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Original article

The effect of different measurement modalities in the association of lean mass with mortality: A systematic review and meta-analysis

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ABSTRACT

Objectives: Lean mass is commonly measured by 3 modalities, dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and computerized tomography (CT). CT is considered the most accurate, while lean mass measured by DXA and BIA often consists of non-muscle compartment, and hence considered less accurate when compared with CT. It remains unclear if the association of lean mass with mortality would differ using different measurement modalities.

Methods: A systematic review and meta-analysis of lean mass and mortality was conducted. The analysis was stratified by different measurement modalities and health conditions. Pooled hazard ratios were estimated using a random effects model.

Results: This meta-analysis included 188 studies with 98 468 participants. Reduced lean mass measured by BIA, DXA, and CT, was associated with increased risk of mortality with a hazard ratio (HR) of 1.35 (95% CI, 1.21−1.49), 1.18 (95% CI, 1.06−1.30), and 1.44 (95% CI, 1.32−1.57), respectively. Similarly, low lean mass defined by BIA-, DXA-, and CT-measurement was associated with increased risk of mortality, with an HR of 1.81 (95% CI, 1.56−2.10), 1.44 (95% CI, 1.29−1.60), and 1.78 (95% CI, 1.64−1.93).

Conclusions: Reduced and low lean mass were robustly associated with increased mortality in studies using different measurement modalities.

1. Introduction

Lean mass is commonly used interchangeably with muscle mass. In fact, they are not the same. Muscle mass can be accurately measured by 24-hour creatinine excretion, D_3 creatinine dilution method, computerized tomography (CT), and magnetic resonance imaging [1]. Although these methods are considered accurate, they may not be suitable for large-scale population studies. Thus, lean mass and fat-free mass, which often consist of muscle mass, non-fat non-bone soft tissues, or water, are commonly measured as a surrogate of muscle mass in large-scale research studies.

Dual energy X-ray absorptiometry (DXA) measures lean mass indirectly by subtracting the fat tissue mass and bone mineral density from the soft tissue mass [2]. Thus, DXA-derived lean mass consists of not only muscle mass, but also other non-bone and non-fat mass, including soft tissue and water. Bioelectrical impedance analysis (BIA) uses single- or multi-frequency electrical current for measuring fat-free mass (commonly used as a proxy of muscle

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mass in studies) which is the conducting volume containing electrolyte-rich fluids that allows electric current to pass, implying the measurement of fat-free mass by BIA includes water content. In general, DXA is considered a better choice when compared with BIA due to its higher accuracy. The BIA equations and cutoff decision points vary according to the population and the device, and results can be altered with hydration status.

Given that measurement of lean mass (or fat free mass) cannot accurately reflect muscle mass, this limitation may affect the validity of the findings, and the association between measured lean-mass and clinically important outcomes, such as mobility and exercise performance, cannot be accurately evaluated. For example, lower muscle mass measured by D_3 creatinine dilution was shown to be significantly associated with worse physical performance, lower strength, increased risk of incident mobility limitation, and injurious falls. However, such associations were either weaker or absent when DXA-derived lean mass was used instead of D_3 creatinine dilution measured muscle mass in the analyses [3]. Different modalities used in measuring lean mass would lead to different estimates in prevalence of sarcopenia [4]. Since it is unclear if the association between lean mass and mortality would differ by the measurement modalities, and that the identification and diagnosis of sarcopenia offer clinically important implications, such as prognostication purposes, in patients with a wide variety diseases, this study aims to evaluate the association of BIA-, DXA- and CT-measured lean mass with mortality.

2. Methods

The materials and methods have been described in Cheung et al [24] in the same issue.

In short, a systematic search of PubMed, Cochrane Library and Embase was performed for cohort studies published before Dec 20, 2017 which examined the relationship between lean mass and mortality. We included studies reporting lean mass measurement by DXA, BIA, or CT, as continuous (per standard deviation decrease) or binary variables (using sarcopenia cutoffs). We excluded studies which used muscle mass surrogates, anthropometric measurement of muscle, rate of change in muscle mass, and sarcopenia defined by composite criteria. A total of 188 studies were included in the current meta-analysis (Fig. 1). Quality of studies were assessed using a modified NOS because certain criteria were not applicable in the current study. Good quality was defined as 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 1 or 2 stars in the outcome/exposure domain. Fair quality was defined as 1 star in the selection domain AND 1 or 2 stars in the comparability domain AND 1 or 2 stars in the outcome/exposure domain. Poor quality was defined as those studies not meeting the criteria for good or fair quality. Among the 188 studies, 2 studies did not meet the criteria for good or fair quality. Both studies were excluded in the current meta-analysis.

Studies were stratified according to the modality used to measurement lean mass (DXA, BIA, or CT). The primary study outcome was all-cause mortality. Hazard ratio for each group was calculated using a random effects model. In subgroup analysis, studies were further stratified according to underlying conditions, namely elderly, cancer, cardiovascular disease, liver disease, lung disease, renal disease and other conditions. Definitions for elderly were slightly different among studies, ranging from age above 50 to age above 74.

3. Results

The detailed descriptive information for each study is provided in Supplement Tables 2-5 in Cheung et al in the same issue. There were 16, 10, and 42 studies reporting the association of BIA-, DXA-, and CT-measured reduced lean mass and mortality, respectively (Table 1). The forest and funnel plots are presented in Supplementary Figs. S1 and S2, respectively. In general, 1 standard deviation (SD) decrease in BIA-, DXA-, and CT-measured lean mass was associated with increased all-cause mortality with an hazard ratio (HR) of 1.35 (95% CI, 1.21−1.49), 1.18 (95% CI, 1.06−1.30), and 1.44 (95% CI, 1.32−1.57), respectively. By further stratifying by clinical conditions, DXA-measured lean mass was not associated with all-cause mortality in patients with renal diseases and other conditions; while CT-measured lean mass was not associated with all-cause mortality in the elderly, people with cardiovascular disease, and other conditions. For the remaining analyses of reduced lean mass with mortality, the HR was similar across different modalities in each clinical condition, except for patients with renal diseases. In patients with renal diseases, HR estimated using CT-measured lean mass (HR, 2.02; 95% CI, 1.45−2.80) was significantly higher than that of BIA-measured lean mass (HR, 1.20; 95% CI, 1.02−1.42).

To examine the heterogeneity of the studies included in the meta-analysis of each subgroup, leave-one-out analysis was performed by examining the I [2] statistics after removing the most influential study (Table 3). It was observed that the I [2] statistics were over 60% in the studies investigating CT-measured lean mass and mortality in patients with cancer and cardiovascular disease, indicating potentially moderate to substantial heterogeneity even after removing the most influential study.

There were 17, 12, and 109 studies reporting the association of BIA-, DXA-, and CT-measured low lean mass and mortality, respectively (Table 2). The forest and funnel plots are presented in Supplementary Figs. S3 and S4, respectively. In general, low lean mass defined using BIA, DXA, and CT was significantly associated with increased risk of all-cause mortality, with an HR of 1.81 (95% CI, 1.56−2.10), 1.44 (95% CI, 1.29−1.60), and 1.78 (95% CI, 1.64−1.93), respectively. Such significant association was observed across different measurement modalities and clinical conditions.

In each clinical condition, the HR was similar across different modalities, except in patients with renal diseases. In patients with renal diseases, HR estimated using CT-measured lean mass (HR, 12.10; 95% CI, 3.31−44.2) was significantly higher than that using BIA- (HR, 1.66; 95% CI, 1.42−1.93) and DXA-measured (HR, 1.40; 95% CI, 1.17−1.68) lean mass. Since there was a substantial heterogeneity observed in the meta-analysis, we performed leave-one-out analysis by removing the most influential study. In general, moderate to high heterogeneity was still present in those analyses with I [2] $\geq$ 50% after removing the most influential study.

4. Discussion

The current study showed that lean mass was significantly associated with all-cause mortality regardless of measurement modalities. Low lean mass was significantly associated with mortality across different measurement modalities and clinical conditions; while associations in some subgroups were not statistically significant when lean mass was used as a continuous variable.

CT, BIA and DXA were 3 common modalities used to measure lean mass. Among the 3, BIA is the least preferred modality in evaluating lean mass [5]. Nevertheless, BIA-measured lean mass, like those measured by DXA- or CT- was also shown to be associated with mortality. Given the cost-effectiveness, safety, portability, and non-invasiveness [6], BIA may therefore be considered a valid method in evaluating lean mass, especially when the outcome of interest is mortality. This also suggests that even though lean mass is only a proxy of muscle mass, it is useful in predicting death, which is in agreement with the recent study from the Sarcopenia

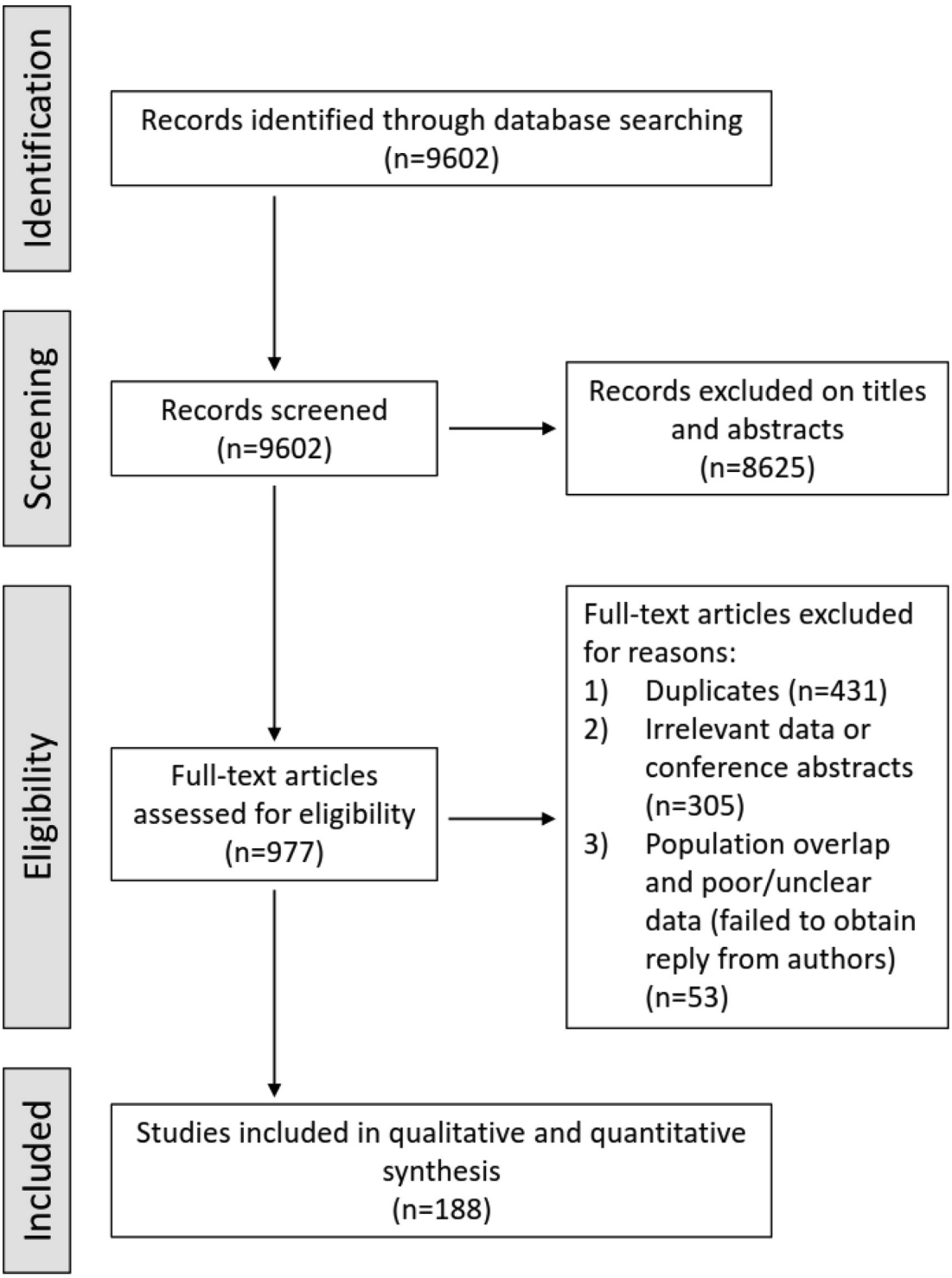

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Definitions and Outcomes Consortium (SDOC). Although DXA-measured lean mass was inconsistently associated with incident falls, mobility limitations, and hip fractures, its association with mortality was consistent in both men and women [7].

Notably, we do not intend to directly compare the performance of different modalities on mortality prediction, since direct comparison of these estimates requires cautious interpretation. For example, although the overall CT-measured reduced lean mass had a significantly higher HR in the association with mortality when compared with DXA-measured reduced lean mass, such difference could be driven by the number of studies included in the subgroup of cancer patients with CT-measured lean mass. Thus, a fairer comparison should be done within each clinical condition. For each clinical condition, the HRs were not significantly different among subgroups using lean mass measured by different modalities, except in the patients with renal diseases. In both analyses of

Table 1
Summary of studies included in the meta-analysis of reduced lean mass and mortality.

Sub-groups	BIA				DXA				CT			
	n (no. of studies)	I^2	HR	95% CI	n (no. of studies)	I^2	HR	95% CI	n (no. of studies)	I^2	HR	95% CI
Elderly	2481 (3)	46%	1.51	[1.13, 2.03]	4628 (5)	48%	1.14	[1.01, 1.29]	934 (1)[a]	NA	1.16	[0.92, 1.47]
Cancer	222 (1)	NA	1.29	[1.14, 1.47]	NA				3159 (16)	76%	1.43	[1.24, 1.65]
Cardiovascular disease	NA				89 (1)	NA	1.25[b]	[1.06, 1.48]	1723 (6)	80%	1.38	[0.97, 1.96]
Liver disease	383 (1)	NA	1.69	[1.36, 2.11]	NA				2973 (9)	24%	1.55	[1.39, 1.72]
Lung disease	684 (4)	42%	1.58	[1.08, 2.29]	NA				462 (3)	32%	1.60	[1.23, 2.07]
Renal disease	5513 (7)	57%	1.20	[1.02, 1.42]	1424 (3)	78%	2.08	[0.85, 5.05]	177 (2)	0%	2.02	[1.45, 2.80]
Other conditions	NA				664 (1)	NA	1.11	[0.74, 1.67]	1647 (5)	63%	1.13	[0.91, 1.39]
Overall	9283 (16)	58%	1.35	[1.21, 1.49]	6805 (10)	49%	1.18	[1.06, 1.30]	11075 (42)	72%	1.44	[1.32, 1.57]

BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; CT, computerized tomography; n, number of individuals; HR, hazard ratio.
NA, not available.
[a] Newman 2006 used both CT and DXA for lean mass measurements in the elderly, DXA measurement was chosen and CT measurement was not included in the meta-analysis.
[b] Unadjusted results were used for Doehner et al, 2005 because the multivariable analysis in the article reported p-value only.

Table 2
Summary of studies included in the meta-analysis of low lean mass and mortality.

Study group	BIA				DXA				CT			
	n (no. of studies)	I^2	HR	95% CI	n (no. of studies)	I^2	HR	95% CI	n (no. of studies)	I^2	HR	95% CI
Elderly	2506 (3)	0%	1.55	[1.33, 1.80]	10211 (6)	0%	1.36	[1.23, 1.50]	NA			
Cancer	1150 (3)	83%	1.87	[1.02, 3.41]	471 (1)	NA	2.86	[1.67, 4.90]	26797 (86)	62%	1.68[b]	[1.55, 1.82][b]
Cardiovascular disease	NA				NA				1754 (5)	30%	1.85	[1.32, 2.59]
Liver disease	382 (1)	NA	2.66	[1.54, 4.62]	NA				2095 (9)	65%	2.43[a]	[1.64, 3.61][a]
Lung disease	610 (3)	0%	2.56	[1.73, 3.77]	NA				178 (2)	0%	3.75	[1.94, 7.24]
Renal disease	11316 (7)	0%	1.66	[1.42, 1.93]	12905 (4)	17%	1.40	[1.17, 1.68]	137 (1)	NA	12.10	[3.31, 44.20]
Other conditions	NA				750 (1)	NA	1.65	[1.11, 2.45]	8147 (6)	87%	2.22	[1.16, 4.26]
Overall	15964 (17)	48%	1.81	[1.56, 2.10]	24337 (12)	24%	1.44	[1.29, 1.60]	39108 (109)	67%	1.78	[1.64, 1.93]

BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; CT, computerized tomography; n, number of individuals; HR, hazard ratio; NA, not available.
[a] Yadav 2013 unadjusted results were used because the multivariable analysis in the article suggested a level of precision that did not correspond with the number of observed events.
[b] Nakamura 2015 HR for overall population were excluded due to data mismatch, male population was used instead.

Table 3
'Leave-one-out' analysis for the health status sub-groups using continuous measures of lean mass.

	BIA		DXA		CT	
	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study
Elderly	46% (3)	0%	48% (5)	25%	NA	–
Cancer	NA	–	NA	–	76% (16)	65%
Cardiovascular disease	NA	–	NA	–	80% (6)	76%
Liver disease	0% (1)[a]	–	NA	–	24% (9)	0%
Lung disease	42% (4)	0%	NA	–	32% (3)	0%
Renal disease	57% (7)	47%	78% (3)	0%	0% (2)	–
Other diseases	NA	–	NA	–	63% (5)	38%

NA: only 1 or no study in sub-group.
BIA; bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; CT, computerized tomography; NA, not available.
[a] one study with two cohorts.

reduced lean mass and low lean mass, the estimates obtained from the meta-analyses of CT-measured lean mass were significantly higher. This could be because of the higher accuracy of CT than BIA in lean mass measurement, heterogeneity in study design and/or characteristics of individuals included in the studies. For example, low lean mass was found to be significantly associated with increased mortality with an HR of 12.1 in the study performed by Ishihara et al. [8] The study was conducted in patients with urothelial carcinoma of the upper urinary tract who underwent radical nephrectomy [8], whereas the comparator groups of BIA [9–13] and DXA [14–18] were mainly conducted in patients with end-stage renal diseases who required dialysis. Meanwhile, in the elderly subgroup, although the CT-measured reduced lean-mass generated an HR lower than that generated by BIA, only 1 study was included in the CT arm, giving rise to the wide confidence intervals and insignificant association. Further studies are required to confirm the association between CT-measured reduced lean-mass and mortality in the elderly population.

Low lean mass was consistently associated with mortality in all subgroups. However, insignificant associations were observed in several subgroups when lean mass was analyzed as a continuous variable. This could be due to the presence of U-shaped association of lean mass with mortality [19], implying that the analytical method used may affect the result of association, as a linear relationship has been assumed. Thus, our analysis further supports the development of an operational cutoff point to define low lean mass.

Table 4
'Leave-one-out' analysis for the health status sub-groups using binary cut-offs for low lean mass.

	BIA		DXA		CT	
	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study	Heterogeneity I^2 (no. of studies)	I^2 after removing the most influential study
Elderly	0% (3)	–	0% (6)	–	NA	–
Cancer	83% (3)	37%	NA	–	62% (86)	53%
Cardiovascular disease	NA	–	NA	–	30% (5)	4%
Liver disease	NA	–	NA	–	65% (9)	4%
Lung disease	0% (3)	–	NA	–	0% (2)	–
Renal disease	0% (7)	–	17% (4)	0%	NA	–
Other diseases	NA	–	NA	–	87% (6)	57%

NA: only 1 or no study in sub-group.
BIA; bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; CT, computerized tomography; NA, not available.

To our knowledge, this is the largest meta-analysis of lean mass on mortality to date, with stratification by different measurement modalities. This is unique as most published meta-analyses usually account for one measurement modality only [20–23]. Given the large number of studies and sample size involved, our study provides robust evidence for the association between low lean mass and increased risk of mortality. However, there are limitations. First, cautious interpretation is required since moderate to substantial heterogeneity were observed in some analyses even after removal of the most influential study (Tables 3 and 4), especially in the analyses of reduced lean mass. Nevertheless, both low lean mass and reduced lean mass were consistently associated with increased mortality, suggesting that the association is robust. Second, the estimates obtained in the subgroup analysis with CT-measured lean mass requires cautious interpretation. Most studies using CT-measured lean mass were conducted in patients with cancer. The reason why some of them were not classified into a cancer subgroup was that they aimed to evaluate the relationship of lean mass on mortality after a surgical procedure, and hence they were grouped into other categories. We should therefore always refer to the studies included in a particular subgroup for proper interpretation. Third, the difference in estimate (HR) between different modalities could be contributed by multiple factors, such as study population and study design instead of purely difference between the modalities used. The best way to compare the performance of different modalities should be done using the same cohort with lean mass measured by different modalities.

5. Conclusions

Reduced and low lean mass measured by BIA, DXA, and CT were consistently associated with increased mortality.

CRediT author statement

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

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.2021.02.004.

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