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Original article

Different definition of sarcopenia and mortality in cancer: A meta-analysis

Hang-Long Li [a, 1], Philip Chun-Ming Au [b, 1], Grace Koon-Yee Lee [b, 1], Gloria Hoi-Yee Li [b], Marcus Chan [a], Bernard Man-Yung Cheung [c], Ian Chi-Kei Wong [b], Victor Ho-Fun Lee [d], James Mok [a], Benjamin Hon-Kei Yip [e], Kenneth King-Yip Cheng [f], Chih-Hsing Wu [g, h], Ching-Lung Cheung [b, *]

[a] Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
[b] Department of Pharmacology and Pharmacy, The University of Hong Kong, Pokfulam, Hong Kong
[c] Department of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
[d] Department of Clinical Oncology, The University of Hong Kong, Pokfulam, Hong Kong
[e] JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, Hong Kong
[f] Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hung Hom, Hong Kong
[g] Department of Family Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[h] Institute of Geriatrics, College of Medicine, National Cheng Kung University, Tainan, Taiwan

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ABSTRACT

Objectives: Sarcopenia has been an emerging theme in clinical oncology. Various definitions of sarcopenia have been proposed, but their prognostic performance have yet to be evaluated and compared. The aim of this meta-analysis is to comprehensively evaluate the performance of different cutoff definitions of sarcopenia in cancer mortality prognostication.

Methods: This is a meta-analysis. Cohort studies on lean mass and mortality published before December 20, 2017 were obtained by systematic search on PubMed, Cochrane Library, and Embase. Inclusion criteria were cohort studies reporting binary lean mass categorized according to clearly defined cutoffs, and with all-cause mortality as study outcome. Studies were stratified according to the cutoff(s) used in defining low lean mass. The cutoff-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of low lean mass on cancer mortality were pooled with a random-effects model and compared.

Results: Altogether 81 studies that studied binary lean mass were included. The pooled HRs on cancer mortality using the 3 most used definitions were: 1.74 (95% CI, 1.46–2.07) using the definition proposed by International Consensus of Cancer Cachexia, 1.45 (95% CI, 1.21–1.75) using that by Martin, and 1.58 (95% CI, 1.35–1.84) using that by Prado. The associations between sarcopenia and cancer mortality using other definitions were all statistically significant, despite different estimates were observed.

Conclusions: The association of low lean mass with increased mortality was consistent across different definitions; this provides further evidence on the poorer survival in cancer patients with sarcopenia. However, further studies evaluating the performance of each definition are warranted.

1. Introduction

Sarcopenia has been an emerging theme in clinical oncology, not only because it is an important prognostic factor of cancer, but also it is associated with increased economic burden to individuals and society [1,2]. Sarcopenia is a hallmark of cachexia [3,4]. It reduces tolerance to anti-cancer treatments [5,6] and increases susceptibility to infection, immobility, and other comorbidities. Preclinical study showed that reversal of muscle wasting led to prolonged survival in a cancer cachexia model [7], and randomized controlled trials (RCTs) demonstrated that muscle mass in cancer cachexia could be improved by pharmacological agents [8]. In the

* Corresponding author. Department of Pharmacology and Pharmacy, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong.
E-mail address: lung1212@hku.hk (C.-L. Cheung).
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[1] Co-first authors.

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same issue of the journal, Cheung et al [9] have demonstrated that low lean mass is significantly associated with cancer mortality. Thus, sarcopenia is now increasingly recognized as a modifiable condition and prognostic factor in cancer patients.

In the process of developing the protocol, there were several unsolved questions in cancer sarcopenia, such as: what was the best cutoff value for sarcopenia definition? [4] The first available cutoff value for sarcopenia was suggested by Prado et al [10] from a population of obese cancer patients. Since then, multiple cutoff values had been suggested by different authors. Moreover, the optimal cutoff value for sarcopenia may depend on cancer types [4], and whether using non-dichotomized lean mass (ie, instead of sarcopenic vs non-sarcopenic) is useful as a prognostic factor is still unclear [11]. Although sarcopenia is common in cancer, especially in advanced cancer, its prevalence is highly heterogeneous among different cancer types. Therefore, it is unclear if muscle mass plays an important role in all cancers or in specific types of cancer. Currently, muscle mass can be evaluated by multiple modalities, such as bioimpedance, dual-energy X-ray absortiometry (DXA) and computer tomography (CT). However, there is no consensus on which modality performs the best in assessing muscle mass in cancer patients [4]. In CT, L3 skeletal muscle surface measurement at the abdomen is recommended [10,12]. A simplified single-muscle approach using surface and/or density of the psoas muscle to represent total skeletal mass was proposed, however, this approach has not been validated [4,13]. Martin et al [14] proposed a definition using body mass index (BMI), but its inability to differentiate fat mass from lean mass may provide misleading information [15,16], and whether sarcopenia assessed using this definition is significantly associated with cancer mortality has yet to be evaluated. Therefore, there remains a knowledge gap on the definition, measurement, and cancer (-specific) implications of sarcopenia.

In order to address these unanswered questions, we performed a meta-analysis of cohort studies to evaluate the associations of different lean mass measurements (continuous lean mass, dichotomized low lean mass, lean mass measured by different modalities and skeletal sites, and low lean mass defined by different cutoff values) with cancer mortality.

2. Methods

The detailed materials and methods have been described in Cheung et al [9] in this same issue.

In brief, this meta-analysis included study of lean mass and mortality in cancer patients. Studies were classified according to the 3 most used definitions for low lean mass: International Consensus of Cancer Cachexia [3,17], Martin [14], or Prado [10]. The pooled HRs and the respective 95% CI for each definition used were compared. Furthermore, the pooled HRs for studies which used other less commonly used definitions, such as receiver operating characteristic (ROC) and quantiles/percentiles, were also calculated and compared.

Compared to other diseases, methods in studying lean mass in cancer is more consistent. For example, the majority of them used CT in evaluating lean mass (n = 95 using CT vs n = 5 using non-CT), studied binary lean mass instead of continuous lean mass (83 studied binary lean mass, 10 studied continuous lean mass, 7 studied both binary and continuous lean mass), and studied L3 skeletal muscle index (n = 70) or L3 psoas index (n = 11) instead of other lean mass derived index (n = 14). Thus, to further reduce heterogeneity, we included 81 cancer studies that studied binary lean mass using either L3 skeletal muscle index or L3 psoas index in the subsequent analysis.

3. Results

A total of 81 studies were included. The definition proposed by the International Consensus of Cancer Cachexia used in 8 studies (n = 1600), that by Martin was used in 20 (n = 5752), and that by Prado used in 15 (n = 5379). L3 skeletal muscle index was used to assess lean mass in all included studies. Other cutoff/definitions included: optimal stratification (9 studies, n = 7291), ROC (8 studies, n = 4394), median (8 studies, n = 791), quantiles/percentiles (7 studies, n = 2156), other cohort cutoffs (6 studies, n = 757), and others (6 studies, n = 2467). Six studies evaluated 2 cutoff definitions.

The pooled HRs using the definition by the International Consensus of Cancer Cachexia, Martin, and Prado were 1.74 (95% CI, 1.46–2.07), 1.45 (95% CI, 1.21–1.75), and 1.58 (95% CI, 1.35–1.84), respectively (Fig. 1). The estimates were not statistically different. The forest plots and funnel plots for each definition are shown in Figs. 2–4 and Supplementary figures S1 – S3, respectively.

The pooled HRs using other definitions were shown in Table 1. Significant association of low lean mass with mortality was observed in all definitions. The highest HR was observed with other cohort cutoffs (HR, 2.47; 95% CI, 1.74–3.53), while the lowest HR was observed with quantiles/percentiles (HR, 1.37; 95% CI, 1.11–1.70). In general, there was a moderate to high heterogeneity in each cutoff point analysis, with the highest and lowest I [2] being observed for others (I [2] = 86.0%) and International Consensus of Cancer Cachexia (I [2] = 0%), respectively. The forest plots and funnel plots for other definitions are shown in Supplementary figures S4 – S9 and Supplementary figures S10 – S15, respectively.

4. Discussion

To the authors' knowledge, this study is the first systematic review and meta-analysis to evaluate the association between low lean mass and cancer mortality using different definitions. We identified a significant association between low lean mass and cancer mortality regardless of the definition used, while the associations using different definitions were not statistically heterogeneous.

Due to the lack of consensus on a universal cutoff value, different definitions have been employed by different studies, ranging from statistically-derived to study-established cutoffs. Over 50% of cancer studies used cutoffs established by Martin [14], Prado [10] and the International Consensus of Cancer Cachexia [3,17]; the performance of these 3 most commonly used cutoff values for sarcopenia appeared to be comparable, all consistently showing that sarcopenia is associated with poor survival in cancer patients. The current study shows that these established cutoff values are all useful in cancer prognosis. However, it is worth noting that the Martin definition, which stratifies lean mass cutoff according to BMI, may introduce bias since BMI does not distinguish between lean mass and fat mass, which carry different implications in cancer prognosis [16,18]. Therefore, although the association observed using the Martin definition was consistent with others, it may not be the most appropriate definition to accurately reflect the presence and pathophysiological implications of sarcopenia in cancer.

Although the associations were comparable, none of the definitions/cutoff points demonstrated superiority in predicting cancer mortality. Among the 3 most used definitions, the association was numerically strongest using the definition by the International Consensus of Cancer Cachexia, but its difference compared to other definitions was not statistically significant. The strongest association was observed using other cohort cutoffs, but its generalizability was greatly limited by the low number of studies (6) and patients (757) included, and the heterogeneous definitions used across the 6

Health conditions	N	No. of studies	HR	95% CI	P_{hetero}
International consensus of cancer cachexia	1600	8	1.74	1.46 to 2.07	Ref
Martin	5752	20	1.45	1.21 to 1.75	0.16
Prado	5379	15	1.58	1.35 to 1.84	0.42

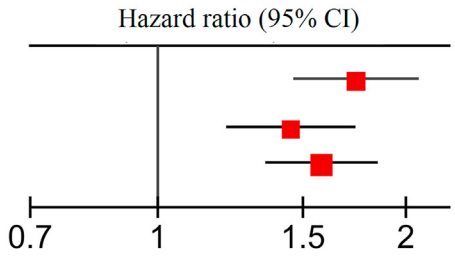


Fig. 1. Pooled hazard ratios of common definitions of low lean mass with all-cause mortality in persons with cancer.
All low lean mass was based on L3 skeletal muscle index.

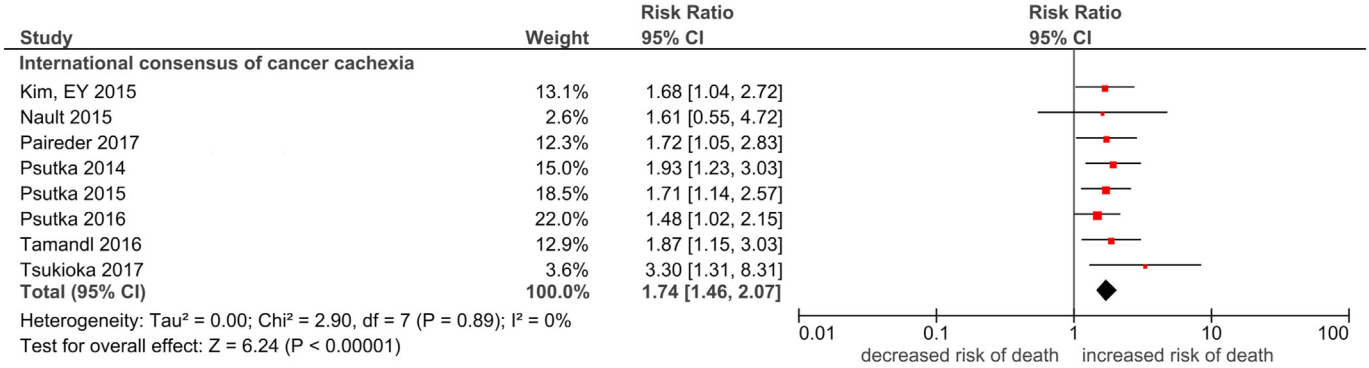
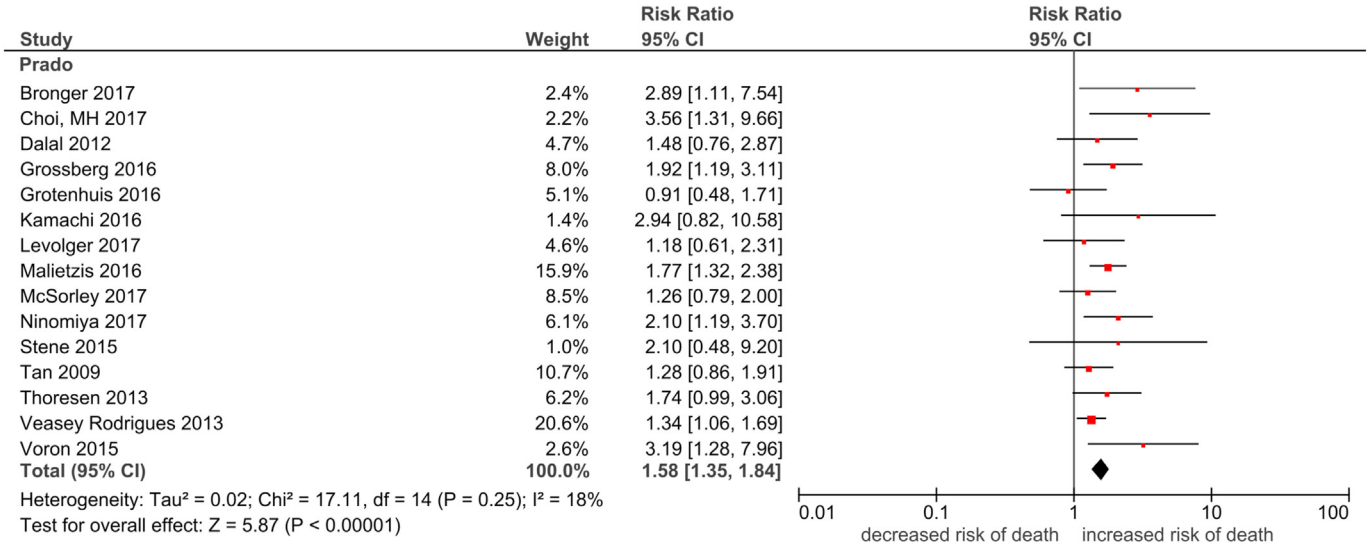


Fig. 2. Forest plot of the association of low lean mass with overall mortality using the definition proposed by International Consensus of Cancer Cachexia.



All low lean mass was based on L3 skeletal muscle index.

Fig. 3. Forest plot of the association of low lean mass with overall mortality using the definition proposed by Prado.
All low lean mass was based on L3 skeletal muscle index.

included studies. Therefore, it remains uncertain which definition/cutoff best predicts cancer death. Further and larger cohorts of cancer patients are required to evaluate the associations using different definitions/cutoffs and to identify the ideal definition/cutoff point of sarcopenia in the context of cancer.

Moreover, it is possible that there are different optimal cutoff values for different cancers. The meta-analysis by Au et al [19] in the same issue of this journal found that the association between low lean mass and cancer mortality was insignificant in certain types of cancer, suggesting that sarcopenia may have variable prognostic implications in different types of cancer. Therefore, it is important to derive cancer type-specific cutoff values by pooling individual cohort data, like the FNIH sarcopenia project which pooled several large population cohorts in deriving cutoff values for sarcopenia in a geriatric population [20]. This would allow an accurate reflection of the prognostic implications of sarcopenia on survival specific to each type of cancer.

The roles of sarcopenia in cancer prognosis were described in

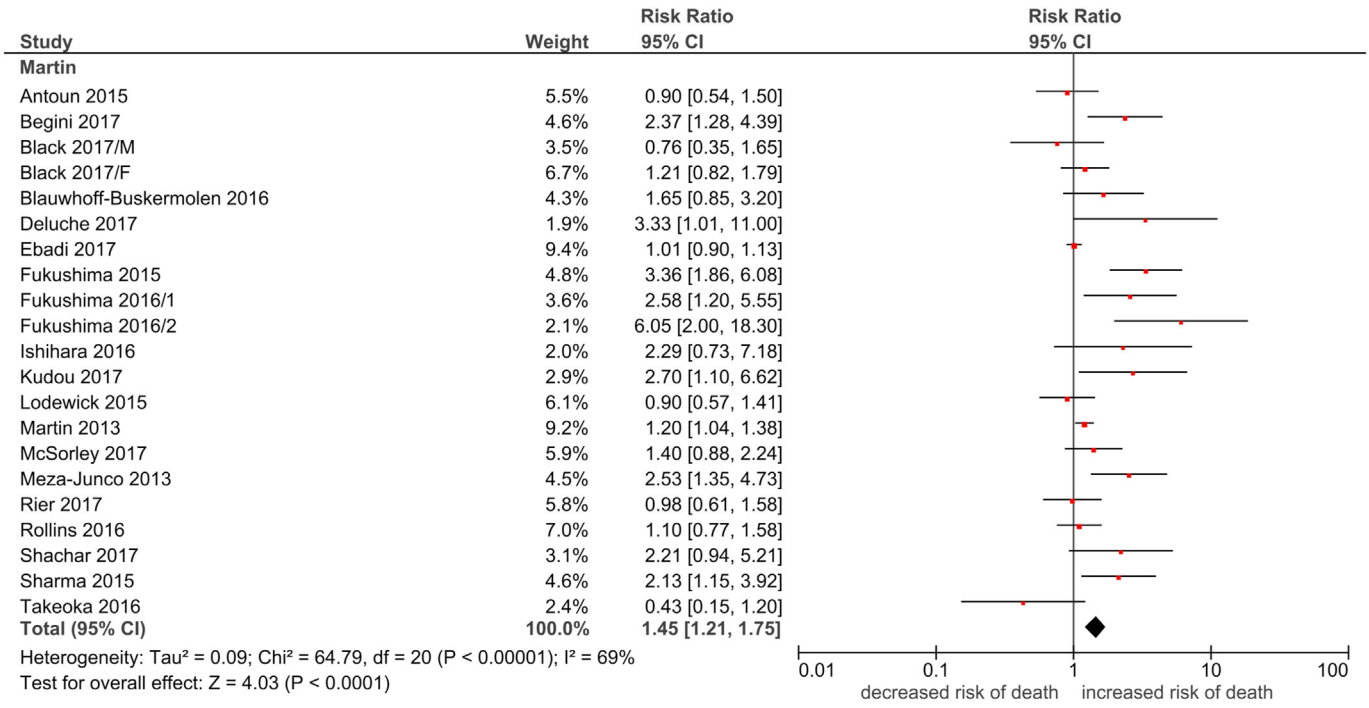


Fig. 4. Forest plot of the association of low lean mass with overall mortality using the definition proposed by Martin.

Table 1
Pooled hazard ratios of all-cause mortality in persons with cancer according to different cutoff point defining sarcopenia.

Cutoffs	n (no. of studies)	I^2	HR	95% CI
Martin	5752 (20)	69%	1.45	[1.21, 1.75]
Prado	5379 (15)	18%	1.58	[1.35, 1.84]
International Consensus of Cancer Cachexia	1600 (8)	0%	1.74	[1.46, 2.07]
Other cohort cutoffs	757 (6)	52%	2.47	[1.74, 3.53]
Optimal stratification	7291 (9)	70%	1.61	[1.35, 1.92]
Receiver operating characteristic	4394 (8)	65%	1.77	[1.41, 2.24]
Quantiles/percentiles	2156 (7)	50%	1.37	[1.11, 1.70]
Median	791 (8)	48%	1.43	[1.03, 1.99]
Others	2467 (6)	86%	1.56	[1.10, 2.23]

Note: There were 81 studies included in the cutoff point analyses (from Martin to Others), with 6 studies evaluated 2 cutoff definitions.

detail by Au et al in the same issue of the journal. In brief, reduced lean mass is a hallmark of cancer cachexia [3,21]; lower lean mass was associated with increased mortality across multiple medical conditions [22]. These observations suggest that sarcopenia could confer poor survival in both cachexia-dependent and -independent manners. Furthermore, lean mass is an independent factor affecting toxicity of cancer treatment [5,6,23]. Therefore, it is critically important to evaluate the presence of sarcopenia in cancer patients to achieve optimal prognostication and management.

There are several limitations in the current study. First, the study had a high heterogeneity and caution must be taken when interpreting the estimates of effect sizes. The high heterogeneity could be explained by differences in adjustment models and study protocols. To acknowledge the possibility of heterogeneity, the more conservative random effects model was used [24]. Second, other measures of lean mass, including serum creatinine levels and anthropometry, were not included as they are generally not recommended. Third, no causality could be inferred from this meta-analysis as it is observational in nature. Fourth, eligible literatures could be missed using our screening algorithms. Nevertheless, the overall number of studies included was large and the observed associations were highly significant, so the conclusions were likely to remain the same even if some literatures were missed.

Nevertheless, there were several strengths in our study. First, to our knowledge, this is the first meta-analysis comparing the association between low lean mass and cancer mortality using different definitions, including the 3 most used cutoffs. We showed that these definitions were largely comparable, which has not been shown in any previous literature. Second, a comprehensive search strategy was used to review the existing literature, and most of the independent cohort studies reporting lean mass and mortality data in cancer patients were covered. Third, various cutoff points were evaluated, adding more dimensions to the analysis.

In conclusion, the association between low lean mass and cancer mortality is consistently significant using different definitions of low lean mass. However, it remains uncertain which definition is optimal for each specific type of cancer. Further cohort studies evaluating the performance of the definitions specific to a cancer type are needed to achieve optimal management and prognostication for cancer patients.

CRediT author statement

Hang-Long Li: Writing – review & editing. **Philip Chun-Ming**

Au: Writing – review & editing, Formal analysis, Resources. **Grace Koon-Yee Lee:** Formal analysis, Resources. **Gloria Hoi-Yee Li:** Formal analysis, Resources. **Marcus Chan:** Formal analysis, Resources. **Bernard Man-Yung Cheung:** Writing – review & editing. **Ian Chi-Kei Wong:** Writing – review & editing. **Victor Ho-Fun Lee:** Writing – review & editing. **James Mok:** Writing – review & editing, Formal analysis, Resources. **Benjamin Hon-Kei Yip:** Writing – review & editing. **Kenneth King-Yip Cheng:** Writing – review & editing. **Chih-Hsing Wu:** Writing – review & editing. **Ching-Lung Cheung:** Writing – review & editing, Conceptualization, Methodology, Writing – original draft, Supervision.

Conflicts of interest

The authors declare no competing interests.

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ORCID Hang-Long Li: 0000-0002-2294-2977. Philip Chun-Ming Au: 0000-0002-0736-4726. Grace Koon-Yee Lee: 0000-0002-9362-4319. Gloria Hoi-Yee Li: 0000-0003-0275-2356. Marcus Chan: 0000-0001-6072-7648. Bernard Man-Yung Cheung: 0000-0001-9106-7363. Ian Chi-Kei Wong: 0000-0001-8242-0014. Victor Ho-Fun Lee: 0000-0002-6283-978X. James Mok: 0000-0003-1974-0829. Benjamin Hon-Kei Yip: 0000-0002-4749-7611. Kenneth King-Yip Cheng: 0000-0002-7274-0839. Chih-Hsing Wu: 0000-0002-0504-2053. Ching-Lung Cheung: 0000-0002-6233-9144.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2021.02.005.

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