ABSTRACT. Objective: Muscle atrophy is associated with autologous stem cell transplantation (ASCT)-related outcomes in patients with malignant lymphoma (ML). However, the impact of ASCT on muscle mass remains unclear in patients with ML. The aims of this study were to investigate changes in muscle mass and risk profiles for muscle atrophy after ASCT. Method: We enrolled 40 patients with refractory ML (age 58 [20-74] years, female/male 16/24, body mass index (BMI) 21.1 kg/m² [17.1-29.6]). Psoas muscle mass was assessed using the psoas muscle index (PMI) before and after ASCT. Statistical analysis used: Independent factors associated with a severe decrease rate of change in PMI were evaluated by decision-tree analysis, respectively. Results: PMI was significantly decreased after ASCT (4.61 vs. 4.55 cm²/m²; P=0.0425). According to the decision-tree analysis, the regimen was selected as the initial split. The rates of change in PMI were −5.57% and −3.97% for patients administered MCEC and LEED, respectively. In patients who were administered LEED, the second branching factor was BMI. In patients with BMI < 20.3 kg/m², the rate of change in PMI was −7.16%. On the other hand, the rate of change in PMI was 4.05% for patients with BMI ≥ 20.3 kg/m². Conclusion: We demonstrated that muscle mass decreased after ASCT in patients with ML. Patients who received MCEC and patients with low BMI were at risk for a decrease in muscle mass.

Key words: muscle atrophy, sarcopenia, skeletal muscle index, hematopoietic stem cell transplantation, hematologic malignancies

Sarcopenia is a complex syndrome characterized by the progressive and generalized decrease of skeletal muscle mass and strength[1,2]. The prevalence of sarcopenia ranges from 15% to 50% in patients with cancer, 30% to 45% in patients with liver failure, and 60% to 70% in critically ill intensive care patients[3]. Sarcopenia is associated with infectious complications, prolonged duration of mechanical ventilation, longer hospitalization, greater need for rehabilitation care after hospital discharge, and the pathogenesis of various diseases[3,4]. Furthermore, it is a major feature of cancer cachexia, and is also associated with a reduced quality of life (QOL) and survival[5].

Alongside sarcopenia, muscle atrophy has recently been identified as a poor prognostic factor for survival outcomes in cancer patients[6]. Muscle atrophy can impair the efficacy of many different therapeutic treatments[7]. In addition, treatment-related toxicity due to chemotherapy regimen-related toxicity (RRT) and lying in bed associated with cancer-related fatigue (CRF) are related[8]. CRF is the most commonly reported side effect in cancer patients. This debilitating fatigue often causes skeletal muscle loss with a reduction in overall physical activity, which can lead to a
Hematopoietic stem cell transplantation (HSCT) is a breakthrough curative treatment for patients with hematologic malignancies such as multiple myeloma and refractory malignant lymphoma (ML)\(^{10}\). However, the direct effects of malignancy, effects of chemotherapy/radiation, drug treatment, and sedentary behavior all likely contribute to increased fatigue after HSCT\(^{11}\). In this way, it is the most effective treatment for improving prognosis and QOL. However, HSCT aggravates muscle atrophy as a result of declining physical activity and toxicity due to high-dose chemotherapy\(^{12}\); the association between skeletal muscle reduction and clinical outcomes after HSCT have also been suggested\(^{15}\). There were several reports with regards to changes in skeletal muscle mass and the effects of exercise therapy after HSCT\(^{17}\). The association between skeletal muscle reduction clinical outcomes and prognosis after HSCT has also been suggested in the previous reports\(^{13,15,16}\). While patients with hematological malignancies are treated with HSCT, the influence of HSCT on skeletal muscle mass have not been previously described in detail despite the known relationship between auto-HSCT and muscle atrophy.

Therefore, the aims of this study were to investigate changes in skeletal muscle mass and its risk factors in patients with in-hospital ML after HSCT.

**Ethics**

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in the prior approval given by the institutional review board of Kurume University (Approval number: 18018). An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection. None of the patients were institutionalized.

**Subjects**

We identified 54 ML patients who, between May 2012 and December 2019, underwent autologous stem cell transplantation (ASCT) in Kurume University Hospital. Of these patients, 42 consecutive patients who underwent (1) 20 years of age or more, (2) undergoing rehabilitation or exercise, and (3) who underwent biochemical examination and an abdominal computed tomography (CT) scan including the third lumbar vertebrae level (L3) before and after ASCT were enrolled in this study. Two patients who (1) death during hospitalization and (2) severe complications of pneumonia were excluded from this study. After applying inclusion and exclusion criteria, 40 patients were enrolled (Figure 1).

**Evaluation of Skeletal Muscle Mass**

Skeletal muscle mass was measured by diagnostic CT scans at L3, as previously described\(^{15}\). The CT scans used for analysis were carried out as part of the ML assessment. The CT scans were obtained and evaluated for body com-
position data by two government-certified physical therapists who were blinded to the patients’ information under the guidance of a diagnostic radiologist. Skeletal muscle mass was evaluated by the psoas muscle index (PMI) index, and PMI was calculated by normalizing the L3 psoas muscle areas by the square of the height (m$^2$). This analysis was performed using the diagnostic software ImageJ. Muscle atrophy was defined as a PMI < 6.36 cm$^2$/m$^2$ for male or < 3.92 cm$^2$/m$^2$ for female, according to a previous report in Asian adults.

**Evaluation of Visceral Fat Area (VFA) and Subcutaneous Fat Area (SFA)**

VFA and SFA were measured as previously described. Briefly, the VFA and SFA were measured by diagnostic CT scanning at the umbilical crossing line. CT scan images had already been performed for the assessment of ML. Similarly, the VFA and SFA were measured using the diagnostic software ImageJ.

**Conditioning Regimen Administered Before ASCT**

Patients began treatment with upfront high-dose chemotherapy followed by ASCT after induction and consolidation chemotherapy. The conditioning regimen administered before ASCT was the LEED regimen, consisting of cyclophosphamide (60 mg/kg on days before ASCT 4 and 3), etoposide (250 mg/m$^2$ twice daily from days before ASCT 4 to 2), melphalan (130 mg/m$^2$ on the day before ASCT 1), and dexamethasone (40 mg/body from days before ASCT 4 to 1) and the MCEC regimen consisting of ranimustine (200 mg/m$^2$ on days before ASCT 8 and 3), carboplatin (300 mg/m$^2$ from days before ASCT 7 to 4), etoposide (500 mg/m$^2$ from days before ASCT 6 to 4), and cyclophosphamide (50 mg/kg on days before ASCT 3 and 2).

**Rate of Change in PMI**

To investigate changes in PMI before and after ASCT, the rate of change in PMI after ASCT relative to before ASCT was calculated.

**ASCT Rehabilitation Protocol**

To maintain physical ability during the hospitalization for ML treatment, enrolled patients were treated with equivalents/40 minutes/day of therapeutic exercise instructed by physical therapists certified for the rehabilitation of ML patients. The therapeutic exercise was developed according to the guidelines of the American College of Sports Medicine and our hospital cancer rehabilitation protocol. These therapeutic exercise protocols were performed in a clean room and consisted of the four types of exercise below:

1) **Stretching**

At the beginning of therapeutic exercise, patients performed a series of stretching exercises for 3 minutes, which targeted the quadriceps femoris muscles, hamstrings, and gastrocnemius. Static stretching was held for 10-20 seconds until the point of feeling tightness or slight discomfort.

2) **Strength training**

Patients participated in strength training targeting the lower limb muscles. Squat and standing calf raise were performed 20 times each.

3) **Balance training**

Patients practiced tandem stand or one-legged stand for 4 minutes.

4) **Endurance training.**

Finally, patients were trained with bicycle ergometers or walking for 10 minutes. The intensity of exercise was adjusted by 11-13 points on the Borg scale, a subjective rating of perceived exertion.

**Statistical Analysis**

Data are expressed as median (interquartile range [IQR]), range, or number. Changes in PMI before and after ASCT were evaluated by Wilcoxon signed-rank tests. Rate of change in skeletal muscle mass VFA and SFA were evaluated by the difference in PMI, VFA, and SFA between before and after ASCT. Besides, independent factors and a cutoff value of revealed risk factors associated with the rate of change in PMI were analyzed by using decision-tree analysis, as previously described. Decision tree analysis, the objective variable is the rate of change of PMI. Explanatory variables were selected from the following variables: age, sex, BMI, colonization of resistant bacteria, conditioning regimen, grip strength, rehabilitation implementation rate, VFA, SFA, levels of hemoglobin, albumin, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR). We examined the rate of change in PMI of each factor derived from the decision tree analysis using ANOVA analysis of variance followed by Tukey’s multiple comparison test. All analyses were performed using JMP Pro 13 (SAS Institute Inc., Cary, North Carolina, USA). The level of statistical significance was set at $P < 0.05$.

**Results**

**Patient Characteristics**

Patient characteristics are summarized in Table 1. The median age was 58 years, and the ratio of females to males was 1:1.5 (16/24). The median body mass index was 21.1 kg/m$^2$. The majority of patients had a performance status (PS) of 0 or 1 (PS0 = 42.5%; PS1 = 30.0%). Colonization of resistant bacterial infections occurred in 25% (10/40) of the enrolled patients. Patients began treatment with upfront high-dose chemotherapy followed by ASCT after induction and consolidation chemotherapy. The conditioning regimen administered before ASCT was 37.5% and 62.5% for LEED and MCEC, respectively. The median level of PMI
before ASCT was 3.75 cm\(^2\)/m\(^2\) in female patients and 5.82 cm\(^2\)/m\(^2\) in male patients (Table 1).

**Differences in Variables Before and After ASCT**

The median period of hospitalization was 24 days (range: 17-126 days). During this period, all patients underwent cancer rehabilitation and a significant decrease was observed in PMI (Figure 2). Table 2 shows a summary of differences in body composition, and biochemical examinations before and after ASCT. During hospitalization, BMI, VFA, SFA, and grip strength decreased significantly (Table 2), along with red blood cell count and platelet count. Additionally, serum albumin and total protein levels significantly decreased during hospitalization. However, no change was seen in BUN, creatinine, and eGFR levels during hospitalization (Table 2).

**Decision Tree Analysis for Rate of Change in PMI**

To clarify the clinical profile of the reduction in PMI, a decision-tree analysis was created using two divergence variables to classify three groups of patients (Figure 3). According to the decision-tree analysis, the regimen was selected as the initial split. In patients administered MCEC, the median rate of change in PMI was \(-5.57\%\). In patients administered LEED, the median rate of change in PMI was \(-3.97\%\) and the second branching factor was BMI. In patients with BMI < 20.3 kg/m\(^2\), skeletal muscle decrease was observed and the median rate of change in PMI was \(-7.16\%). Conversely, Patients with BMI \(\geq 20.3\) kg/m\(^2\) had increased PMI, with the median rate of change of 4.05% (Figure 3).

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Reference Value</th>
<th>Median (IQR)</th>
<th>Range (min–max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 (52–67)</td>
<td>20–74</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>16/24</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>18.5-24.9</td>
<td>17.1–29.6</td>
</tr>
<tr>
<td>Performance Status (0/1/2/3/4)</td>
<td>21.1 (19.8–23.2)</td>
<td>(17/12/9/2)</td>
</tr>
<tr>
<td>PMI (female) (cm(^2)/m(^2))</td>
<td>(\geq 3.92)</td>
<td>2.19–4.92</td>
</tr>
<tr>
<td>PMI (male) (cm(^2)/m(^2))</td>
<td>(\geq 6.36)</td>
<td>3.02–9.00</td>
</tr>
<tr>
<td>PMI (low/normal)</td>
<td>24/16</td>
<td></td>
</tr>
<tr>
<td>Colonization of resistant bacteria (yes/no)</td>
<td>10/30</td>
<td></td>
</tr>
<tr>
<td>Regimen (LEED/MCEC)</td>
<td>15/25</td>
<td></td>
</tr>
<tr>
<td>Bathel index</td>
<td>100 (100–100)</td>
<td>85–100</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>24 (21–35)</td>
<td>17–126</td>
</tr>
<tr>
<td>Period to engagement (days)</td>
<td>11 (10–11)</td>
<td>10–25</td>
</tr>
<tr>
<td>Rehabilitation implementation rate (%)</td>
<td>72.5 (58.2–81.5)</td>
<td>12.5–100</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; BMI, body mass index; PMI, psoas muscle index.

### Difference in Rate of Change in PMI for Factors Derived from the Decision Tree Analysis

In Table 3, we clarified the rate of change in PMI patients with MCEC (Group 1), LEED/BMI < 20.3 kg/m\(^2\) (Group 2), and LEED/BMI \(\geq 20.3\) kg/m\(^2\) (Group 3) derived from the decision tree analysis (Table 3). The ANOVA analysis of the rate of change in PMI was found to be significant (Table 3). Concerning the rate of change for PMI in Tukey’s multiple comparison test, Group 1 was significantly lower than Group 3. There was no significant difference between Groups 1 and 2. Also, no significant difference was seen in Groups 2 and 3 (Table 3).

### Discussion

In this study, we demonstrated that skeletal muscle mass after ASCT was significantly decreased compared to that before ASCT in ML patients. Besides, we revealed that regimen and BMI before ASCT, but not age and sex, were factors associated with PMI. Thus, ML patients with “administered MCEC regimen” and “administered LEED regimens with BMI < 21.3 kg/m\(^2\)” were at risk for decreased skeletal muscle mass after ASCT.

PMI significantly decreased after ASCT. Patients who undergo HSCT frequently experience considerable deterioration of their health status as a result of high-dose chemotherapy, resulting in reduced physical activity. Physical inactivity is sufficient to cause prolonged, physical dysfunction, muscle atrophy, and weakness. In addition, muscle atrophy that occurs frequently during ASCT hospitalization has been suggested to be related to nutritional intake. Similarly, serum albumin levels also decreased significantly in enrolled patients. A decrease in serum albumin level also occurs after ASCT, similar to a previous re-
Table 2. Differences in body composition, muscle mass, and biochemical examinations before and after ASCT

<table>
<thead>
<tr>
<th></th>
<th>Before ASCT</th>
<th></th>
<th>After ASCT</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Range (min–max)</td>
<td>Median (IQR)</td>
<td>Range (min–max)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.1 (19.8–23.2)</td>
<td>17.1–29.6</td>
<td>19.9 (18.4–22.3)</td>
<td>15.9–27.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td>54.0 (27.2–85.9)</td>
<td>7.3–200.2</td>
<td>50.3 (19.4–85.1)</td>
<td>4.85–189.4</td>
<td>0.0318</td>
</tr>
<tr>
<td>SFA (cm²)</td>
<td>92.2 (55.0–143.3)</td>
<td>15.0–296.7</td>
<td>84.3 (51.3–130.0)</td>
<td>19.0–270.3</td>
<td>0.0035</td>
</tr>
<tr>
<td>Grip strength (female) (Kg)</td>
<td>18.9 (16.3–23.5)</td>
<td>7.1–30.2</td>
<td>16.4 (13.0–20.3)</td>
<td>9.4–28.3</td>
<td>0.0117</td>
</tr>
<tr>
<td>Grip strength (male) (Kg)</td>
<td>31.5 (28.8–38.5)</td>
<td>22.4–45.5</td>
<td>29.1 (26.7–34.1)</td>
<td>13.7–41.8</td>
<td>0.0151</td>
</tr>
<tr>
<td>Red blood cell count (×10⁰/μL)</td>
<td>307 (280–345)</td>
<td>230–473</td>
<td>288 (258–316)</td>
<td>217–392</td>
<td>0.007</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9 (8.6–10.9)</td>
<td>7.2–14.1</td>
<td>9.0 (8.2–10.0)</td>
<td>6.8–12.2</td>
<td>0.148</td>
</tr>
<tr>
<td>White blood cell count (μL)</td>
<td>4000 (2625–4875)</td>
<td>1500–20500</td>
<td>4400 (3200–5100)</td>
<td>1100–12000</td>
<td>0.8144</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>17.1–29.6</td>
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<td>4400 (3200–5100)</td>
<td>1100–12000</td>
<td>0.8144</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ASCT, autologous peripheral blood stem cell transplantation; BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Figure 2. Changes in PMI, before and after ASCT. Abbreviations: PMI, psoas muscle index.

The serum albumin level is a negative acute-phase protein that decreases in concentration with ongoing systemic inflammation, poor health, and malnutrition. Because these unfavorable conditions lead to decrease in skeletal muscle mass, low albumin concentrations might reflect low muscle mass. The results of the present study are consistent with these findings and indicate that low serum albumin levels may serve as an early warning sign of muscle atrophy. Thus, our data were in good agreement with previous reports and indicate that rapid depletion occurs in patients with ML who have undergone ASCT. Moreover, a decrease in serum albumin levels has been reported to be associated with prognosis, and requires further investigation. Thus, in patients who underwent ASCT may experience muscle atrophy alongside reduced physical activity and malnutrition.

In this study, a conditioning regimen was administered before the ASCT was selected as the variable for the initial split for the change rate in PMI. It remains unclear why the rate of change in PMI was significantly lower in patients administered MCEC than in patients administered LEED. Sarcopenia, including skeletal muscle atrophy, is associated with RRT in cancer patients. Factors associated with RRT include the type of chemotherapy and dosage and duration of administration. Administered regimen MCEC has a higher dose and frequency of chemotherapy than Adminis-
Table 3. Rate of change in PMI of “MCEC Group”, “LEED/BMI<20.3 kg/m² Group” and “LEED/BMI≥20.3 kg/m² Group” patients with ML

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Group1 MCEC</th>
<th>Group2 LEED/BMI&lt;20.3 kg/m²</th>
<th>Group3 LEED/BMI≥20.3 kg/m²</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>25</td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Rate of change in PMI (%)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>0.0196</td>
</tr>
<tr>
<td>All Patients</td>
<td>n=40</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median: -4.79%</td>
<td>9.86 to -0.14%</td>
<td>42.93 to 26.21%</td>
<td></td>
</tr>
</tbody>
</table>

†Group 1 vs. Group 3; P<0.05

Abbreviations: IQR, interquartile range; BMI, body mass index; PMI, psoas muscle index.

Figure 3. Decision-tree analysis for rate of change in PMI patients with ML underwent ASCT.

Abbreviations: IQR, interquartile range; PMI, psoas muscle index.
sociated with an increased risk of febrile neutropenia. And, febrile neutropenia has been reported to be associated with decreased skeletal muscle mass\(^6\). Thus, patients with low BMI or frailty may experience skeletal muscle loss after ASCT.

This study has several limitations. First, this was an observational study conducted at a single center. Second, due to the retrospective nature of the study, the CT evaluation date and hospitalization for ASCT were not constant. Third, physical activity in daily living and several nutrition-related factors were not evaluated. Fourth, this study included only a limited number of patients, therefore the risk factors for skeletal muscle atrophy could not be examined by multivariate analysis, and prognostic studies were inadequate. Thus, there is a possibility of selection bias, suggesting that further prospective multicenter validation studies that include physical activity and nutritional assessment are required for patients in various conditions. Moreover, a prognosis study of skeletal muscle loss during the HSCT period is also needed.

**Conclusion**

In conclusion, we demonstrated that skeletal muscle mass was significantly decreased before and after ASCT in patients with ML. Moreover, we found that BMI and a conditioning regimen administered before the ASCT were both associated with muscle atrophy. Thus, patients who were administered MCEC and patients with low BMI who were administered LEED were at risk of decreased skeletal muscle mass after ASCT. Therefore, cancer prehabilitation, including nutrition therapy, before ASCT would be useful for maintaining skeletal muscle mass in patients with ML preparing for ACST.

**Conflict of Interest:** There is no conflict of interest to disclose.

**References**