Sarcopenia and risk of infection in adult heart transplant recipients in Japan

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Abstract

Aims Heart transplantation (HT) is an effective therapeutic option for end-stage heart failure. Infection is a major cause of morbidity and mortality after HT. Sarcopenia, defined as the loss of muscle mass and strength, is a common comorbidity in HT candidates with end-stage heart failure. However, the effects of sarcopenia on the occurrence of post-HT infections are not well understood. Therefore, we explored the association between the skeletal muscle mass and post-transplant infections in adult HT recipients.

Methods and results We retrospectively examined the records of 135 patients who underwent HT between August 2007 and November 2019 at our institution. Pre-transplant computed tomography was used to calculate the skeletal muscle index (SMI) at the level of the third lumbar vertebra. Muscle wasting was defined as the SMI of the lowest sex-based tertiles. The primary endpoint was infections within 6 months of HT. The study included 109 patients (80 men, mean age: 41.6 ± 12.0 years): 37 patients in the muscle wasting group and 72 patients in the non-muscle wasting group. The mean SMI values in the muscle wasting and non-muscle wasting groups were 29.9 ± 4.8 cm²/m² and 40.7 ± 6.7 cm²/m², respectively. Prior to HT, 108 (99.1%) patients were on left ventricular assist device support, and during that support, the rate of late right heart failure was significantly higher in the muscle wasting group than non-muscle wasting group (P = 0.012). Sixteen infections occurred within 6 months of HT. The most common infection sites included the respiratory tract (n = 5) and the upper gastrointestinal tract (n = 5), followed by the urinary tract (n = 4). Overall, 10 patients experienced infections in the muscle wasting group (27.0%) and 6 in the non-muscle wasting group (8.3%) (P = 0.009). Two patients in the muscle wasting group required intensive care unit admission, compared to none in the non-muscle wasting group. Low skeletal muscle mass was associated with infections in the univariate and multivariate logistic regression models (hazard ratio: 3.68, 95% confidence interval: 1.19–11.3; P = 0.023). However, the duration of all-cause mortality within 3 years did not differ between the groups (P = 0.56).

Conclusions Low skeletal muscle mass is a predictor of post-HT infections within 6 months of HT.

Keywords Heart failure; Heart transplantation; Infection; Sarcopenia

Introduction

Heart transplantation (HT) improves survival and quality of life in patients with end-stage heart failure.1 One-year survival rate of 91% and a median survival of 12 to 13 years have been reported.2 Despite advances in immunosuppressive therapy and anti-microbial prophylaxis, HT recipients remain at a high risk for infection, which can result in morbidity and mortality. Infection, especially during the period immediately after HT, is a leading cause of death, and its prevention contributes to improved outcomes.3 While the number of patients with end-stage heart failure who require HT has been
increasing in Japan, the number of donor hearts has not increased significantly; therefore, risk stratification and optimal patient selection for HT are crucial to maximize donor heart utilization.

Recently, the role of frailty in cardiovascular disease has been recognized, and pre-transplant frailty has been observed to be associated with increased mortality after HT. Sarcopenia, first described by Rosenberg in 1989, is defined as the loss of muscle mass and strength that occurs with aging and is a notable phenotype of frailty. Sarcopenia is now classified into primary and secondary categories. Primary sarcopenia is caused by age-related physical inactivity, impaired mobility, and malnutrition. On the other hand, secondary sarcopenia is related with various chronic diseases and is highly prevalent in patients with chronic heart failure. Several factors contribute to the development of sarcopenia in heart failure patients, such as malnutrition, hormonal change, inflammation, oxidative stress, apoptosis, overactivation of ubiquitin-proteasome system, low muscle blood flow, and endothelial dysfunction.

Sarcopenia is also observed in candidates for solid organ transplantation and is reported to be associated with poor outcomes following liver, kidney, and lung transplantations. Preoperative sarcopenia was found to be associated with an increased risk of infection after liver transplantation. However, there are few studies on sarcopenia in HT recipients, and the influence of sarcopenia on the occurrence of post-HT infections has not been well investigated. Therefore, we performed this study to explore the association between sarcopenia and post-transplant infections in HT recipients.

**Methods**

We reviewed the records of patients who underwent orthotopic HT at the University of Tokyo between August 2007 and December 2019. We excluded patients who were younger than 18 years of age, presented with neuromuscular diseases, died in the hospital, or were not discharged within 6 months from HT.

The muscle mass was assessed using computed tomography (CT), which was performed within 150 days before HT. We assessed the skeletal muscle area (SMA) at the level of the third lumbar vertebra (L3), as previously described. The muscles in the area included the psoas and paraspinal muscles, erector spinae, quadratus lumborum, transversus abdominis, obliquus externus abdominis, obliquus internus abdominis, and rectus abdominis. We analysed the CT images using ImageJ v1.42q (National Institutes of Health, http://rsb.info.nih.gov/ij). The cross-sectional SMAs were measured based on the attenuation thresholds of −29 to +150 Hounsfield units. We calculated the skeletal muscle indices (SMIs, cm²/m²) by normalizing the SMA by height in meters. Patients were categorized into the muscle wasting group if their SMIs were in the lowest sex-based tertile. We examined the clinical characteristics and outcomes between the muscle wasting group and non-muscle wasting group.

Fasting blood samples were collected within 3 days before HT for laboratory investigations, and each laboratory parameter was assessed using the standard laboratory methods at the University of Tokyo Hospital (Tokyo, Japan). The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (approval number: 2650) of the University of Tokyo. Informed consent was obtained from all patients.

**Immunosuppressive therapy**

Heart transplantation was performed according to the standard procedures using the modified bicaval anastomosis technique. In accordance with the institutional policy, induction therapy was not performed routinely. All patients received a standard immunosuppressive regimen, which included a calcineurin inhibitor (CNI), mycophenolate mofetil (MMF), and prednisolone. Some recipients received everolimus with or without discontinuation of MMF or reduction of CNI for coronary allograft vasculopathy, severe renal failure, intractable gastrointestinal symptoms, and refractory rejection. The doses of these immunosuppressants were based on scheduled monitoring of trough concentrations, as described previously. The prednisolone dose was reduced stepwise to 5 to 10 mg by 6 months when cardiac allograft rejection, as assessed by endomyocardial biopsy, was negative or mild.

**Endomyocardial biopsy**

Cardiac allograft rejections were determined using endomyocardial biopsies. Beginning on postoperative day 7 following HT, endomyocardial biopsies of the right ventricle were performed every week for the first month, every 2 weeks until 3 months, and every month up to 6 months (1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 weeks after HT). From October 2019, the schedule of endomyocardial biopsy was changed to 1, 2, 3, 4, 6, 8, 12, 18, and 24 weeks after HT. When moderate-to-severe acute cellular rejection (ACR) was identified, methylprednisolone pulse therapy was initiated at 1000 mg/day for 3 days, and the immunosuppressive regimen was optimized. Endomyocardial biopsy was repeated 1 week later and continued until resolution of the moderate-to-severe ACR.

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Prophylaxis

In cases in which the donor was positive for Cytomegalovirus (CMV) antibodies and the recipient was negative (CMV mismatch), patients were prescribed oral valganciclovir for 3 months from April 2016. Acyclovir was used to prevent infections due to Herpes simplex and Varicella zoster. For prophylaxis against Pneumocystis jiroveci, all recipients were prescribed trimethoprim-sulfamethoxazole, atovaquone, or pentamidine inhalation. For prophylaxis against fungal infections, patients were prescribed oral miconazole, amphoterin B, or itraconazole.

Outcome and definitions

The primary outcomes were severe infections within 6 months of HT. We defined severe infections as those that required hospitalization and intravenous or prolonged courses of antimicrobials. The diagnosis of every specific type of infection, including respiratory tract, gastrointestinal tract (GI), urinary tract and skin or soft tissue infections, was made according to the Centers for Disease Control and Prevention/National Healthcare Safety Network criteria. CMV disease was defined as the presence of clinical signs or symptoms along with the documentation of CMV in the relevant tissues. The presence of CMV antigen was not used to diagnose CMV disease. We also compared the survival between the two groups following HT within 3 years or until 31 May 2020.

Statistical analysis

Data are presented as means ± standard deviation or medians with interquartile ranges. Statistical analyses were performed using JMP pro v14 (SAS Institute, Cary, NC, USA). A P-value < 0.05 was considered statistically significant. We evaluate the differences between the two groups using the Student’s t-test or the Mann-Whitney U test for continuous variables and the χ² test for categorical variables. Univariate and multivariate analyses were performed using a logistic regression model to identify the risk factors for infections that occurred within 6 months after HT. Variables with P < 0.05 in the univariate analysis were included in the final multivariate analysis. All continuous parameters were dichotomized at the 25th, 33rd, 50th, and 75th percentiles, and the percentile value with the lowest P-value was chosen as the threshold for the analysis. The Kaplan–Meier method was used to estimate survival within 3 years and the log-rank tests were used to compare the survival between the two groups.

Results

Patient characteristics

One hundred and thirty-five patients underwent HT during the study period. Of these, 14 patients were younger than 18 years of age, two had neuromuscular diseases, two were not discharged within 6 months, two died in the hospital, and six lacked abdominal CT data. After excluding these patients, the final study cohort included 109 patients. Our study population consisted of 80 (73.4%) men and 29 (26.6%) women. The overall mean age was 41.6 ± 12.0 years. The most common aetiology of heart failure was non-ischaemic dilated cardiomyopathy.

The overall mean SMA was 103.9 ± 27.8 cm², and the mean SMI was 37.1 ± 8.0 cm²/m². The overall mean SMA and the mean SMI in men were 115.5 ± 22.1 cm² and 39.8 ± 6.9 cm²/m², respectively, and in women were 71.9 ± 13.1 cm² and 29.4 ± 5.3 cm²/m², respectively. The SMI cut-off value was 36.3 cm²/m² in men and 28.3 cm²/m² in women. Subsequently, 37 (33.9%) patients were categorized into the muscle wasting group and 72 (66.1%) patients into the non-muscle wasting group (Figure 1).

Table 1 summarizes the baseline patient characteristics in each group. The mean SMA values in the muscle wasting and non-muscle wasting groups were 83.9 ± 18.4 cm² and 114.2 ± 26.2 cm², respectively. The mean SMI values in the muscle wasting and non-muscle wasting groups were 29.9 ± 4.8 cm²/m² and 40.7 ± 6.7 cm²/m², respectively. The body weight, body mass index, and body surface area were significantly lower in the muscle wasting group. The serum haemoglobin and glycosylated haemoglobin levels were significantly lower in the muscle wasting group; however, other laboratory data including CMV mismatch and Epstein–Barr virus-negative serostatus of donor were similar between the two groups.

Overall, 108 (99.1%) patients required left ventricular assist devices (LVADs) before HT. At the time of HT, 83 patients had implantable LVADs, while the remaining 25 patients had paracorporeal LVADs. Three patients were supported by a biventricular assist device: two in the muscle wasting group and one in the non-muscle wasting group.

We assessed the readmission events during LVAD support (Figure 2). The duration of implantable and paracorporeal LVAD support was 1178 ± 385 days in the muscle wasting group and 1162 ± 411 days in the non-muscle wasting group (P = 0.84). The rates of readmission for cerebrovascular disease and driveline infection did not differ; however, that for late right heart failure (RHF), as defined in a previous report, was significantly higher in the muscle wasting group (P = 0.012).
**Post-transplant course**

The lengths of hospital and intensive care unit stay following HT were similar between the two groups. Two patients required induction therapy with basiliximab for renal dysfunction. Table 2 summarizes the immunosuppressive therapy and the number of moderate-to-severe ACR episodes. Some patients required an immunosuppressive regimen of CNI, MMF, everolimus, and prednisolone (multiple immunosuppressive therapy) for intractable rejection. There was no difference in the immunosuppressive regimen at baseline and at 6 months after HT. The trough concentrations of CNI at 3 and 6 months after HT were similar. However, the dose of prednisolone at 6 months was higher in the muscle wasting group. The number of moderate-to-severe ACR episodes did not differ between the groups.

**Post-transplant infections**

Sixteen patients experienced infection within 6 months of HT: 10 (27.0%) in the muscle wasting group vs. 6 (8.3%) in the non-muscle wasting group; \( P = 0.009 \). The median hospital length of stay due to infection was 18 (14–34) days in muscle wasting group and 17 (10–18) days in non-muscle wasting group. Two patients required intensive care unit admission in the muscle wasting group compared with none in the non-muscle wasting group.

The sites of infection and the causative organisms are summarized in Table 3. The most common infection sites included the respiratory tract \( (n = 5) \) and the upper GI \( (n = 5) \), followed by the urinary tract \( (n = 4) \). Bacterial and viral infections were observed in six and five cases, respectively. All bacterial infections occurred in the muscle wasting group and were caused by Gram-negative bacteria: *Klebsiella pneumoniae* \( (n = 5) \), *Enterobacter aerogenes* \( (n = 2) \), and *Pseudomonas aeruginosa* \( (n = 1) \). Two patients experienced blood stream infections complicated by urinary tract infections.

Viral infections were all caused by CMV (three cases each in the muscle wasting group and the non-muscle wasting group). The sites of CMV involvement included multiple organs \( (n = 3) \), lung and upper GI \( (n = 1) \), and upper and lower GI \( (n = 2) \).

**Risk factors of post-transplant infections**

We evaluated the clinical characteristics associated with infections that occurred within 6 months of HT. The results of the logistic regression analysis are summarized in Table 4. Muscle wasting was a predictor of infections in both univariate and multivariate analyses (hazard ratio: 3.68, 95% confidence interval: 1.19–11.3; \( P = 0.023 \)).
Post-transplant survival

The mean follow-up period was 886 ± 312 days. During this period, four (3.7%) patients died: two (5.4%) with muscle wasting and two (2.8%) without muscle wasting. Kaplan–Meier curves comparing the 3-year survival between the two groups demonstrated no differences in the mortality ($P = 0.56$, Figure 3).

Discussion

To our knowledge, this is the first report to demonstrate a relationship between skeletal muscle mass and infections following HT. We observed that 14.7% of the HT recipients experienced infections within 6 months. Infections were significantly more common in HT recipients with muscle wasting than in those without. Muscle wasting before HT
Figure 2  The rate of complications during LVAD support.

Table 2  Immunosuppressive therapy and ACR episodes in patients with and without muscle wasting

|                          | Muscle wasting group | Non-muscle wasting group | P-value |
|--------------------------|----------------------|--------------------------|---------|
| **CNI at baseline**      |                      |                          |         |
| TAC                      | 18 (49%)             | 40 (56%)                 | 0.49    |
| CYA                      | 19 (51%)             | 32 (44%)                 |         |
| **Immunosuppression at 6 months** |                   |                          |         |
| TAC                      | 18 (49%)             | 41 (58%)                 | 0.37    |
| EVL                      | 25 (68%)             | 37 (52%)                 | 0.12    |
| MMF                      | 14 (20%)             | 39 (55%)                 | 0.09    |
| PSL                      | 36 (97%)             | 71 (100%)                | 0.16    |
| Multiple immunosuppression | 2 (5%)              | 5 (7%)                   | 0.74    |
| **Trough concentrations of TAC (ng/mL)** |                 |                          |         |
| 3 months                 | 11.1 ± 3.1           | 12.0 ± 3.1               | 0.36    |
| 6 months                 | 10.5 ± 3.0           | 11.0 ± 3.6               | 0.66    |
| **Trough concentrations of CYA (ng/mL)** |                 |                          |         |
| 3 months                 | 278.6 ± 72.2         | 280.2 ± 69.9             | 0.94    |
| 6 months                 | 226.8 ± 71.5         | 260.0 ± 74.1             | 0.14    |
| **PSL dose per day**     |                      |                          |         |
| 3 months                 | 10.4 ± 5.3           | 9.7 ± 5.4                | 0.52    |
| 6 months                 | 8.3 ± 4.5            | 6.3 ± 3.2                | 0.011   |
| ACR episode              | 14 (38%)             | 35 (49%)                 | 0.28    |

ACR, acute cellular rejection; CNI, calcineurin inhibitor; CYA, cyclosporine; EVL, everolimus; MMF, mycophenolate mofetil; PSL, prednisolone; TAC, tacrolimus.

Table 3  Pathogens and sites of infections within 6 months of HT

|                        | Klebsiella pneumoniae | Enterobacter aerogenes | Pseudomonas aeruginosa | CMV | Mucor species | Unknown | Total |
|------------------------|-----------------------|------------------------|------------------------|-----|---------------|---------|-------|
| Respiratory            | 1                     | 0                      | 0                      | 1   | 1             | 2       | 5     |
| Upper GI               | 0                     | 0                      | 0                      | 5   | 0             | 0       | 5     |
| Lower GI               | 0                     | 0                      | 0                      | 3   | 0             | 0       | 3     |
| Urinary tract          | 3                     | 1                      | 0                      | 0   | 0             | 0       | 4     |
| Surgical wound         | 0                     | 0                      | 1                      | 0   | 0             | 1       | 2     |
| Blood stream           | 1                     | 1                      | 0                      | 0   | 0             | 0       | 2     |
| Total                  | 5                     | 2                      | 1                      | 9   | 1             | 3       | 21    |

GI, gastrointestinal tract.
was associated with development of infections within 6 months of HT.

Right heart failure during left ventricular assist device support

In Japan, most patients awaiting HT are supported with LVAD due to donor shortage. In our study, all patients except one were supported by LVAD before HT, over a period of 3 years. In our analysis, the rate of readmission for late RHF during LVAD implantation was significantly higher in the muscle wasting group than in the non-muscle wasting group.

Right heart failure was related with cardiac cachexia, which is characterized by severe loss of body weight and fat, bone, and muscle mass due to heart failure. Increased right atrial pressure leads to venous congestion, which results in liver dysfunction and intestinal congestion. Liver dysfunction is associated with reduced protein synthesis, while intestinal congestion is associated with gut dysbiosis, appetite loss, postprandial fullness, and malabsorption. Although LVAD implantation improves nutrition status and muscle function, late RHF prevents the improvement in these pa-
Sarcopenia and immunity

Sarcopenia is associated with various pathophysiological mechanisms, and inflammation plays a key role. Low-grade inflammation increases serum levels of inflammatory markers, such as interleukin (IL)-6, tumour necrosis factor alpha, and C-reactive protein, which are linked to activation of the ubiquitin-proteasome system, resulting in muscle catabolism and muscle atrophy.

Sarcopenia is also associated with impairment of the immune system via inflammation. Skeletal muscle is considered a secretory organ because myocytes secrete myokines, such as IL-6, IL-7, and IL-15, which modulate the immune system. IL-6 produced by macrophages leads to inflammation, while that produced by muscle lymph cells do not activate the inflammatory pathway; instead, it stimulates anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist. IL-7 is associated with the development and maintenance of immature lymphocytes, and IL-15 is required for the development and survival of natural killer cells. The secretion of these myokines, which helps in maintaining immune function, is reduced in patients with low skeletal muscle mass.

Inflammation also affects the adaptive immune system. CD8+ T-cells, such as cytotoxic T lymphocytes, are important in the defence against intracellular pathogens, including viruses and bacteria. IL-15 modulates CD8+ T-cell homeostasis, and a reduced number of CD8+ T-cells are present in patients with low muscle mass. Therefore, sarcopenia is closely linked to impairments in both innate and adaptive immunities.

Post-transplant infections and mortality

We observed no correlations between skeletal muscle mass and mortality. It was demonstrated that a low psoas muscle area was an independent predictor of mortality following HT. Survival rates in Japan are better than those reported by the international registry. In our study, in-hospital deaths were excluded, and the number of deaths was small; therefore, we need more robust studies to investigate the relationship between skeletal muscle mass and mortality.

The incidence of post-transplant infection varies depending upon the definition of infections and the duration of follow-up. Our study had a lower incidence of infections compared with previous studies, which may be due to the shorter follow-up period and the fact that we did not record perioperative infections. Previous studies have reported that infections were commonly due to bacteria and viruses, and Gram-negative bacteria were the most frequent causative organisms. The respiratory tract, urinary tract, blood, and GI system were the major sites of infections. Similar characteristics of pathogens and sites of infection were observed in our study.

Furthermore, CMV accounted for 31% of the infections in our study, with GI being the most commonly affected site. There were three cases of CMV disease in both groups; however, two cases in the non-muscle wasting group did not receive valganciclovir despite CMV mismatch because of the prophylaxis protocol before 2016, and it is possible that these cases might have been preventable. CMV infection is mainly controlled by cytotoxic CD8+ T-cells. The severity of CMV infection and the extent of organ involvement are inversely correlated with the restoration of an efficient CD8+ T-cell immune response.

Besides CD8 expression, CD28 expression, a co-stimulatory molecule for T-cell activation and survival, is required for CMV infection control. Furthermore, CD8+ and CD28− T-cell alterations have been reported in frail patients. Low skeletal muscle mass is a major component of frailty and may be involved in CD28 expression.

Coronavirus disease 2019

The coronavirus disease 2019 (COVID-19) pandemic has spread worldwide. Although no cases of COVID-19 were identified within 6 months of HT in our population, one patient experienced non-severe COVID-19 5 years after HT.

The severity of COVID-19 and the mortality associated with it were higher in recipients of solid organ transplants than in nontransplant recipients. A mortality rate of 15% was reported in HT recipients with COVID-19. The use of ‘triple therapy regimen’, including CNI, antimetabolite, and prednisone, was associated with a 7.3-fold risk of severe disease and a 17.8-fold increased risk of death. However, the relationship between immunosuppressive regimen and COVID-19, and appropriate immunosuppressive management, needs further validation. Sarcopenia evaluated by chest CT scans was independently associated with prolonged hospital stay and death in patients with COVID-19.

Treatment approach to sarcopenia

Interventions for sarcopenia with heart failure are crucial to improve prognosis after HT. Exercise training is highly recommended for patients with heart failure. Preoperative exercise training prevents physical deconditioning while being on the heart transplant waiting list and post-surgical complications in patients undergoing non-urgent cardiovascular procedures. The safety and efficacy of exercise training have also been reported in patients with an LVAD.

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Although some preliminary data exist, specific nutritional support in sarcopenic patients with heart failure is still unclear. Adequate energy protein intake with essential amino acid supplementation improved exercise capacity.\textsuperscript{34} Skeletal muscle dysfunction is linked to impaired growth hormone/insulin-like growth factor signalling and low testosterone levels. Therefore, testosterone, growth hormone, vitamin D are under study as a treatment for sarcopenia in heart failure patients. However, there is no established treatment yet.\textsuperscript{35}

**Limitations**

This study has several limitations that must be considered. First, this was a retrospective study at a single centre with a small number of patients. Second, the biopsy schedule and prophylaxis protocol changed during the study period, which affected the immunosuppressive regimen and outcomes. Third, there was selection bias as CT was not performed in all HT patients. Fourth, the timing of CT varied between patients, and the median number of days between CT and HT was 1 (1–10 days). Finally, a single observer measured the muscle mass in all patients and our intraobserver reliability analysis for the value of SMI yielded an intraclass correlation of 0.95.

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**Conclusions**

Skeletal muscle mass measurement should be considered for infection risk stratification in HT candidates. It can be used to establish a strategy for preventing skeletal muscle loss prior to HT. In cases requiring long-term LVAD support prior to HT, management of RHF during LVAD support may be useful in preventing skeletal muscle loss. In conclusion, a low skeletal muscle mass before HT is a prognostic predictor of post-HT infections in HT recipients.

**Conflict of interest**

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