Bioimpedance analysis and physical functioning as mortality indicators among older sarcopenic people

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ABSTRACT
Objectives: To assess the prognostic significance of various characteristics and measurements of sarcopenia and physical functioning on all-cause mortality among home-dwelling older people with or at-risk of sarcopenia.
Design: Cross-sectional and longitudinal analyses.
Setting: Porvoo sarcopenia trial in open care.
Participants: Community-dwelling people aged 75 and older (N = 428, of which 182 were re-examined at one year) with four years of follow-up.
Measurements: Body mass index (BMI), physical functioning (physical component of the RAND-36) and physical performance tests (Short Physical Performance Battery (SPPB)), hand grip strength, walking speed, Charlson Comorbidity Index, bioimpedance-based surrogates for muscle mass: Single Frequency Skeletal Muscle Index (SF-SMI), and Calf Intracellular Resistance Skeletal Muscle Index (CRI-SMI). Date of death was retrieved from central registers. Survival analyses were performed using Life-Table analyses and Cox models.
Results: Most test variables (except BMI) were associated with four-year mortality in a dose-dependent fashion. After controlling for age, gender and co-morbidity, physical performance and functioning (both SPPB and RAND-36), muscle strength (hand grip strength) and CRI-SMI appeared to be independent mortality risk indicators (p < 0.001) whereas SF-SMI was not. When CRI-SMI values were grouped by gender-specific cut-off points, the probability of surviving for four years decreased by 66% among the older people with low CRI-SMI (HR = 0.34, 95%CI 0.15–0.78, p = 0.011). When low CRI-SMI was further controlled for SPPB, the prognostic significance remained significant (HR = 0.55, 95%CI 0.33–0.92, p = 0.021). After controlling for age, gender, comorbidity, and CRI-SMI, the physical component of the RAND-36 (p = 0.007), SPPB (p < 0.001) and hand grip strength (p = 0.009) remained significant mortality predictors. Twelve-month changes were similarly associated with all-cause mortality during the follow-up period.
Conclusion: CRI-SMI, muscle strength, physical performance and physical functioning are each strong independent predictors of all-cause mortality among home-dwelling older people. Compared to these indicators, BMI seemed to be clearly inferior. Of two bioimpedance-based muscle indices, CRI SMI was better predictor of mortality than SF-SMI. In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention of sarcopenia-related over-mortality.

1. Introduction
Sarcopenia, age-related muscle loss, has been recognized as a major clinical problem among older people as it is common and associates with poorer health outcomes. A recent consensus panel has defined it as low muscle strength, low muscle quantity and quality, and low physical performance (Cruz-Jentoft et al., 2019). Compared with the determination of strength and performance, the assessment of muscle mass is challenging in clinical practice.

Different body imaging techniques such as computed tomography, magnetic resonance imaging, dual energy X-ray absorptiometry (DEXA) and Bioimpedance analysis (BIA) have been recommended for the measurement of muscle mass (Cruz-Jentoft et al., 2019). However, the three first imaging techniques require a visit to a laboratory or a hospital, which may be problematic for some older sarcopenic people with disabilities. BIA is a portable alternative for assessing body composition

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The study was approved by the Ethics Committee of the Helsinki University Central Hospital. Informed consent was obtained from each patient or, if necessary, from their closest proxy for MMSE of <19 points.

2.3. Statistics

We used SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) for the statistical analyses. Continuous variables with normal distribution were expressed by means with standard deviations (SD) and those with skewed distribution by medians with first and fourth quartile cut-off points. For the variables with normal distribution, we performed statistical comparisons between the groups using Student’s t-test, and for those with skewed distribution we used the Mann-Whitney U test. We used the Chi-Square test to examine the relationships between two categorical variables, and Fischer’s exact test when appropriate.

We used Kaplan-Meier analyses to study time-dependent differences in survival, and Cox survival analyses to test the prognostic significance of various risk conditions. Age, gender and comorbidity as common confounders for mortality were forced into the regression analysis as covariates when appropriate.

3. Results

3.1. Baseline characteristics as mortality risk indicators

The participants (N = 428) were old (83.4 ± 4.6 years), women outnumbered men (285 vs. 143) and the majority (56%) lived alone. They used a mean of 5.4 ± 3.0 prescribed regular medications. Their mean BMI was 27.2 ± 4.6 kg/m² and that of MMSE 25.6 ± 3.5. Up to 40% were considered to have a sedentary lifestyle.
Of the screened participants, 88 died within four years. Mortality was twice as high among the men than among the women and was closely associated with characteristics of physical functioning (RAND-36), physical performance (SPPB, CSPPS, walking speed, two-minute walking distance, and chair tests) among both genders (Table 1). We found no difference between the BMI of the survivors and deceased women. Of the bioimpedance measures, only CRi-SMI values were significantly lower among the deceased than among the survivors.

The survival analyses (Kaplan-Meier curves) revealed that case-fatality increased with CRi-SMI over time (Fig. 1). The same also held true for several other indicators of sarcopenia, physical functioning and Charlson comorbidity index (data not shown).

We further tested the significance of the risk indicators in Cox regression analyses, into which we entered age, gender and comorbidity as covariates (Table 2). The indices of physical performance and functioning (SPPB and RAND-36), muscle strength (hand grip strength), and CRi-SMI as an indicator of muscle mass appeared to be independent mortality risk indicators. In this analysis, the prognostic value of SF-SMI and BMI remained insignificant. When CRi-SMI values were grouped by age-specific cut-off points, the probability of surviving for four years decreased by 66% among the older people with low CRi-SMI (Fig. 1). When CRi-SMI was further controlled for SPPB, the prognostic significance of low CRi-SMI remained significant (HR = 0.55, 95%CI 0.33–0.92, p = 0.021).

Finally, when we forced the muscle mass indicator CRi-SMI into the Cox survival analysis as an additional covariant, both the hand grip strength and physical functioning indices retained statistical significance as mortality predictors, whereas the prognostic value of BMI remained insignificant (Table 2).

### Table 1
Baseline characteristics of men and women by four-year mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive (N = 97)</th>
<th>Dead (n = 46)</th>
<th>p-Value</th>
<th>Alive (N = 243)</th>
<th>Dead (N = 42)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>83.2 (4.4)</td>
<td>84.0 (4.2)</td>
<td>0.307</td>
<td>82.9 (4.6)</td>
<td>86.1 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2.33 (1.85)</td>
<td>3.45 (3.06)</td>
<td>0.008</td>
<td>1.84 (1.65)</td>
<td>2.86 (1.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.2 (3.1)</td>
<td>25.0 (5.3)</td>
<td>0.812</td>
<td>26.2 (2.6)</td>
<td>24.1 (5.0)</td>
<td>0.015</td>
</tr>
<tr>
<td>RAND-36, Physical function scale</td>
<td>57.8 (28.5)</td>
<td>46.2 (32.9)</td>
<td>0.036</td>
<td>51.4 (25.9)</td>
<td>31.2 (24.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Short Physical Performance Battery (0–12)</td>
<td>8.7 (2.7)</td>
<td>7.2 (3.3)</td>
<td>0.006</td>
<td>8.7 (2.7)</td>
<td>5.5 (3.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Continuous summary physical performance score</td>
<td>68.1 (16.4)</td>
<td>57.5 (21.9)</td>
<td>0.002</td>
<td>68.0 (15.1)</td>
<td>47.0 (22.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Walking speed, m/s</td>
<td>0.95 (0.28)</td>
<td>0.79 (0.35)</td>
<td>0.005</td>
<td>0.93 (0.29)</td>
<td>0.61 (0.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chair test, s</td>
<td>15.5 (7.8)</td>
<td>18.6 (7.5)</td>
<td>0.028</td>
<td>15.4 (8.0)</td>
<td>22.1 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-min walking distance, m</td>
<td>81.3 (27.7)</td>
<td>74.0 (23.6)</td>
<td>0.141</td>
<td>79.1 (23.1)</td>
<td>58.4 (24.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hand Grip Strength, kg</td>
<td>28.8 (7.1)</td>
<td>25.9 (6.4)</td>
<td>0.020</td>
<td>18.1 (4.2)</td>
<td>14.1 (4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body Mass Index kg/m²</td>
<td>27.3 (4.0)</td>
<td>25.8 (3.7)</td>
<td>0.034</td>
<td>27.4 (4.6)</td>
<td>27.1 (6.6)</td>
<td>0.783</td>
</tr>
<tr>
<td>SF-SMI, kg/m²</td>
<td>9.83 (1.14)</td>
<td>9.42 (1.29)</td>
<td>0.055</td>
<td>6.96 (0.94)</td>
<td>6.82 (1.34)</td>
<td>0.406</td>
</tr>
</tbody>
</table>

**MMSE** = Mini Mental State Examination.

*Single Frequency Skeletal Muscle Index.

*CRi-SMI = Calf Intracellular Resistance Skeletal Muscle Index.

**Fig. 1.** Calf intracellular resistance muscle index (CRi-SMI) as independent four-year mortality indicator. The age-specific cut-off points for low CRi-SMI were 1.50 cm²/Ω for women and 2.06 cm²/Ω for men. Data adjusted for age, gender and Charlson comorbidity index. OR = 0.34 (0.15–0.78, p = 0.011).

### Table 2
Baseline measurements of physical functioning, physical performance and sarcopenia as independent indicators of four-year mortality.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Hazard ratio</th>
<th>95% confidence intervals</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age, gender, and comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.96</td>
<td>0.91–1.00</td>
<td>0.080</td>
</tr>
<tr>
<td>SPPB</td>
<td>0.85</td>
<td>0.79–0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAND-36, physical function scale</td>
<td>0.987</td>
<td>0.978–0.995</td>
<td>0.003</td>
</tr>
<tr>
<td>Hand grip strength, kg</td>
<td>0.93</td>
<td>0.90–0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRi-SMI, cm²/Ω</td>
<td>0.41</td>
<td>0.28–0.69</td>
<td>0.001</td>
</tr>
<tr>
<td>SF-SMI, kg/m²</td>
<td>0.85</td>
<td>0.70–1.04</td>
<td>0.120</td>
</tr>
<tr>
<td>Adjusted for age, gender, comorbidity, and CRi-SMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.97</td>
<td>0.92–1.02</td>
<td>0.264</td>
</tr>
<tr>
<td>SPPB</td>
<td>0.85</td>
<td>0.79–0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RAND-36, physical function scale</td>
<td>0.988</td>
<td>0.979–0.997</td>
<td>0.007</td>
</tr>
<tr>
<td>Hand grip strength, kg</td>
<td>0.95</td>
<td>0.91–0.99</td>
<td>0.009</td>
</tr>
</tbody>
</table>

**SPPB** = Short Physical Performance Battery (0–12), **BMI** = Body Mass Index, **SF-SMI** = Single Frequency Skeletal Muscle Index, **CRi-SMI** = Calf Intracellular Resistance Skeletal Muscle Index.
Table 3
Percentage twelve-month changes (SE) of physical functioning, physical performance and sarcopenia measures as predictors of four-year mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alive (N = 149)</th>
<th>Dead (N = 33)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.38 (4.6)</td>
<td>-0.53 (4.7)</td>
<td>0.453</td>
</tr>
<tr>
<td>SPPB</td>
<td>2.0 (2.7)</td>
<td>-12.2 (7.5)</td>
<td>0.045</td>
</tr>
<tr>
<td>RAND-36, physical function scale</td>
<td>18.9 (7.8)</td>
<td>-6.2 (8.9)</td>
<td>0.151</td>
</tr>
<tr>
<td>CSSPS</td>
<td>-0.4 (1.6)</td>
<td>-6.5 (3.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Hand grip strength</td>
<td>-6.5 (1.6)</td>
<td>-17.7 (4.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>SF-SMI</td>
<td>0.3 (0.5)</td>
<td>-2.3 (1.0)</td>
<td>0.035</td>
</tr>
<tr>
<td>CRI-SMI</td>
<td>-1.0 (1.1)</td>
<td>-8.5 (2.6)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

SPPB = Short Physical Performance Battery (0–12), BMI = Body Mass Index, CSSPS = Continuous Summary Physical Performance Scores (0–100), SF-SMI = Single Frequency Skeletal Muscle Index, CRI-SMI = Calf Intracellular Resistance Skeletal Muscle Index.

bioimpedance data were only moderate. The age- and gender-adjusted correlation between the two bioimpedance datasets at entry was 0.374 and at 12-month changes 0.384. Changes in BMI correlated significantly only with SF-SMI (r = 0.284, p < 0.001) but not with changes in CRI-SMI. Of the 80 participants who lost weight during the 12-month follow-up, SF-SMI decreased among 51, CRI-SMI among 56, and CSSPS deteriorated among 46. Changes in hand grip strength were associated with those of CRI-SMI (r = 0.238 p < 0.01) but not at all with changes in SF-SMI (r = 0.068).

In order to test the extent to which these variables were independent risk indicators, we first forced age, gender and the Charlson comorbidity index into the equation of logistic regression analysis (Table 4). A 1% decrease in CRI-SMI was associated with a 4% increase in four-year mortality. The respective figure for the loss of hand grip strength was 2%. The prognostic values of changes in the SF-SMI, weight and physical functioning scores were of similar magnitude but did not reach statistical significance.

4. Discussion

This study shows that most characteristics of sarcopenia and frailty are associated with a significant long-term all-cause mortality risk among older community-dwelling people who are at a high risk of or already suffer from age-related muscle loss. In addition, mortality risk is increased by most test variables in a dose-dependent fashion. The results were essentially similar in the two analyses (baseline measurements vs. 12-month changes) of the present study, although due to the attrition of the study population, the statistical significances were not as strong among the 12-month follow-up participants (N = 182) as among the baseline screening population (N = 428).

When seeking potential prevention targets of sarcopenia-related health consequences, it is important to distinguish between causes and consequences, as well as a plethora of epiphenomena. In this respect, our data provide new valuable information.

Simultaneous testing of muscle mass, muscle strength, physical functioning scores and BMI revealed that the three sarcopenia measures were superior to BMI as mortality predictors. It is worth noting that the intercorrelations of different sarcopenia indicators were rather low at baseline and their changes were not congruent during the one year of this study. It is conceivable that muscle strength and physical functioning are influenced by several factors other than muscle mass. Our data clearly showed that muscle strength (hand grip strength) and physical performance and functioning (SPPB and RAND-36) were mortality predictors independently of CRI-SMI. Compared to these indicators, BMI seemed clearly inferior. This observation accords well with the newest data on sarcopenic obesity (Hamer and O'Donovan, 2017). In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention of sarcopenia-related over-mortality.

The superiority of CRI-SMI compared to SF-SMI as a mortality predictor, and their relatively weak intercorrelations, deserve special attention. SF-SMI is based on an algorithm derived from relatively healthy subjects, which may be a source of error among the older multimorbid disabled people of the present study. This is why, in the present study, we used CRI-SMI, which is based on BIS data that does not require population-specific algorithms to avoid these inaccuracies. Muscle atrophy during ageing decreases the intracellular compartment of the muscle, but the extracellular fluid is maintained, resulting in an increase in the proportion of non-functional muscle volume (Yamada et al., 2010; Yamada et al., 2013). This extracellular water compartment may result in overestimation of actual muscle mass with SF-BIA and imaging techniques. This overestimation in turn may mask age-related muscle loss (Yamada et al., 2014). This could explain the low association between SF-SMI and physical performance, as well as the mortality in the present study.

CRI-SMI is closely related to the intracellular water compartment, as fat and bone cells have low intracellular water content. Thus, CRI-SMI may be considered a surrogate for skeletal muscle cell mass. The results of the present study are in good accordance with those of our previous longitudinal study, in which the changes in CRI-SMI associated with mobility decline among typical nursing home residents (Björkman et al., 2012). Further research for comparisons of these methods are still warranted.

The main weakness of this study is the lack of confirmatory measurement of muscle mass (dual x-ray absorptiometry, etc.). However, the usefulness of bioimpedance analysis in the estimation of muscle mass and quality has been investigated thoroughly (Heymsfield et al., 2015). These measurements require the presence of stable patient conditions at time of measurement, because hydration of the participant, time of day, and meticulous adherence to manufacturer-specific conditions are important for the reliability of the results.

Major strengths in turn are the representativeness of the population sample, the simultaneous use of a large test battery, repeated measurements of key indicators, long follow-up and the consistency of results. Furthermore, this is the first study to investigate the role of CRI-SMI as a mortality predictor among community-dwelling older people.

5. Conclusions

CRI-SMI, muscle strength, and physical functioning are each strong independent predictors of all-cause mortality in home-dwelling older people. Compared to these indicators, BMI seemed to be clearly inferior. Of two bioimpedance-based muscle indices, CRI-SMI was better predictor of mortality than SF-SMI. In this regard, muscle mass, muscle strength and physical performance are all suitable targets for the prevention sarcopenia-related over-mortality.

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