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Original article

Systematic review and meta-analysis of lean mass and mortality: Rationale and study description

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

[a] Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
[b] Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
[c] Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong
[d] Li Ka Shing Faculty of Medicine, 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: Muscle mass is one of the key components in defining sarcopenia and is known to be important for locomotion and body homeostasis. Lean mass is commonly used as a surrogate of muscle mass and has been shown to be associated with increased mortality. However, the relationship of lean mass with mortality may be affected by different clinical conditions, modalities used, cut-off point to define low or normal lean mass, and even types of cancer among cancer patients. Thus, we aim to perform a comprehensive meta-analysis of lean mass with mortality by considering all these factors.
Methods: Systematic search was done in PubMed, Cochrane Library and Embase for articles related to lean mass and mortality. Lean mass measured by dual X-ray absorptiometry, bioelectrical impedance analysis, and computerized tomography were included.
Results: The number of relevant studies has increased continuously since 2002. A total of 188 studies with 98 468 people were included in the meta-analysis. The association of lean mass with mortality was most studied in cancer patients, followed by people with renal diseases, liver diseases, elderly, people with cardiovascular disease, lung diseases, and other diseases. The meta-analysis can be further conducted in subgroups based on measurement modalities, site of measurements, definition of low lean mass adopted, and types of cancer for studies conducted in cancer patients.
Conclusions: This series of meta-analysis provided insight and evidence on the relationship between lean mass and mortality in all directions, which may be useful for further study and guideline development.
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1. Introduction

Muscles are critical for normal human anatomical and physiological functioning, including posture, locomotion, respiration, and regulation of whole body metabolism and energy balance [1]. Loss of muscle mass (sarcopenia) not just affects mobility, but also causes frailty and increases risk of mortality [2]. It is known that obesity is associated with increased mortality, while lean mass (a proxy of muscle mass) is at the opposite end of the spectrum to obesity, with low lean mass being detrimental to health. A previous meta-analysis comprising more than 9 million people showed a J- or U-shaped association between body mass index (BMI) and all-cause mortality [3]. However, as BMI reflects both lean mass and fat mass, the independent relationship of the former with mortality remains uncertain.

* 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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Given the importance of sarcopenia, it has been endorsed as an independent condition by the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) Code in 2016. Nevertheless, there is no consensus on the definition of sarcopenia, although several definitions have been proposed for sarcopenia in elderly and cancer patients [4–7]. The Asian Working Group for Sarcopenia (AWGS) recommended using dual X-ray absorptiometry (DXA) as one of the diagnostic tools for sarcopenia [4]. However, a recent study suggested that lean mass measured by DXA should not be used in defining sarcopenia, since inconsistent associations were observed for DXA-derived lean mass with various clinical outcomes, such as fall, mobility limitation, and hip fractures [8]. Notably, the authors [8] and others [9] acknowledged the limitation of measurement method (measurement of lean mass instead of muscle mass) and studied population (relatively healthy elderly) may affect the validity of the conclusion.

Indeed, it is commonly observed in the literature that muscle mass was measured using different methods, and different cut-offs of muscle mass were adopted in defining people as having normal or low muscle mass, making the comparison and interpretation difficult. Although a few meta-analyses were conducted to evaluate the relationship between lean mass and mortality, the analyses were either small-scale, conducted in a subgroup with a particular health condition only, or combined the data based on dichotomized lean mass phenotype [10–13]. We are thus lacking a comprehensive overview of how lean mass contributes to mortality. The performance of lean mass in predicting mortality in different health conditions and measurement modalities are also unknown. To evaluate the relationship of lean mass with mortality comprehensively, we conducted a large-scale meta-analysis of the association between lean mass and mortality.

2. Methods

2.1. Search strategy and selection criteria

In this systematic review and meta-analysis, we searched PubMed, Cochrane Library and Embase for articles published up to December 20, 2017. The following algorithms were used for the literature search:

("lean mass" OR "ALM" OR "muscle mass") AND ("death" OR "mortality" OR "outcome");

("lean mass" OR "Body composition" OR "muscle mass" OR "sarcopenia" OR "bio-impedance" OR "frailty") AND ("death" OR "mortality" OR "cause of death" OR "fatal outcome" OR "mortality, premature" OR "survival rate" OR "mortal" OR "fatal") AND ("cohort studies" OR "follow-up studies" OR "longitudinal studies" OR "prospective studies" OR "retrospective studies" OR "cohort" OR "longitudinal" OR "prospective" OR "follow-up" OR "retrospective") AND ("association" OR "associated"); ("lean mass" OR "Body composition" OR "muscle mass" OR "sarcopenia" OR "bio-impedance" OR "bioimpedance") AND ("death" OR "mortality" OR "cause of death" OR "fatal outcome" OR "mortality, premature" OR "survival rate" OR "mortal" OR "fatal" OR "survival" OR "prognosis" OR "prognostic").

The inclusion criteria were original studies investigating the relationship between lean mass and all-cause mortality or overall survival. The reference lists of systematic reviews and meta-analyses were also checked for inclusion of additional literatures. We only included studies reporting the association between all-cause mortality and muscle mass measured by computerized tomography (CT), dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) reported as “reduced lean mass” (ie, lean mass was treated as continuous variable) or “low lean mass” (ie, lean mass was treated as a binary variable, low vs normal lean mass). The pre-specified exclusion criteria were as follows: non-human studies; studies using the following exposures: other surrogates of muscle mass (estimated glomerular filtration rate [eGFR], creatinine level, or lean mass ratio), anthropometric measurement of muscle mass (such as skinfold measurement, mid-arm circumference, etc), rate of change in muscle mass, sarcopenia defined using composite criteria (low lean mass in combination with muscle strength and physical performance); and studies with insufficient data for meta-analysis (studies reporting lean mass as continuous variable without providing standard deviation [SD] for standardized hazard ratio [HR] calculation and studies providing P-values only). Notably, although mid-arm muscle area was considered an acceptable assessment of muscle mass in cancer cachexia [6], the European Working Group on Sarcopenia in Older People (EWGSOP) commented that this method is prone to error and it is not recommended for routine use in the diagnosis of sarcopenia [5].

The PRISMA guideline was followed when evaluating search results. Each paper was screened by title and abstract for eligibility independently by 3 investigators (G.K.L, M.C, C.L.C). Any discrepancy was resolved by consensus. Data extraction was performed by 2 investigators (G.K.L and M.C) and cross-checked by a third investigator (G.H.L). The following information was recorded for each study: first author’s name, year of publication, study design, population, sex, ethnicity, health status, median or mean age, follow-up duration, source of lean mass, types of lean mass, lean mass unit, cut-off definition of sarcopenia, HR with associated 95% confidence intervals (95% CI) and P-values for overall survival. HR and 95% CI were obtained from the fully-adjusted model if available. Otherwise, the crude model would be used. We contacted the corresponding authors if any of the required information was unclear in the article, and the paper was included when the relevant information was provided. Additionally, quality appraisal was done using a modified Newcastle Ottawa Scale (NOS) by J.M and cross-checked by G.K.L (Supplementary Table 1). A modified NOS was applied because some questions were not applicable in the current study, such as selection of non-exposed cohort, demonstration that outcome of interest (ie, mortality in the current study) was not present at start of the study. In the current meta-analysis, studies of good quality were defined as 2 stars in selection domain AND 1/2 stars in comparability domain AND 1/2 stars in outcome/exposure domain; studies of fair quality were defined as 1 star in selection domain AND 1/2 stars in comparability domain AND 1/2 stars in outcome/exposure domain, and poor quality was defined as studies not meeting the criteria of good or fair quality. Any discrepancy in the data extraction and quality appraisal was addressed by discussion and consensus, with involvement of another author if necessary.

We attempted to identify and exclude duplicate data from research studies presented in separate publications. For cases in which we identified multiple studies with duplicated or overlapping data (by population, time and place), we selected the study with the longest follow-up time. When these studies had the same follow-up time, the study with the largest sample size was selected. If lean mass was measured at different sites in the same cohort, we selected the lean mass data based on the following order: whole body lean mass > appendicular lean mass > skeletal muscle > psoas muscle. If various muscle mass indices were used, the index was selected according to the following order: lean mass/height^2 > lean mass/BMI > lean mass only. For various low lean mass cut-offs in cancer, the result was selected according to the following order: Martin > Prado > Optimal stratification > cut-off based on median of study population.

2.2. Data analysis

For studies with lean mass as a continuous variable, data could not be directly combined because different units of lean mass were used in different studies. Therefore, in order to combine the estimates across different studies, HR and 95% CI were expressed in standardized units [14] (per SD decrease in lean mass). For studies using lean mass as a binary cut-off, high lean mass was used as reference. The HR and 95% CI of each study were entered into Review Manager 5.3 (RevMan, Cochrane, United Kingdom) by G.K.L and cross-checked by P.C.A. If there was mismatch in 95% CI between the calculated values in Revman and those reported in the study publication, either upper or lower 95% CI was chosen as reference according to the calculated P-value in Revman, with the one with a P-value closest to the P-value reported in the study chosen. If numeric HR and/or 95% CI were not available in the literature, these were calculated based on beta, SE, and/or P-value provided in the literature.

All statistical analyses were performed using RevMan. The pooled HR and corresponding 95% CI were estimated using a random-effect model. Publication bias was appraised using funnel plots to test for asymmetry. We used the I^2 statistic to evaluate the proportion of total variation in the study estimates which was due to heterogeneity.

3. Results

We identified 9,602 articles, of which 977 met the inclusion criteria. After excluding 431 duplicate studies, 546 full-text articles were retrieved. We excluded another 358 articles due to the irrelevant data, population overlap, poor/unclear data, or the articles were conference abstracts without available details. A total of 188 studies were included in the current meta-analysis (Fig. 1). Detailed characteristics of included studies are provided in Supplementary Tables 2–5. The number of studies by publication year (including those first published online) is shown in Fig. 2, and the number of studies increased continuously over time. Among the 188 included articles, 104, 81, and 3 of them were respectively classified as good-, fair-, and poor-quality studies (Supplementary Table 6).

Data from a total of 98 468 people were included in the meta-analysis (Table 1, Supplementary Table 2). The association of sarcopenia with mortality was most studied in cancer patients (n = 100) [15–114], followed by people with renal diseases (n = 21) [115–135], liver diseases (n = 18) [136–153], elderly (n = 16) [154–169], people with cardiovascular diseases (n = 11) [170–180], lung diseases (n = 11) [181–191], and other diseases (n = 11) [192–202]. For the method used to measure lean mass (Table 1, Supplementary Table 3), computed tomography (CT) was the most used modality (n = 138) [20–114,133–135,138–153,171–180,188–191,194–202], followed by BIA (n = 29) [15–18,115–126,136,137,154–157,181–187], and DXA (n = 21) [19,127–132,158–168,170,192,193]. After excluding cancer-related studies in the calculation, CT remained the most commonly used method in assessing lean mass (n = 43), followed by BIA (n = 25) and DXA (n = 20). Majority (n = 120) of the studies used low lean mass as the exposure (Table 1, Supplementary Table 4). Fifty studies used reduced lean mass, while 18 studies investigated both low lean mass and reduced lean mass. After excluding cancer-related studies in the calculation, majority of the studies (n = 40) used reduced lean mass as exposure, 37 studies used low lean mass as exposure, while 11 studies examined both.

Among studies conducted in cancer populations, 95 of them studied CT-measured lean mass with mortality (Table 2). The most frequently studied cancer type was gastrointestinal cancer (n = 21), followed by liver and intrahepatic bile duct (n = 20), urinary tract (n = 13), pancreatic (n = 10), lung (n = 8), ovarian and endometrial (n = 7), multiple (n = 5), hematopoietic (n = 4), breast (n = 3), bile duct (n = 2), head and neck (n = 1), and prostate (n = 1) cancer. The most frequently studied lean mass index was L3 skeletal muscle index (n = 70), followed by L3 psoas index (n = 11) (Table 2).

In defining low lean mass in cancer studies (Table 3,

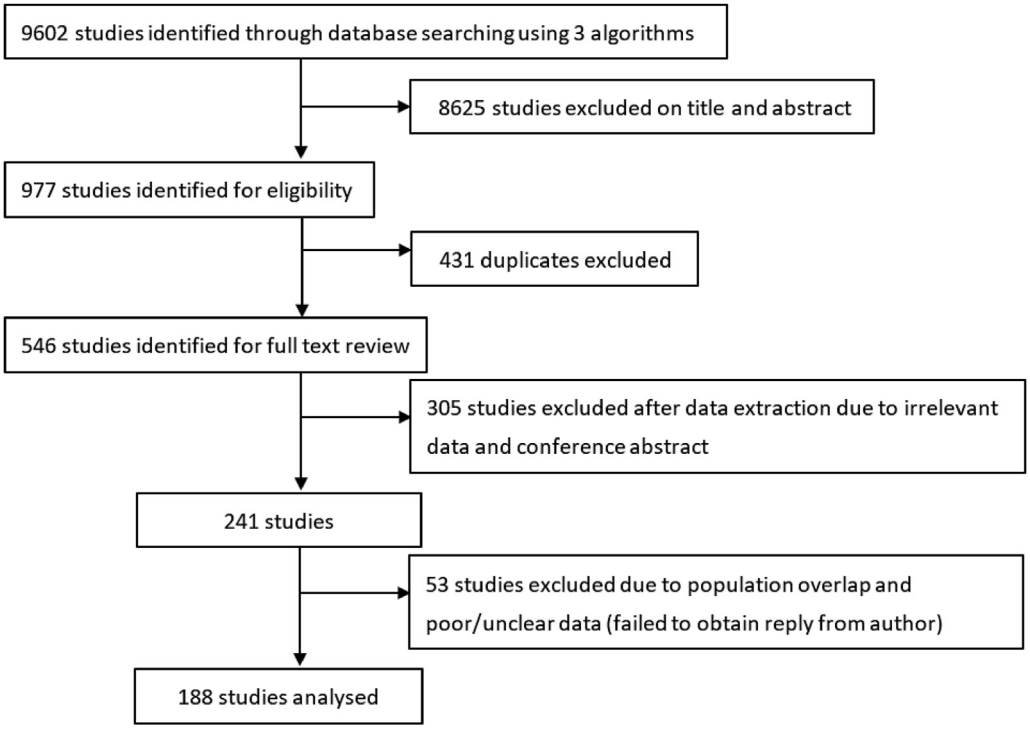

Fig. 1. Study attrition diagram.

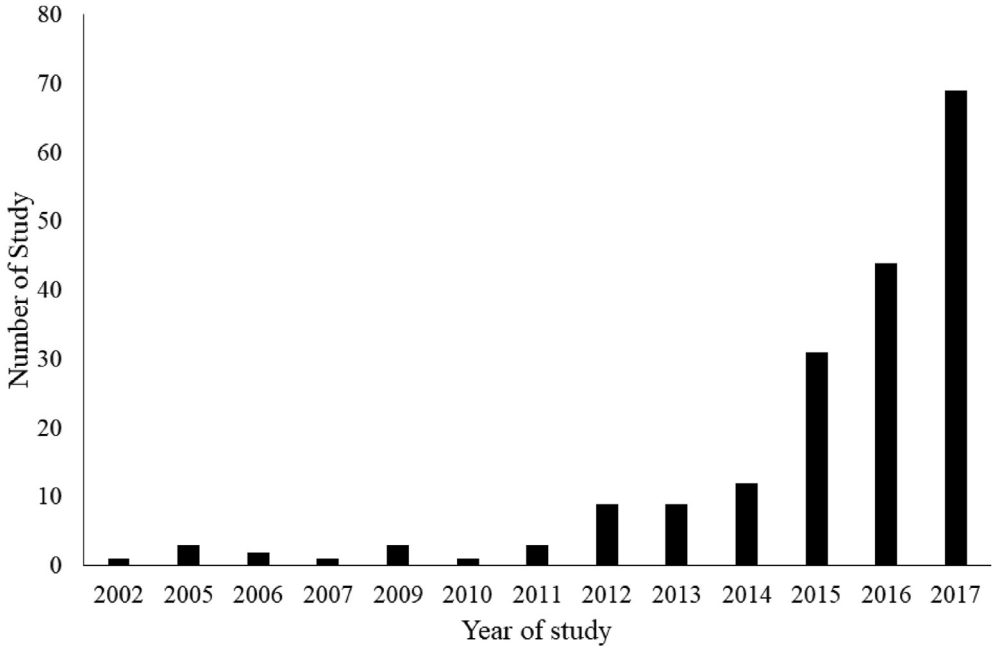

Fig. 2. Number of studies by publication year included in the meta-analysis.

Table 1
Summary of studies included in the meta-analysis.

Subgroups	Number of studies	Sample size	Number of studies by measurement modality			Number of studies by type of variables that lean mass was investigated		
			BIA	DXA	CT	Binary	Continuous	Both
Elderly	16	19320	4(154−157)	11(158−168)	1(169)	7(154, 158−163)	7(157, 164−169)	2(155, 156)
Cancer patients	100	29511	4(15−18)	1(19)	95(20−114)	83(15−17, 19−33, 35, 37−39, 41−45, 47, 48, 50−56, 58, 59, 62, 64−67, 69−72, 74−85, 87−89, 93−96, 98−114)	10(18, 34, 36, 46, 49, 57, 60, 61, 68, 86)	7(40, 63, 73, 90−92, 97)
People with cardiovascular diseases	11	2793	0	1(170)	10(171−180)	4(171−174)	6(170, 176−180)	1(175)
People with liver diseases	18	4356	2(136, 137)	0	16(138−153)	8(137, 138, 140, 141, 143−146)	8(136, 147−153)	2(139, 142)
People with lung diseases	11	1792	7(181−187)	0	4(188−191)	4(181−183, 188)	6(184−187, 190, 191)	1(189)
People with renal diseases	21	30042	12(115−126)	6(127−132)	3(133−135)	9(115−117, 119, 121, 127, 128, 130, 133)	9(122−126, 131, 132, 134, 135)	3(118, 120, 129)
People with other diseases	11	10654	0	2(192, 193)	9(194−202)	5(192, 195, 197−199)	4(193, 200−202)	2(194, 196)
Total	188	98468	29	21	138	120	50	18

Supplementary Table 4), threshold suggested by Martin et al was the most often used (n = 20), followed by Prado et al (n = 15), and international consensus of cancer cachexia (n = 8). Other definitions were mostly derived from different statistical methods based on the study cohort, such as optimal stratification, ROC, median, etc.

4. Discussion

In this study involving 188 studies and 98 468 participants from 34 countries, we examined the associations of lean mass with all-cause mortality across a wide range of healthy people and patients, across different measurement modalities, and various definition of sarcopenia. As we can see the number of studies in relation to lean mass and mortality has increased continuously since 2002, this is therefore a timely comprehensive systematic review and meta-analysis of the relationship between lean mass and mortality, especially when efforts are being put in the definition of sarcopenia.

Although sarcopenia is a well-recognized issue in the elderly population, this systematic review and meta-analysis found that only 16 out of 188 studies were conducted in the elderly population. On the other hand, more than half (n = 100; 53.2%) of the studies were conducted in patients with cancer. This could be explained by the clinical management of cancer as CT is routinely used to monitor disease progression in cancer patients. Thus, lean mass measurement can be retrieved from existing CT data in many studies, which facilitated the research of sarcopenia in cancer patients. This also explained why CT was the most often used imaging

Table 2
Categories of cancer studies measuring muscle using computed tomography and the muscle indices used in the analysis.

Cancer category	Total	L3 Skeletal Muscle Index	L3 Psoas Index	Others
Bile duct (excludes intrahepatic)	2	1	1	
Breast	3	3		
Gastrointestinal	21	18		3
Head and neck	1	1		
Hematopoietic	4	3		1
Liver and intrahepatic bile duct	20	15	2	3
Lung	8	4	1	3
Ovarian and endometria	7	4	2	1
Pancreatic	10	5	3	2
Prostate	1	1		
Urinary tract	13	10	2	1
Multiple	5	5		
Overall	95	70	11	14

modality in evaluating lean mass (138 out of 188 studies). However, given the high radiation dose of CT, it is not justifiable to use CT purely for sarcopenia research. On the other hand, DXA has a much lower dose of radiation, while BIA is radiation-free. Therefore, these DXA and BIA may be more suitable for lean mass measurement in sarcopenia research in non-cancer patients.

For DXA and BIA, sarcopenia is usually defined using appendicular lean mass, as suggested by consensus. On the other hand, the most common skeletal site in defining sarcopenia in cancer was cross-sectional area (CSA) of muscles at the L3 vertebral level. Two indices can be derived from the muscles at the L3 vertebral level, namely L3 skeletal muscle index and L3 psoas index. L3 skeletal muscle index calculated the CSA of all muscles at the L3 vertebral level, whereas L3 psoas index calculated the CSA of psoas muscle only at the L3 vertebral level. These 2 indices were said to be interchangeable, but whether these indices had similar association with mortality is largely unknown.

Lean mass was commonly analyzed as a binary trait, ie, low vs normal lean mass. There were several operational definitions of low lean mass, such as the International Working Group on Sarcopenia [203], Society of Sarcopenia, Cachexia and Wasting Disorders [204], FNIH [205], and European Working Group on Sarcopenia in Older People (EWGSOP) [5]. Recently, consensus by EWGSOP was updated (known as EWGSOP2) [7], and such update was found to affect study result slightly [206]. It is therefore important to have a consensus on the definition, so that the findings could be compared across studies. Conversely, since there was no consensus on the cut-off point used for defining low lean mass or sarcopenia in cancer patients, many different methods were used to define sarcopenia. The definition provided by Martin et al [207] and Prado et al [208] were most often used. Optimal stratification [209], which defines sarcopenia based on the most significant cut-off point using log rank test, is the third most commonly used method. This is similar to the ROC method, which defines the optimal cut-off point using Youden's index. However, these cut-off points are expected to be study-specific, and may over-estimate the effect if there is no validation study. These methods (optimal stratification or ROC) may be useful in deriving a cut-off point in a specific population, while the generalizability of these findings is largely unknown.

Table 3
Cutoff definition of low lean mass in cancer studies.

Cutoff	n
Martin	20
Prado	15
International consensus of cancer cachexia	8
Other cohort cut-offs	7
Optimal stratification	10
ROC	8
Quantiles/percentiles	7
Median	8
Others	7
Total	90

Our current study aims to provide insight on these issues, especially to address a recent recommendation by the Sarcopenia Definitions and Outcomes Consortium (SDOC). In the latest analyses by SDOC, they found that lean mass measured by DXA was not a good predictor of multiple adverse outcomes in the elderly [8], thus proposing inclusion of gait speed and grip strength, but not lean mass, in the definition of sarcopenia. In fact, low lean mass (defined as ALM/ht^2 < 5.45 and 7.26 in women and men, respectively) was consistently associated with increased risk of mortality in both women and men in their study [8]. Therefore, whether lean mass should be excluded from use in the definition of sarcopenia remains an open question, while our current study has provided further evidence in this aspect.

Although the current study has evaluated the association of different parameters of lean mass on mortality, we acknowledge that our analyses are insufficient to address these questions directly. For example, the best way to compare the usefulness of different modalities, cut-off points, or site of muscle measurements is to compare these differences directly in the same study. The current analysis was only able to summarize evidences from multiple studies, in which the difference in estimates could be due to the study design and population, instead of the intrinsic difference between the modalities, cut-off points, and site of muscle measurement under investigation. However, only a very limited number of studies were conducted for direct comparison. It is important to have an international collaboration in answering these questions directly, which is essential for developing clinical guidelines of sarcopenia, not only for the elderly, but also for patients with different diseases. In addition, due to tremendous work of the current meta-analysis, we only updated the literature until the end of 2017. We understand there were publications on sarcopenia and mortality published from 2018 to 2020, however the number of studies included in the current study should enable us to come up with a conclusion on whether lean mass is associated with mortality. We hope that the current work will provide a useful resource to the field for future research and guideline development.

In conclusion, this series of meta-analysis of lean mass and mortality could provide insight and evidence on the relationship between lean mass and mortality in all directions, which may be useful for further study and guideline development, especially when there are growing efforts to move from risk assessment to intervention of sarcopenia [9].

Credit author statement

Ching-Lung Cheung: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision. **Grace Koon-Yee Lee**: Formal analysis, Resources, Writing - Review & Editing. **Philip Chun-Ming Au**: Formal analysis, Resources, Writing - Review & Editing. **Gloria Hoi-Yee Li**: Formal analysis, Resources, Writing - Review & Editing. **Marcus Chan**: Formal analysis, Resources, Writing - Review & Editing. **Hang-Long Li**: Writing - Review & Editing. **Bernard Man-Yung Cheung**: Writing - Review & Editing. **Ian Chi-Kei Wong**: Writing - Review & Editing. **Victor Ho-Fun Lee**: Writing - Review & Editing. **James Mok**: Formal analysis, Resources, Writing - Review & Editing. **Benjamin Hon-Kei Yip**: Writing - Review & Editing. **Kenneth King-Yip Cheng**: Writing - Review & Editing. **Chih-Hsing Wu**: Writing - Review & Editing.

Conflicts of interest

The authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2021.01.001.

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