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

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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.

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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, D3 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 mass).
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 D3 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 D3 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 of 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 measure lean mass (DXA, BIA, or CT). The primary study outcome was all-cause mortality. Hazard ratio for each group was calculated 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, 1.45–2.80) 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] ≥ 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 primary 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
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

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
Table 1
Summary of studies included in the meta-analysis of reduced lean mass and mortality.

| Sub-groups       | BIA (n. of studies) | DXA (n. of studies) | CT (n. of studies) |
|------------------|---------------------|---------------------|-------------------|
|                  | I² | HR | 95% CI | I² | HR | 95% CI | I² | HR | 95% CI |
| Elderly          | 248 (3) | 46% | 1.51 [1.13, 2.03] | 4628 (5) | 48% | 1.14 [1.01, 1.29] | 934 (1) | 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] | 1723 (6) | 80% | 1.38 [0.97, 1.96] |
| Cardiovascular disease | NA | 89 (1) | 1.25 [1.06, 1.48] | NA | 2973 (9) | 24% | 1.55 [1.39, 1.72] | 462 (3) | 32% | 1.60 [1.23, 2.07] |
| Liver disease    | 383 (1) | NA | 1.69 [1.36, 2.11] | NA | 1777 (2) | 0% | 2.02 [1.45, 2.80] | 1647 (5) | 63% | 1.13 [0.91, 1.39] |
| Lung disease     | 684 (4) | 42% | 1.58 [1.08, 2.29] | 1424 (3) | 78% | 2.08 [0.85, 5.05] | 11075 (42) | 72% | 1.44 [1.32, 1.57] |
| Renal disease    | 5513 (7) | 57% | 1.20 [1.02, 1.42] | 471 (1) | 2.86 [1.67, 4.90] | 26797 (86) | 62% | 1.68 [1.55, 1.82] |
| Other conditions | 664 (1) | NA | 1.11 [0.74, 1.67] | NA | 1754 (5) | 30% | 1.85 [1.32, 2.59] | 2095 (9) | 65% | 2.43 [1.64, 3.61] |
| Overall          | 9283 (16) | 58% | 1.35 [1.21, 1.49] | 6805 (10) | 49% | 1.18 [1.06, 1.30] | 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.

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

| Study group       | BIA (n. of studies) | DXA (n. of studies) | CT (n. of studies) |
|-------------------|---------------------|---------------------|-------------------|
|                   | n (no. of studies) | I² | HR | 95% CI | n (no. of studies) | I² | HR | 95% CI | n (no. of studies) | I² | HR | 95% CI |
| Elderly           | 2506 (3) | 0% | 1.55 [1.33, 1.80] | 10211 (6) | 0% | 1.36 [1.23, 1.50] | NA | 62% | 1.68 [1.55, 1.82] |
| Cancer            | 1150 (3) | 83% | 1.87 [1.02, 3.41] | 471 (1) | NA | 2.86 [1.67, 4.90] | 1754 (5) | 30% | 1.85 [1.32, 2.59] |
| Cardiovascular disease | NA | 26.6 [1.54, 4.62] | NA | 2095 (9) | 65% | 2.43 [1.64, 3.61] |
| Liver disease     | 382 (1) | NA | 2.66 [1.54, 4.62] | NA | 178 (2) | 0% | 3.75 [1.94, 7.24] |
| Lung disease      | 610 (3) | 0% | 2.56 [1.73, 3.77] | NA | 137 (1) | NA | 12.10 [3.31, 44.20] |
| Renal disease     | 11316 (7) | 0% | 1.66 [1.42, 1.93] | 12905 (4) | 17% | 1.40 [1.17, 1.68] | 1777 (2) | 0% | 2.02 [1.45, 2.80] |
| Other conditions  | NA | 26.6 [1.54, 4.62] | NA | 178 (2) | 0% | 3.75 [1.94, 7.24] |
| 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.

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

|           | Heterogeneity I² (no. of studies) | I² after removing the most influential study | Heterogeneity I² (no. of studies) | I² after removing the most influential study | Heterogeneity I² (no. of studies) | I² 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)  | -- | 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.

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 1.21 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 is not necessarily always observed. Thus, our analysis further supports the development of an operational cutoff point to define low lean mass.
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.

### 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.jafos.2021.02.004.

### References

[1] Evans WJ, Hellerstein M, Orwell E, Cummings S, Cawthon PM. D3-creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle 2019;10:14–21.
[2] Wang YM, Visser M, Ma R, Baumgartner RN, Kotler D, Gallagher D, Heymsfield SB. Skeletal muscle mass: evaluation of neutron activation and dual-energy X-ray absorptiometry methods. J Appl Physiol 1985;80:824–31.
[3] Cawthon PM, Orwell ES, Peters KE, Ensorud KE, Cauley JA, Kado DM, et al. Strong relation between muscle mass determined by D3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci 2019;74:844–52.
[4] Muller MJ, Geisler C, Pourhassan M, Gluer CC. Bosy-Westphal A. Assessment and definition of lean body mass deficiency in the elderly. Eur J Clin Nutr 2014;68:1220–7.
[5] Lustgarten MS, Fielding RA. Assessment of analytical methods used to measure changes in body composition in the elderly and recommendations for their use in phase II clinical trials. J Nutr Health Aging 2011;15:368–75.
[6] Scagfogliari A, Clarys JP, Bauer JM, Verlaan S, Van Malderen L, Vantieghem S, et al. Predicting appendicular lean and fat mass with bioelectrical impedance analysis in older adults with physical function decline – the PROVIDE study. Clin Nutr 2017;36:869–75.
[7] Cawthon PM, Minniti T, Patel SM, Newman A, Trivison T, Kiel DP, et al. P Dawson: cut-points in sarcopenia components and incident adverse health outcomes: an SDOC analysis. J Am Geriatr Soc 2017;65:1282–91.
[8] Abad S, Sotomayor G, Vega A, Perez de Jose A, Verdalle U, Jofre R, et al. The phase angle of the electrical impedance is a predictor of long-term survival in dialysis patients. Nefrologia 2011;31:670–6.
[9] Kim JK, Kim SG, Oh JK, Lee YK, Noh JH, Kim HJ, Song YR. Impact of sarcopenia on long-term mortality and cardiovascular events in patients undergoing hemodialysis. Korean J Intern Med 2019;34:599–607.
[10] Barros A, Costa BE, Mottin CC, d’Avila DO. Depression, quality of life, and body composition in patients with end-stage renal disease: a cohort study. Br J Psychiatry 2016;208:301–6.
[11] Jin S, Lu Q, Su C, Pang D, Wang T. Shortage of appendicular skeletal muscle is an independent risk factor for mortality in peritoneal dialysis patients. Perit Dial Int 2017;37:78–84.
[12] Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Barany P, Heimberger O, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. Clin J Am Soc Nephrol 2014;9:1720–6.
[13] Nilsson E, Cao Y, Lindholm R, Ohama Y, Carrero JJ, Qureshi AR, et al. Pregnancy-associated plasma protein-A predicts survival in end-stage renal disease-conditioning and modifying effects of cardiovascular disease, body composition and inflammation. Nephrol Dial Transplant 2017;32:1776. https://doi.org/10.1093/ndt/gfx265.

### Table 4

| BIA | DXA | CT |
|-----|-----|----|
| **Heterogeneity I² (no. of studies)** | **I² after removing the most influential study** | **Heterogeneity I² (no. of studies)** | **I² after removing the most influential study** | **Heterogeneity I² (no. of studies)** | **I² after removing the most influential study** |
| Elderly | 0% (3) | 0% (6) | NA | NA | NA |
| Cancer | 83% (3) | 37% | NA | NA | 62% (86) |
| Cardiovascular disease | NA | NA | NA | NA | 30% (5) |
| Liver disease | NA | NA | NA | NA | 65% (9) |
| Lung disease | NA | NA | NA | NA | 0% (2) |
| Renal disease | 0% (7) | 17% (4) | NA | NA | 87% (6) |
| Other diseases | NA | NA | NA | NA | NA |

NA: only 1 or no study in sub-group.

**BIA**: bioelectrical impedance analysis; **DXA**: dual energy X-ray absorptiometry; **CT**: computed tomography; **NA**: not available.
Kakiya R, Shoji T, Tsujimoto Y, Tatsumi N, Hatsuda S, Shinohara K, et al. Body fat mass and lean mass as predictors of survival in hemodialysis patients. Kidney Int 2006;70:549–56.

Kang SH, Cho KH, Park JW, Do JY. Low appendicular muscle mass is associated with mortality in peritoneal dialysis patients: a single-center cohort study. Eur J Clin Nutr 2017;71:1405–10.

Honda H, Qureshi AR, Axelsson J, Heimburger O, Suliman ME, Barany, et al. Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. Am J Clin Nutr 2007;86:633–8.

Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. BMJ 2018;362:k2575.

van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, Ijzermans JNM. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. Am J Transplant 2016;16:2277–92.

Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. PLoS One 2017;12:e0186990.

Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Canc 2016;57:58–67.

Jones K, Gordon-Weeks A, Coleman C, Silva M. Radiologically determined sarcopenia predicts morbidity and mortality following abdominal surgery: a systematic review and meta-analysis. World J Surg 2017;41:2266–79.

Cheung CL, Lee GK, Au PC, Li GH, Chan M, Cheung BM, et al. Systematic review and metaanalysis of lean mass and mortality: rationale and study description. Osteoporos Sarcopenia 2021;51(Special):1–??.