU discharge in predicting post-ICU mortality and ICU readmission in critically ill surgical patients. *Anaesth Intensive Care.* Mar 2015;43(2):175-186.
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* Jul 2010;39(4):412-423.
9. Kizilarslanoglu MC, Kuyumcu ME, Yesil Y, Halil M. Sarcopenia in critically ill patients. *J Anesth.* Oct 2016;30(5):884-890.
10. Moisey LL, Mourtzakis M, Cotton BA, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. *Crit Care.* Sep 19 2013;17(5):R206.
11. Baggerman MR, van Dijk DPJ, Winkens B, et al. Muscle wasting associated co-morbidities, rather than sarcopenia are risk factors for hospital mortality in critical illness. *J Crit Care.* Nov 26 2019;56:31-36.
12. Yeung SSY, Reijnierse EM, Pham VK, et al. Sarcopenia and its association with falls and fractures in older adults: A systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle.* Jun 2019;10(3):485-500.
13. Zhang X, Huang P, Dou Q, et al. Falls among older adults with sarcopenia dwelling in nursing home or community: A meta-analysis. *Clin Nutr.* Jan 2020;39(1):33-39.
14. Chang KV, Hsu TH, Wu WT, Huang KC, Han DS. Association Between Sarcopenia and Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc.* Dec 1 2016;17(12):1164.e1167-1164.e1115.
15. Ando Y, Ishigami M, Ito T, et al. Sarcopenia impairs health-related quality of life in cirrhotic patients. *Eur J Gastroenterol Hepatol.* Dec 2019;31(12):1550-1556.
16. Xia W, Barazanchi AWH, MacFater WS, Hill AG. The impact of computed tomography-assessed sarcopenia on outcomes for trauma patients - a systematic review and meta-analysis. *Injury.* Sep 2019;50(9):1565-1576.
17. Shibahashi K, Sugiyama K, Kashiura M, Hamabe Y. Decreasing skeletal muscle as a risk factor for mortality in elderly patients with sepsis: a retrospective cohort study. *J Intensive Care.* 2017;5:8.
18. de Hoogt PA, Reisinger KW, Tegels JJW, Bosmans J, Tijssen F, Stoot J. Functional Compromise Cohort Study (FCCS): Sarcopenia is a Strong Predictor of Mortality in the Intensive Care Unit. *World J Surg.* Jun 2018;42(6):1733-1741.
19. Toledo DO, Carvalho AM, Oliveira A, et al. The use of computed tomography images as a prognostic marker in critically ill cancer patients. *Clin Nutr ESPEN.* Jun 2018;25:114-120.
20. Cho WH, Choi YY, Byun KS, et al. Prognostic Value of Sarcopenia for Long-Term Mortality in Extracorporeal Membrane Oxygenation for Acute Respiratory Failure. *Asaio j.* Apr 18 2019.
21. Kou HW, Yeh CH, Tsai HI, et al. Sarcopenia is an effective predictor of difficult-to-wean and mortality among critically ill surgical patients. *PLoS One.* 2019;14(8):e0220699.
22. Ji Y, Cheng B, Xu Z, et al. Impact of sarcopenic obesity on 30-day mortality in critically ill patients with intra-abdominal sepsis. *J Crit Care.* Aug 2018;46:50-54.
23. Hwang F, McGreevy CM, Pentakota SR, et al. Sarcopenia is Predictive of Functional Outcomes in Older Trauma Patients. *Cureus.* Nov 14 2019;11(11):e6154.
24. Tanabe C, Reed MJ, Pham TN, Penn K, Bentov I, Kaplan SJ. Association of Brain Atrophy and Masseter Sarcopenia With 1-Year Mortality in Older Trauma Patients. *JAMA Surg.* May 8 2019.
25. Joyce PR, O'Dempsey R, Kirby G, Anstey C. A retrospective observational study of sarcopenia and outcomes in critically ill patients. *Anaesth Intensive Care.* May 2020;48(3):229-235.
26. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama.* Apr 19 2000;283(15):2008-2012.
27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* Sep 2010;25(9):603-605.
28. Ng KT, Lee ZX, Ang E, Teoh WY, Wang CY. Association of obstructive sleep apnea and postoperative cardiac complications: A systematic review and meta-analysis with trial sequential analysis. *J Clin Anesth.* Jan 24 2020;62:109731.
29. Ju S, Choi SM, Park YS, et al. Rapid Muscle Loss Negatively Impacts Survival in Critically Ill Patients With Cirrhosis. *J Intensive Care Med.* Jul 2020;35(7):663-671.

30. Kim YJ, Seo DW, Kang J, Huh JW, Kim KW, Kim WY. Impact of Body Composition Status on 90-Day Mortality in Cancer Patients with Septic Shock: Sex Differences in the Skeletal Muscle Index. *J Clin Med*. Oct 2 2019;8(10).
31. Weijs PJ, Looijaard WG, Dekker IM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Crit Care*. Jan 13 2014;18(2):R12.
32. Toptas M, Yalcin M, Akkoc İ, et al. The Relation between Sarcopenia and Mortality in Patients at Intensive Care Unit. *Biomed Res Int*. 2018;2018:5263208.
33. Kaplan SJ, Pham TN, Arbabi S, et al. Association of Radiologic Indicators of Frailty With 1-Year Mortality in Older Trauma Patients: Opportunistic Screening for Sarcopenia and Osteopenia. *JAMA Surg*. Feb 15 2017;152(2):e164604.
34. Ebbeling L, Grabo DJ, Shashaty M, et al. Psoas:lumbar vertebra index: central sarcopenia independently predicts morbidity in elderly trauma patients. *Eur J Trauma Emerg Surg*. Feb 2014;40(1):57-65.
35. Akahoshi T, Yasuda M, Momii K, et al. Sarcopenia is a predictive factor for prolonged intensive care unit stays in high-energy blunt trauma patients. *Acute Med Surg*. Oct 2016;3(4):326-331.
36. Liu P, Hao Q, Hai S, Wang H, Cao L, Dong B. Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: A systematic review and meta-analysis. *Maturitas*. Sep 2017;103:16-22.
37. Yang M, Shen Y, Tan L, Li W. Prognostic Value of Sarcopenia in Lung Cancer: A Systematic Review and Meta-analysis. *Chest*. Jul 2019;156(1):101-111.
38. Ravasco P. Nutrition in Cancer Patients. *J Clin Med*. Aug 14 2019;8(8).
39. Bozzetti F. Chemotherapy-Induced Sarcopenia. *Curr Treat Options Oncol*. Jan 30 2020;21(1):7.
40. Sakr Y, Jaschinski U, Wittebole X, et al. Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit. *Open Forum Infect Dis*. Dec 2018;5(12):ofy313.
41. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs. *Crit Care*. 2009;13(1):R15.
42. Magee F, Wilson A, Bailey MJ, et al. Trauma-related admissions to intensive care units in Australia: the influence of Indigenous status on outcomes. *Med J Aust*. Jun 2019;210(11):493-498.
43. Zhang X, Wang C, Dou Q, Zhang W, Yang Y, Xie X. Sarcopenia as a predictor of all-cause mortality among older nursing home residents: a systematic review and meta-analysis. *BMJ Open*. Nov 12 2018;8(11):e021252.
44. Buentzel J, Heinz J, Bleckmann A, et al. Sarcopenia as Prognostic Factor in Lung Cancer Patients: A Systematic Review and Meta-analysis. *Anticancer Res*. Sep 2019;39(9):4603-4612.
45. Su H, Ruan J, Chen T, Lin E, Shi L. CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. *Cancer Imaging*. Dec 3 2019;19(1):82.
46. Ubachs J, Ziemons J, Minis-Rutten IJG, et al. Sarcopenia and ovarian cancer survival: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. Dec 2019;10(6):1165-1174.
47. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: A population-based cohort study. *PLoS One*. 2018;13(4):e0194697.
48. Gropper S, Hunt D, Chapa DW. Sarcopenia and Psychosocial Variables in Patients in Intensive Care Units: The Role of Nutrition and Rehabilitation in Prevention and Treatment. *Crit Care Nurs Clin North Am*. Dec 2019;31(4):489-499.
49. Lee K, Shin Y, Huh J, et al. Recent Issues on Body Composition Imaging for Sarcopenia Evaluation. *Korean J Radiol*. Feb 2019;20(2):205-217.
50. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. Jul 1 2019;48(4):601.
51. Wulan SN, Westerterp KR, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. *Maturitas*. Apr 2010;65(4):315-319.
52. Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am Med Dir Assoc*. Mar 2020;21(3):300-307.e302.
53. Sakr Y, Alhussami I, Nanchal R, et al. Being Overweight Is Associated With Greater Survival in ICU Patients: Results From the Intensive Care Over Nations Audit. *Crit Care Med*. Dec 2015;43(12):2623-2632.
54. Schetz M, De Jong A, Deane AM, et al. Obesity in the critically ill: a narrative review. *Intensive Care Med*. Jun 2019;45(6):757-769.
55. Tieland M, van Dronkelaar C, Boirie Y. Sarcopenic obesity in the ICU. *Curr Opin Clin Nutr Metab Care*. Mar 2019;22(2):162-166.
56. Zhang X, Xie X, Dou Q, et al. Association of sarcopenic obesity with the risk of all-cause mortality among adults over a broad range of different settings: a updated meta-analysis. *BMC Geriatr*. Jul 3 2019;19(1):183.
57. Adams SC, Segal RJ, McKenzie DC, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *Breast Cancer Res Treat*. Aug 2016;158(3):497-507.
58. Beckwee D, Delaere A, Aelbrecht S, et al. Exercise Interventions for the Prevention and Treatment of Sarcopenia. A Systematic Umbrella Review. *J Nutr Health Aging*. 2019;23(6):494-502.
59. Ho KM. Combining sequential organ failure assessment (SOFA) score with acute physiology and chronic health evaluation (APACHE) II score to predict hospital mortality of critically ill patients. *Anaesth Intensive Care*. Aug 2007;35(4):515-521.
60. Zhang XM, Zhang WW, Yu XZ, Dou QL, Cheng AS. Comparing the performance of SOFA, TPA combined with SOFA and APACHE-II for predicting ICU mortality in critically ill surgical patients: A secondary analysis. *Clin Nutr*. Sep 2020;39(9):2902-2909.

61. Yoowannakul S, Tangvoraphonkchai K, Davenport A. The prevalence of muscle wasting (sarcopenia) in peritoneal dialysis patients varies with ethnicity due to differences in muscle mass measured by bioimpedance. *Eur J Clin Nutr.* Mar 2018;72(3):381-387.

Tables

Table 1
Summary of Included Studies on sarcopenia Associated with Mortality among critically ill

Author/year	Time of CT scan	Country	Design	Study interval	Male	Cause of ICU	Prevalence	Sample size	Age/years	Sarcopenia Criteria	Outcomes assessed
Moisey 2013 [10]	On the day of admission	USA	retrospective cohort study	2009–2010	57%	Trauma	71.00%	149	79 (72–85)	SMI	in-hospital mortality
Hoogt 2018[18]	NA	Netherlands	retrospective cohort study	2013–2014	53.40%	Critically ill	34.00%	687	none	SMI	in-hospital mortality
Ji 2018 [22]	Before ICU admission	China	retrospective cohort study	2012–2016	58.80%	sepsis	26.00%	236	≥ 18	SMI	30-day survival
Shibahashi 2017 [17]	On the day of admission	Japan	retrospective cohort study	2012–2016	69%	sepsis	42.00%	150	75 years	SMA	in-hospital mortality
Cho 2019 [20]	1 day before admission	Korea	retrospective cohort study	2014–2017	61.40%	Critically ill	37.00%	127	≥ 18 years	TPA	1 year mortality
Toledo 2018 [19]	Within 72 h or more after ICU admission	Brazil	retrospective cohort study	2010–2014	56%	Critically ill	38.30%	99	61.6 years	SMI	30-day survival
Kou 2019 [21]	Within 30 days of the first SBT	China	retrospective cohort study	2013–2014	56%	Critically ill	31.30%	96	73 years	TPA	in-hospital mortality
Tanabe 2019 [24]	Within 7 days of admission	USA	retrospective cohort study	2011–2014	51.40%	Trauma	22.00%	327	77.8 (8.6)	MCSA	1 year mortality
Kaplan 2016 [33]	Within 2 days of admission	USA	retrospective cohort study	2011–2014	59.80%	Trauma	37.10%	450	65 years	SMI	1 year mortality
Ebbeling 2014 [34]	On the day of admission	USA	Prospective cohort study	2005–2010	57%	Trauma	50.00%	180	≥ 55 years	TPA	in-hospital mortality
Akahoshi 2016 [35]	Before ICU admission	Japan	retrospective cohort study	2012–2015	55.90%	Trauma	29.70%	84	none	SMA	30-day mortality
Baggerman 2020 [11]	CT scan between – 6 and + 2 days from ICU admission	Netherlands	retrospective cohort study	2013–2017	60%	sepsis	31.10%	155	66.0(± 13.6)	SMI	in-hospital mortality
Hwang 2019 [23]	CT scan at the admission	USA	retrospective cohort study	2012–2014	59%	Trauma	32.00%	230	≥ 55 years	SMI	in-hospital mortality
Joyce 2020 [25]	Seven days prior to and one day after ICU admission	Australia	retrospective observational study	2018–2019	58.4%	Critically ill	67.70%	279	63.7 (16.4)	SMA	30-day survival
Abbreviations: SMI: skeletal muscle index; ROS: retrospective observational study; PCS: prospective cohort study; NA: not available											
SMA :skeletal muscle area; TPA: total psoas muscle area; MCSA: masseter cross-sectional area CT: computed tomographic											

Table 2
Computed Tomography Assessment of sarcopenia

Study	Muscles Measured	Level	Cut-off value/Definition
Moisey 2013	Skeletal Muscle Index	L3	Males < 55.4 cm ² /m ² Females < 38.9 cm ² /m ²
Hoogt 2018	Skeletal muscle area index	L3	No definition of sarcopenia
Ji 2018	Skeletal muscle area index	L3	Male < 40.8 cm ² /m ² Female < 34.9 cm ² /m ²
Shibahashi 2017	Skeletal Muscle CSA	L3	No definition of sarcopenia
Cho 2019	psoas cross-sectional area	L3	Males < 5.45 cm ² /m ² Female < 3.85 cm ² /m ²
Toledo 2018	Skeletal muscle area index	L3	Male < 55.27 cm ² /m ² Female < 40.13 cm ² /m ²
Kou 2019	total psoas area	L3	Male < 545mm ² /m ² Female < 385 mm ² /m ²
Tanabe 2019	Masseter cross-sectional area	2 cm below the zygomatic arch in the axial plane	Male < 438.6 (100.2) mm ² Female < 347.8 (87.5) mm ²
Kaplan 2016	Skeletal muscle area index	L3	Males < 52.4 cm ² /m ² Female < 38.5 cm ² /m ²
Ebbeling 2014	Psoas:L4Vertebral Index	L4 inferior body	< 50 percentile of PLVI(≤ 0.83)
Akahoshi 2016	Skeletal muscle area	L3 caudal end	Measured SMA < 80% estimated SMA
Baggerman 2020	Skeletal muscle area index	L3	Males < 41.6 cm ² /m ² Females < and 32.0 cm ² /m ²
Hwang 2019	Skeletal muscle area index	L3	Males < 55.4 cm ² /m ² Females < 38.9 cm ² /m ²
Joyce 2020	Skeletal muscle area	L3	Females < 110 cm ² Males < 170 cm ²
SMA:Skeletal muscle area			

Online Supplementary Material

Table S1: PRISMA checklist

Supplemental File1: Search Strategy

TableS2: Results of all the studies by using Regression Analyses or Multivariate Logistic Regression for adjusting covariates

TableS3: Result of the Newcastle-Ottawa scale quality assessment

TableS4: Overall evidence quality

FigureS1: The flow diagram of studies selection.

FigureS2: The results of trial sequential analysis on mortality.

FigureS3: Subgroup meta-analysis of the association between sarcopenia and mortality in critically ill patients between different age.

Figure S4: Funnel plot of the meta-analysis.

Figure S5: Sensitivity analysis of all studies.

Figures

Figure 1

Pooled prevalence of sarcopenia in critically ill patients

Figure 2

Meta-analysis of the association between sarcopenia and mortality in critically ill patients

Figure 3

Subgroup meta-analysis of the association between sarcopenia and mortality in critically ill patients by outcome type

Figure 4

Subgroup meta-analysis of the association between sarcopenia and mortality in critically ill patients by cause of disease

Figure 5

Subgroup meta-analysis of the association between sarcopenia and mortality in critically ill patients by different definition

Figure 6

Subgroup meta-analysis of the association between sarcopenia and mortality in critically ill patients according to region

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementalstable1.docx](#)
- [Supplementalstable24andsfigure15.doc](#)