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Combined assessment of skeletal muscle mass and quality in allogeneic hematopoietic stem cell transplantation: A longitudinal study of physical function and complications

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Research Article

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Abstract

Background

Longitudinal changes in skeletal muscle mass and quality after allogeneic hematopoietic stem cell transplantation remain unclear. This study used bioelectrical impedance analysis to assess these changes and their associations with physical function, infection, and acute graft-versus-host disease.

Methods

This retrospective study included 111 adults who underwent allogeneic hematopoietic stem cell transplantation. Skeletal muscle mass index and phase angle, an indicator of muscle quality, were assessed by bioelectrical impedance analysis before transplantation, 4 weeks after transplantation, and at discharge. Patients were assigned to four combined categories based on normal or low muscle mass and quality. Outcomes included 6-minute walk distance, infection, and acute graft-versus-host disease.

Results

Skeletal muscle mass index and phase angle decreased significantly after transplantation ($p < 0.05$), with phase angle declining earlier and more markedly. At discharge, 53.1% of patients were classified as Category 3. At 4 weeks, the decline in 6-minute walk distance was significantly greater in Categories 2 and 3 than in Categories 0 and 1. In multivariable analyses, Categories 2 and 3 were independently associated with infection, whereas Category 3 was independently associated with acute graft-versus-host disease.

Conclusion

Skeletal muscle mass and quality deteriorated after allogeneic hematopoietic stem cell transplantation, and low muscle quality was more closely associated with adverse outcomes. Pre-transplant bioelectrical impedance analysis-based assessment of muscle quality may help identify patients at risk of infection, acute graft-versus-host disease, and delayed physical recovery and may support further evaluation of prehabilitation strategies.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for refractory hematological disorders [1, 2]. During the early period after allo-HSCT, skeletal muscle mass may decline because of prolonged bed rest associated with conditioning-related complications and acute graft-versus-host disease (GVHD) [3–6]. Previous studies have shown that pre-transplant muscle depletion is associated with poorer post-transplant outcomes, supporting skeletal muscle assessment

as a clinically relevant marker in this population [7]. Skeletal muscle quality has also received increasing attention because it may deteriorate earlier than muscle mass and has been associated with post-transplant infection and shorter survival [8, 9]. Accordingly, a comprehensive skeletal muscle assessment that incorporates both mass and quality is important in patients undergoing allo-HSCT.

Computed tomography (CT) is widely used to assess skeletal muscle status, but radiation exposure limits its suitability for frequent monitoring. Consequently, longitudinal changes in muscle mass and quality across the transplantation course remain insufficiently characterized. Bioelectrical impedance analysis (BIA) involves no radiation exposure and enables simple, minimally invasive assessment of both dimensions, making it suitable for serial muscle assessment. Combined measures of skeletal muscle mass and quality may characterize patient status and physical function more sensitively than either measure alone. However, no study has evaluated a classification that integrates both measures longitudinally, and it remains unclear how such categories change from before transplantation through the early post-transplant period or relate to physical function and post-transplant complications.

The primary objective was to characterize longitudinal changes in skeletal muscle mass and quality from before transplantation through the early post-transplant period in patients undergoing allo-HSCT. The secondary objective was to evaluate the associations of these muscle characteristics with physical function, infection, and acute GVHD.

Materials and Methods

Patients and data collection

This retrospective observational study included adults who underwent allo-HSCT at a university hospital between April 2017 and January 2025. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Kyoto University (approval number R0715). The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Collected clinical variables included the Eastern Cooperative Oncology Group performance status (ECOG-PS), hematopoietic cell transplantation comorbidity index (HCT-CI), stem cell source, disease status, hematologic parameters (hemoglobin, total serum protein, and albumin), and 6-minute walk distance (6MWD). Post-transplant outcomes included the occurrence of infection and acute GVHD. The classification of acute GVHD was performed based on the National Institutes of Health criteria.

Rehabilitation protocols and physical function assessment

All patients received rehabilitation from before transplantation (before conditioning) until discharge. Before engraftment, rehabilitation was delivered in a clean room and focused primarily on maintaining activities of daily living (ADL) and physical function. Sessions were conducted 5 times per week for 20–

40 min and included stretching, strength training, walking, and bicycle ergometry. Exercise intensity was targeted at “somewhat hard” on the modified Borg scale, and target heart rate was calculated using the Karvonen method for an exercise intensity of 40%–60% exercise intensity. After engraftment, rehabilitation was conducted in the rehabilitation center, with emphasis on improving physical function and regaining ADL skills in preparation for discharge. Activities included ADL training, such as stair-climbing practice and floor-mobility exercises, and other individualized exercises. Sessions lasted up to 1 h, and exercise intensity was set at “somewhat hard” or “hard” [10].

Physical function was assessed by 6MWD before transplantation, 4 weeks after transplantation, and at discharge. The 6MWD was measured according to the American Thoracic Society 6-minute walk test protocol [11]. Change in 6MWD (Δ6MWD) were calculated between pre-transplantation and 4 weeks post-transplantation, as well as between 4 weeks post-transplantation and discharge.

Assessment of body composition and classification of skeletal muscle categories

Body composition was assessed with a bioelectrical impedance analyzer (InBody 770; InBody Japan Inc., Tokyo, Japan). Measurements were obtained with patients standing and included body weight, extracellular water/total body water ratio (ECW/TBW), skeletal muscle mass index (SMI), and phase angle. Measurements were performed before transplantation, 4 weeks after transplantation, and at discharge.

Based on SMI and phase angle measured by BIA, patients were assigned to four skeletal muscle categories (Fig. 1). SMI was classified as normal or low according to the criteria of the Asian Working Group for Sarcopenia 2025 (men, 7.6 kg/m^2 for those aged < 65 years and 7.2 kg/m^2 for those aged ≥ 65 years; women, 5.7 kg/m^2) [12]. Phase angle, a n indicator of skeletal muscle quality, was classified as normal or low using previously reported reference values for healthy Asian populations (men: 4.65°; women: 4.25°) [13]. The measures were combined into four categories: Category 0, normal skeletal muscle mass (SMI: ≥7.6 kg/m² for men aged < 65 years and ≥ 7.2 kg/m² for men aged ≥ 65 years, women ≥ 5.7 kg/m^2) and normal skeletal muscle quality (phase angle: ≥4.65 for men and ≥ 4.25 for women); Category 1, low skeletal muscle mass (SMI: <7.6 kg/m² for men aged < 65 years and < 7.2 kg/m² for men aged ≥ 65 years, women < 5.7 kg/m^2) and normal skeletal muscle quality; Category 2, normal skeletal muscle mass and low skeletal muscle quality (phase angle: <4.65 for men and < 4.25 for women); and Category 3, low skeletal muscle mass and low skeletal muscle quality.

Statistical analyses

All analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. For longitudinal comparisons of body weight, SMI, and phase angle across the three time points (before transplantation, 4 weeks after

transplantation, and discharge), repeated-measures of variance (ANOVA) was performed, followed by Tukey post hoc testing. Differences in skeletal muscle category distributions at each time point and categorical baseline characteristics among categories were analyzed using Fisher's exact test. Continuous baseline characteristics and Δ6MWD were compared among categories at each time point using one-way ANOVA, followed by Tukey post hoc testing when the overall test was significant.

To examine associations between pre-transplant skeletal muscle categories and post-transplant complications, the incidences of infection and acute GVHD were compared among the four categories using Fisher's exact test. Multivariable logistic regression was then used to identify factors independently associated with each complication. Each model included the pre-transplant skeletal muscle categories and clinical covariates associated with the outcome at $p < 0.10$ in univariable analysis, including age, disease status, and stem cell source. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A two-sided p value < 0.05 was considered statistically significant.

Results

A total of 159 patients scheduled for allo-HSCT were screened for eligibility. Forty-eight were excluded because body composition data were missing before or after transplantation. Thus, 111 patients (58 men and 53 women) with a median age of 50.0 years were analyzed. Most patients (99%) had a favorable ECOG-PS, and 68.5% were classified as low risk according to the HCT-CI. In addition, 83% underwent transplantation while in remission, and unrelated bone marrow was the most common stem cell source.

The distribution of skeletal muscle categories before transplantation was as follows: Category 0, 28.9% (n = 32); Category 1, 22.5% (n = 25); Category 2, 22.5% (n = 25); and Category 3, 26.1% (n = 29). Primary diagnosis and disease status did not differ significantly among categories. However, patients in Categories 2 and 3 were significantly older than those in Category 1, and body weight in Categories 1, 2, and 3 was significantly lower than that in Category 0. In addition, umbilical cord blood was used significantly more often as the stem cell source in Categories 2 and 3 than in Category 0 (Table 1).

Changes in body composition and skeletal muscle categories

Body weight was significantly lower at discharge than before transplantation (median: baseline, 58.2 kg; at 4 weeks, 56.1 kg; at discharge, 54.0 kg; $p = 0.04$). SMI was significantly lower at discharge than before transplantation (median: baseline, 6.6 kg/m^2; at 4 weeks, 6.5 kg/m^2; at discharge, 6.1 kg/m^2; $p = 0.03$). Phase angle was significantly lower at 4 weeks after transplantation and at discharge than before transplantation (median: baseline, 4.4°; at 4 weeks, 3.9°; at discharge, 3.8°; $p < 0.001$). Conversely, ECW/TBW was significantly higher at 4 weeks after transplantation and at discharge than before transplantation (median: baseline, 0.391; at 4 weeks, 0.399; at discharge, 0.400; $p < 0.001$).

The distribution of skeletal muscle categories changed significantly from before transplantation to discharge (Fig. 2). Before transplantation, Category 0 was the most common classification (n = 32, 28.9%). Four weeks after transplantation, the proportions of patients in Category 2 (n = 44, 39.6%) and Category 3 (n = 46, 41.4%) increased significantly. At discharge, the proportion in Category 3 had increased significantly (n = 59, 53.1%). Of the 32 patients classified as Category 0 before transplantation, 20 (62.5%) transitioned to Category 1 or higher. Among the 25 patients classified as Category 1, 64.0% (n = 16) transitioned to Category 3. Of the 59 patients classified as Category 3 at discharge, 59.3% (n = 35) were already in Category 3 at 4 weeks.

Figure 3 shows the sex-stratified distributions of SMI and phase angle before transplantation, 4 weeks after transplantation, and at discharge. In both men and women, the distributions shifted toward lower muscle quality after transplantation.

Associations of skeletal muscle categories with clinical outcomes and physical function

Pre-transplant 6MWD did not differ significantly among categories (p = 0.14). At 4 weeks after transplantation, the decline in 6MWD was significantly greater in Categories 2 (-102.4 m) and 3 (-106.4 m) than in Categories 0 (-1.0 m) and 1 (-30.0 m). At discharge, 6MWD was significantly lower in Categories 2 (466.1 m) and 3 (478.7 m) than in Category 1 (566.0 m) (p = 0.01).

The incidences of infection and acute GVHD differed significantly among the pre-transplant skeletal muscle categories. The incidence of infection was significantly higher in Category 2 (52%) and Category 3 (52%) than in Category 0 (9%) and Category 1 (20%) (p < 0.001). Similarly, the incidence of acute GVHD was significantly greater in Categories 2 (56%) and 3 (69%) than in Categories 0 (34%) and 1 (32%) (p = 0.012). After adjustment for age, disease status, and stem cell source, the associations differed by outcome and category. Categories 2 (OR: 4.40, 95% CI: 1.37–14.1, p = 0.01) and 3 (OR: 5.50, 95% CI: 1.87–16.1, p = 0.002) were independently associated with infection relative to Category 0 (Table 2). Category 3 (OR: 3.07, 95% CI: 1.14–8.27, p = 0.02) was independently associated with acute GVHD (Table 3).

Discussion

This study characterized longitudinal changes in SMI and phase angle in patients undergoing allo-HSCT and examined associations between pre-transplant skeletal muscle categories and post-transplant outcomes. Phase angle declined earlier and more markedly than SMI. Categories 2 and 3 were associated with infection, Category 3 was associated with acute graft-versus-host disease (GVHD), and patients with low muscle quality had greater early declines in 6MWD.

Although both SMI and phase angle declined after transplantation, phase angle changed earlier and more markedly. This pattern is consistent with reports that qualitative muscle changes can precede

quantitative loss [14, 15]. A key contribution of this study is the serial evaluation of both indices during the early post-transplant period, when repeated CT assessment is impractical because of radiation exposure. BIA enables repeated assessment, although phase angle reflects cell membrane integrity and is also influenced by systemic inflammation [16]. Following allo-HSCT, systemic inflammation may arise from conditioning-related complications, acute GVHD, and engraftment syndrome. The shift of many patients to Categories 2 or 3 at 4 weeks may therefore reflect changes in cellular integrity and inflammation associated with transplant-related complications. The concurrent increase in ECW/TBW also suggests that altered hydration may have contributed to the decline in phase angle.

A major finding was that pre-transplant muscle quality, rather than low muscle mass alone, was associated with post-transplant complications. Categories 2 and 3 were independently associated with infection, whereas only Category 3 was independently associated with acute GVHD. These findings suggest that phase angle may capture aspects of physiologic vulnerability not reflected by muscle mass alone in allo-HSCT candidates. Because many candidates for allo-HSCT are relatively young, muscle mass alone may not fully characterize pre-transplant risk. A low pre-transplant phase angle may indicate greater vulnerability to conditioning-related tissue injury. In acute GVHD, host tissue injury and subsequent inflammatory cytokine release are important triggers of donor T-cell activation [17, 18]. In patients with a low phase angle, this vulnerability may promote an exaggerated inflammatory response, but the present data do not establish this mechanism. The association with infection may similarly reflect reduced systemic resilience during profound post-transplant immunosuppression. Even when muscle mass was preserved (Category 2), impaired muscle quality remained associated with infection, suggesting that muscle mass alone may not reflect host defense capacity. Corticosteroid treatment for GVHD could further increase infection risk.

Patients classified as having low muscle quality at 4 weeks after transplantation had a greater decline in 6MWD from pre-transplant levels. At discharge, 6MWD recovery was also more limited in Categories 2 and 3 than in Category 1. These findings suggest that impaired muscle quality and associated post-transplant complications may delay recovery of physical function. The results therefore have potential clinical relevance but do not establish that an intervention would improve outcomes. BIA screening could help identify patients for targeted nutritional and exercise support, and the effectiveness of prehabilitation should be evaluated prospectively.

To our knowledge, this is the first study to serially examine skeletal muscle mass and quality in relation to physical function and clinical outcomes before and after allo-HSCT. Several limitations should be considered. First, the single-center retrospective design, relatively small sample, and exclusion of patients with missing body composition data may limit generalizability and introduce selection bias; confirmation in larger multicenter cohorts is needed. Second, BIA measurements may be affected by rapid fluid shifts during the peri-transplant period, particularly because ECW/TBW increased after transplantation. Finally, direct imaging-based assessment of muscle composition with CT or magnetic resonance imaging was not performed, limiting mechanistic interpretation of changes in phase angle [7, 8, 19–21].

Conclusion

Patients undergoing allo-HSCT experience early declines in skeletal muscle mass and quality, with impaired muscle quality more closely associated with post-transplant complications and delayed physical recovery. Pre-transplant phase angle may be a useful risk indicator, but its clinical utility and the value of prehabilitation require prospective validation.

Declarations

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Kyoto University Institutional Review Board (approval no. R0715).

Consent to participate

Informed consent was obtained in the form of opt-out on the hospital's website. The study was approved by the Ethics Committee of Kyoto University.

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Author Contributions

R.H. and A.T. designed the study, reviewed and analyzed the data, and wrote the paper; J.K., Y.A., A.T-K., and R.I. interpreted the data and revised the manuscript; M. Murao, J.M., M. Matsushita, A.O., and T.A. contributed to the data collection and provided critiques on the manuscript.

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Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

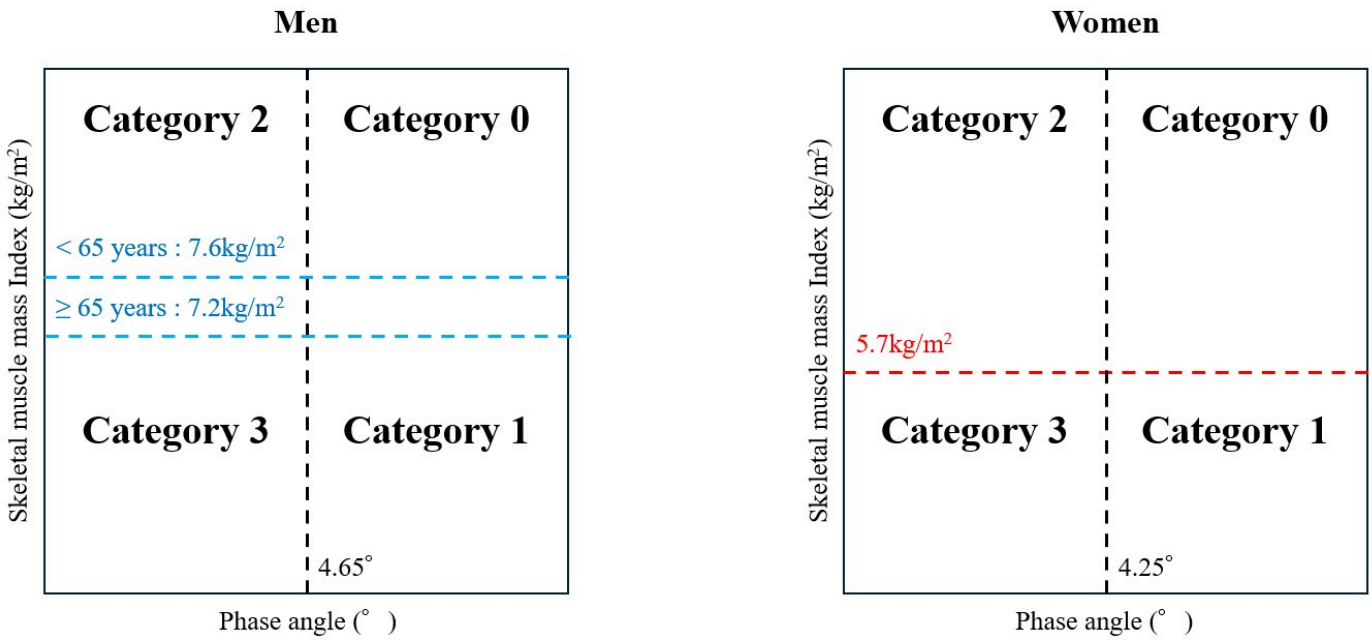


Figure 1

Classification based on skeletal muscle mass and quality

SMI was classified according to the AWGS 2025 criteria [Ref. 12], and phase angle was classified using previously reported [Ref. 13] sex-specific cutoff values (4.65° for men and 4.25° for women). The measures were combined into four categories: Category 0, normal muscle mass and normal muscle quality; Category 1, low muscle mass and normal muscle quality; Category 2, normal muscle mass and low muscle quality; and Category 3, low muscle mass and low muscle quality. The SMI cutoffs were ≥7.6 kg/m² for men aged <65 years, ≥7.2 kg/m² for men aged ≥65 years, and ≥5.7 kg/m² for women; corresponding lower values indicated low muscle mass. Phase angle values below the sex-specific cutoffs indicated low muscle quality. AWGS, Asian Working Group for Sarcopenia; SMI, skeletal muscle mass index

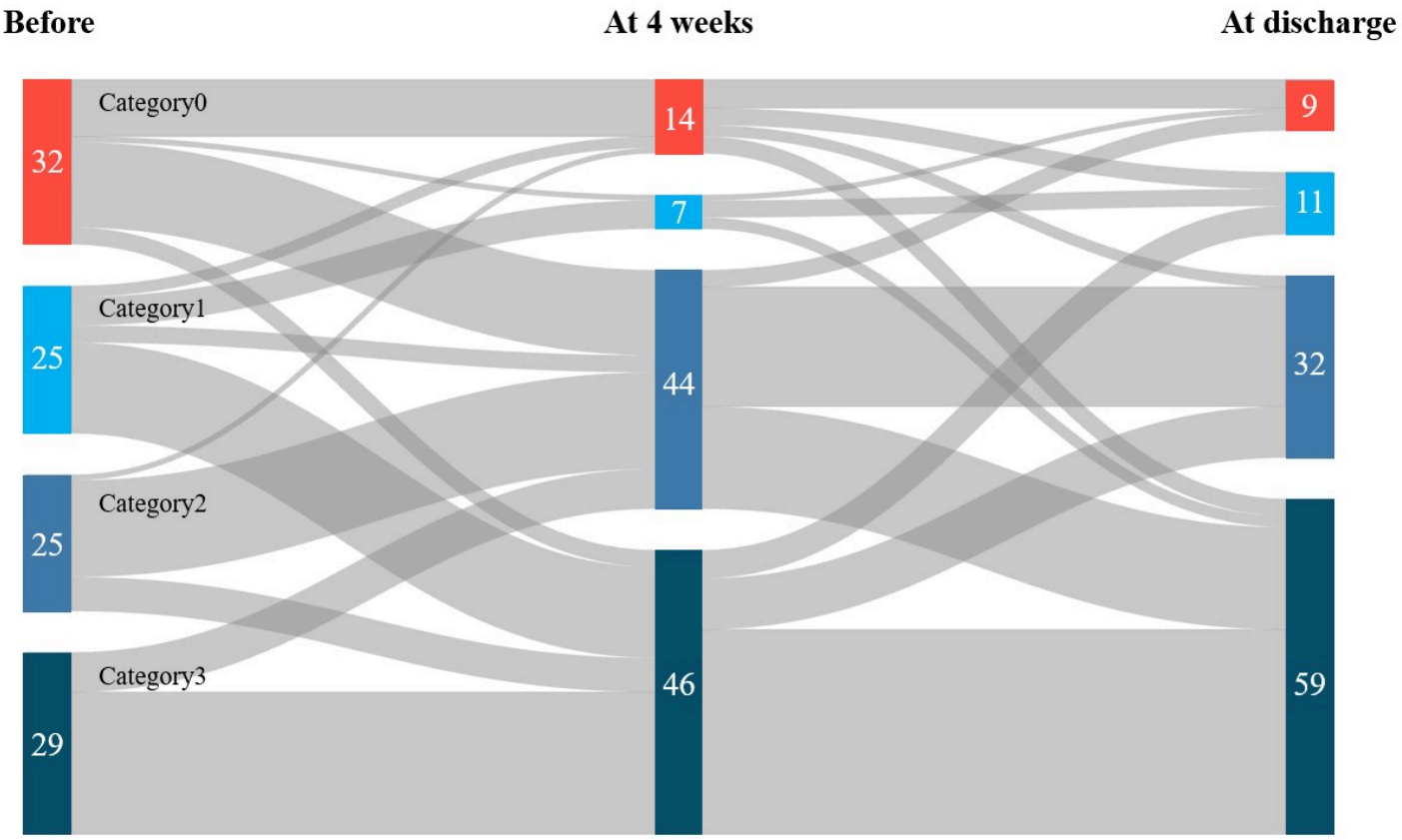


Figure 2

Changes in skeletal muscle categories from before transplantation through discharge

The Sankey diagram shows transitions among the four skeletal muscle categories before transplantation, 4 weeks after transplantation, and at discharge. The category distribution changed significantly between the pre-transplant assessment and discharge

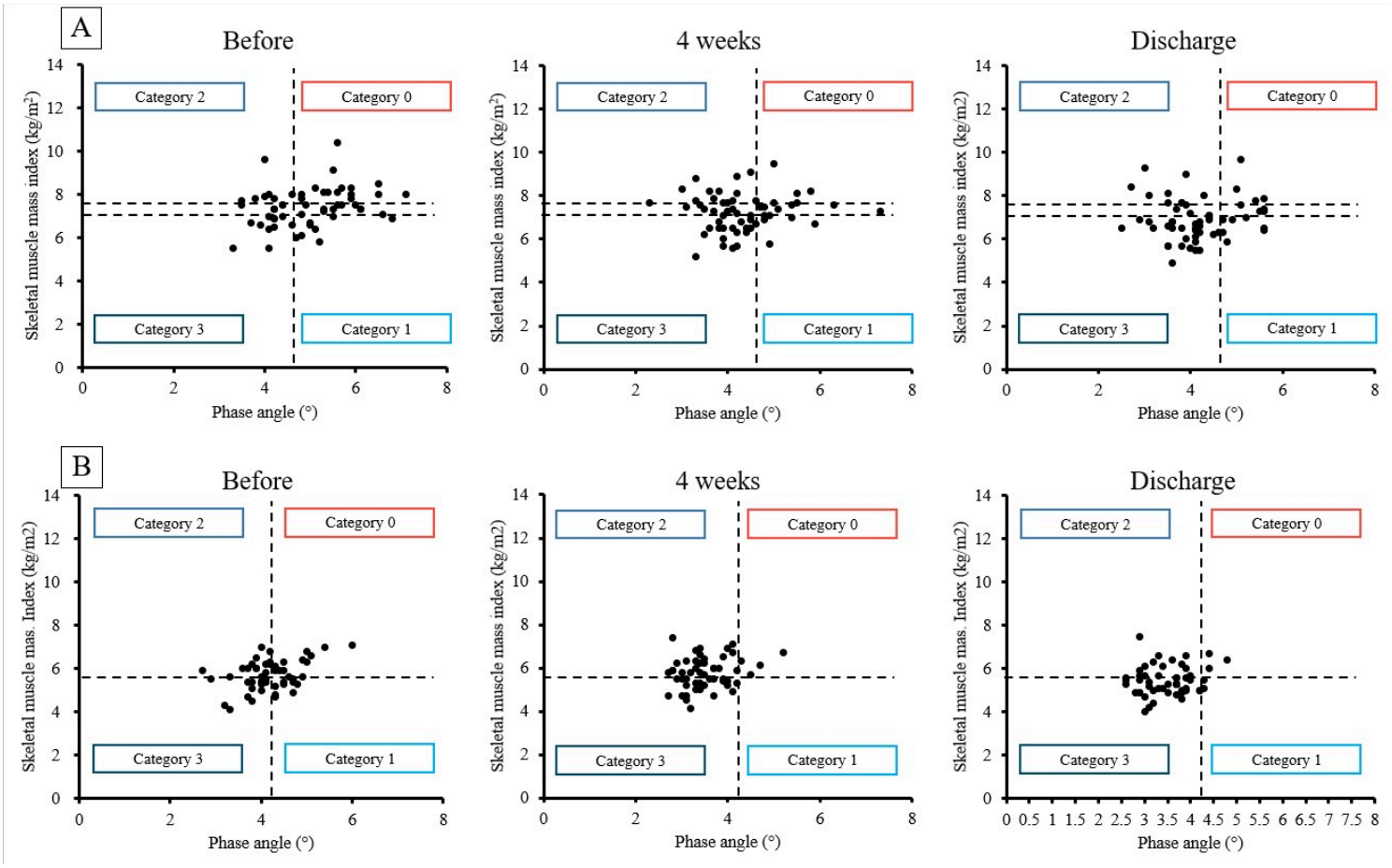


Figure 3

Sex-stratified distributions of SMI and phase angle from before transplantation through discharge

SMI and phase angle distributions are shown before transplantation, 4 weeks after transplantation, and at discharge. Both distributions shifted toward lower values after transplantation, with similar shifts in men (A) and women (B). SMI, skeletal muscle mass index

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx