INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a highly invasive treatment that can lead to a decline in physical capacity.1,2 Such a decrease in physical capacity during hospitalization may prolong the patient’s length of stay (LOS) and, consequently, its prevention is important. Exercise-based rehabilitation is safe for HSCT patients3 and is known to help improve physical capacity. Several meta-analyses have shown that exercise intervention in patients undergoing HSCT has positive effects on cardiorespiratory fitness4; upper muscle strength4; lower muscle strength4,5; fatigue4–6; quality of life (QOL)4–6; and physical, emotional, and cognitive functioning.4

Rehabilitation for hospitalized transplant patients is divided into two parts: pre-transplant and post-transplant rehabilitation. Pre-transplant rehabilitation is important because HSCT patients have reduced physical capacity...
resulting from both the effects of the disease itself and the treatments delivered before HSCT. Further, studies have indicated the effectiveness of pre-transplantation exercise for improving physical capacity after transplantation. Liang et al. reported a sub-analysis of a meta-analysis indicating that exercise had a favorable effect on physical capacity, fatigue, and QOL when started before HSCT.

Pre-transplant rehabilitation may prevent the deterioration of physical capacity and contribute to a shorter hospital stay. However, the relationship between pre-transplant rehabilitation and post-transplant hospital LOS remains unclear. Consequently, the purpose of this study was to investigate, using real-world data from Japanese acute care hospitals, the impact of pre-transplant rehabilitation on post-transplant hospital LOS in patients with hematologic malignancy undergoing allo-HSCT.

**MATERIALS AND METHODS**

**Study Design and Patients**

This was a retrospective observational study using the Japanese Diagnosis Procedure Combination (DPC) database. The subjects were patients with hematological malignancy who underwent allo-HSCT (n=8340). The patients were identified and classified using the ICD-10 codes C81 (Hodgkin lymphoma), C82–C85 and C96 (non-Hodgkin lymphoma), C90 (multiple myeloma), C91 (lymphoid leukemia), C92–94 (myeloid leukemia), and D46 (myelodysplastic syndrome) in reference to a previous study. The exclusion criteria were (1) age younger than 18 years, (2) not independent in activities of daily living (ADLs) at the time of admission [Barthel index (BI) score <100], (3) hospitalization for longer than 30 days between hospitalization and allo-HSCT, (4) multiple transplants during hospitalization or unknown stem cell source, (5) death during hospitalization, and (6) missing data.

This study was approved by the institutional review board of the University of Occupational and Environmental Health, Japan (R2-007), which deemed that written informed consent from participants was unnecessary.

**Data Source**

The DPC is a case-mix patient classification system launched in 2002 by the Ministry of Health, Labour, and Welfare of Japan. It contains information on lump-sum per-diem payment for hospitalized patients and other data including date of birth, hospitalization, discharge, sex, name of main injury or illness (ICD-10 code), complications, comorbidity (Charlson comorbidity index, CCI), surgical procedures, other major measures, and patient status at the time of discharge. The database stores data for approximately 7 million patients annually from more than 1000 participating hospitals. Furthermore, the database covers more than 50% of all acute-care inpatients and approximately 90% of all tertiary-care emergency hospitals in Japan. In the current study, we used case data for patients discharged between April 2014 and March 2017.

**Analysis of Variables**

We selected patient-level factors and hospital-level factors that could potentially affect post-transplant hospital LOS. Patient-level factors were age, sex, body mass index (BMI), stem cell source, underlying disease, CCI, secondary disease [graft-versus-host disease (GVHD: T860, T868), cytomegalovirus infection (B259), bacterial infection (A499), candidiasis (B37)], pressure ulcer (L89), performance of pre-transplant rehabilitation, and frequency of rehabilitation. In this study, pre-transplant rehabilitation was defined as the execution of at least one rehabilitation session prior to transplantation. The hospital-level factor was the status as a university or non-university hospital.

**Statistical Analysis**

Unpaired t-tests and chi-squared tests were used to compare the characteristics of the pre-transplant rehabilitation [PTR(+)] group and the no-pre-transplant rehabilitation [PTR(–)] group. Multilevel linear regression analyses (univariate/multivariate) were conducted to identify the effects of pre-transplant rehabilitation on post-transplant hospital LOS; this approach was used because it is possible that the hospitals to which patients were admitted influenced both the treatment during hospitalization and the post-transplant LOS. Multilevel analysis was used to simultaneously analyze the impact of hospital factors and patient factors and to examine the impact of hospital characteristics on patients. The natural-logarithm-transformed post-transplant hospital LOS was used as the outcome variable; this transformation was applied because LOS data exhibited a positive distortion in its distribution. The explanatory variables used were age, sex, BMI, stem cell source, diagnosis, CCI, secondary disease, university hospital status, pre-transplant rehabilitation (binary variable), and rehabilitation frequency. The absence of strong correlations (>0.8) between explanatory variables was confirmed beforehand by correlation analysis. All statistical analyses were performed using STATA release 16.
RESULTS

In total, 3614 patients with hematological malignancy who underwent allo-HSCT were included in this study (Fig. 1). Table 1 shows the patient characteristics. Overall, 2728 patients underwent pre-transplant rehabilitation. The stem cell source (P=0.038) and the percentage of patients with GVHD complications (P=0.030) were significantly different between the PTR(+) group and the PTR(–) group. The interval between HSCT and the start of post-transplant rehabilitation, the duration of rehabilitation, and the frequency of rehabilitation were also significantly different between the two groups (all P<0.001).

Table 2 shows the comparison of patient outcomes between the two groups. Post-transplant hospital LOS was significantly shorter in the PTR(+) group than that in the PTR(–) group (mean: 74.2 vs. 90.2 days, P<0.001). The overall LOS was also significantly shorter in the PTR(+) group (mean: 89.9 vs. 104.2 days, P<0.001). Furthermore, the BI score at discharge was not significantly different between the two groups (mean: 93.8 vs. 93.1, P=0.430). The overall cost of hospitalization was lower in the PTR(+) group (mean: $84,594 vs. $95,285; P<0.001).

Table 3 shows the results of multilevel linear regression analysis with the log-transformed post-transplant LOS as the explained variable. Pre-transplant rehabilitation was associated with a significant reduction in post-transplant LOS (β=−0.134, P<0.001). Peripheral blood transplantation was also significantly associated with a shorter post-transplant LOS (β=−0.072, P<0.001). In contrast, cord blood transplantation (β=0.034, P=0.038), lymphoid leukemia (β=0.078, P=0.002), GVHD complications (β=0.091, P<0.001), cytomegalovirus infection (β=0.127, P<0.001), and frequency of rehabilitation (β=0.138, P=0.006) were significantly associated with a longer post-transplant LOS.

DISCUSSION

The effect of pre-transplant rehabilitation on the post-transplant hospital LOS in hematologic malignancy patients undergoing allo-HSCT is not clear. Our results show that pre-transplant rehabilitation has the potential to shorten the hospital LOS for hematological malignancy patients who undergo allo-HSCT. The mean duration of pre-transplant rehabilitation in this study was 10.8 days, which is consistent with previous studies in Japan that initiated pre-transplant re-
Hematological malignancy patients who undergo allo-HSCT have impaired physical capacity before transplantation.7,8) Although the current study included only patients

### Table 1. Patient characteristics

|                        | Total          | Pre-transplant rehabilitation | P-value |
|------------------------|----------------|------------------------------|---------|
|                        | n (%)          | Yes n (%)                  | No n (%)|
| Number of patients     | 3614 (100)     | 2728 (75)                  | 886 (25) |
| Age (years), mean (SD) | 49.3 (13.7)    | 49.3 (13.7)                | 49.6 (13.8) |
| Sex                    |                |                             |         |
| Female                 | 1507 (42)      | 1148 (42)                  | 359 (41) |
| Male                   | 2107 (58)      | 1580 (58)                  | 527 (59) |
| Body mass index (kg/m²) |                |                             |         |
| <18.5                  | 585 (16)       | 445 (16)                   | 140 (16) |
| 18.5 to <25.0          | 2490 (69)      | 1876 (69)                  | 614 (69) |
| ≥25.0                  | 539 (15)       | 407 (15)                   | 132 (15) |
| Stem cell source       |                |                             |         |
| Bone marrow            | 1532 (42)      | 1131 (41)                  | 401 (45) |
| Peripheral blood       | 1085 (30)      | 848 (31)                   | 237 (27) |
| Cord blood             | 997 (28)       | 749 (27)                   | 248 (28) |
| Underlying disease     |                |                             |         |
| Myeloid leukemia       | 1656 (46)      | 1252 (46)                  | 404 (46) |
| Lymphoid leukemia      | 973 (27)       | 715 (26)                   | 258 (29) |
| Myelodysplastic syndrome | 560 (16)     | 442 (16)                   | 118 (13) |
| Non-Hodgkin lymphoma   | 363 (10)       | 278 (10)                   | 85 (10) |
| Multiple myeloma       | 36 (1)         | 23 (1)                     | 13 (2) |
| Hodgkin lymphoma       | 26 (1)         | 18 (1)                     | 8 (1)   |
| Charlson comorbidity index |            |                             |         |
| 0                      | 2835 (78)      | 2155 (79)                  | 680 (77) |
| 1                      | 477 (13)       | 354 (13)                   | 123 (14) |
| ≥2                     | 302 (8)        | 219 (8)                    | 83 (19) |
| Secondary disease      |                |                             |         |
| Graft-versus-host disease | 490 (11)     | 277 (10)                   | 113 (13) |
| Cytomegalovirus infection | 193 (5)       | 145 (5)                    | 48 (5)  |
| Bacterial infection    | 12 (0)         | 9 (0)                      | 3 (0)   |
| Candidiasis            | 70 (2)         | 53 (2)                     | 17 (2)  |
| Rehabilitation, mean (SD) |            |                             |         |
| Interval between start of pre-transplant rehabilitation and HSCT (days) | 10.8 (5.2) | | |
| Interval between HSCT and start of post-transplant rehabilitation (days) | 11.8 (20.9) | 5.2 (10.1) | 31.8 (30.3) | <0.001 |
| Duration of rehabilitation (days) | 35.9 (24.5) | 38.3 (24.2) | 28.2 (23.9) | <0.001 |
| Frequency of rehabilitation (days/length of stay) | 0.39 (0.2) | 0.43 (0.2) | 0.26 (0.1) | <0.001 |
| University hospital (yes) | 1750 (49) | 1376 (50) | 374 (42) | <0.001 |

SD, standard deviation.
Table 2. Comparison of outcomes between the pre-transplant rehabilitation and no-pre-transplant rehabilitation groups

| Pre-transplant Rehabilitation | Yes                  | No                  |
|------------------------------|----------------------|---------------------|
|                              | Mean  | SD    | 95% CI      | Mean  | SD    | 95% CI      | P-value |
| Post-transplant length of stay (days) | 74.2  | 39.5  | 72.7–75.7   | 90.2  | 52.3  | 86.7–93.6   | <0.001  |
| Total length of stay (days)    | 89.9  | 40.5  | 88.3–91.4   | 104.2 | 53.3  | 100.7–107.7 | <0.001  |
| Barthel index score at discharge | 93.8  | 22.3  | 92.9–94.6   | 93.1  | 22.2  | 91.6–94.6   | 0.430   |
| Total cost of hospitalization (USD) | 84,594 | 43,260 | 82,970–86,218 | 95,285 | 54,873 | 91,667–98,903 | <0.001 |

CI, confidence interval.

Table 3. Multilevel linear regression analysis of factors influencing post-transplant length of hospital stay (log transformed)

|                      | Univariate analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | β        | SE       | P-value | β        | SE       | P-value |
| Intercept            |          | 4.251    | <0.001  |          | 0.042    | <0.001  |
| Age (years)          | 0.001    | 0.001    | 0.023   | <0.001  | 0.001    | 0.378   |
| Male sex             | −0.023   | 0.014    | 0.100   | −0.016  | 0.014    | 0.238   |
| Body mass index (kg/m²) |          |          |         |          |          |         |
| <18.5                | 0.026    | 0.019    | 0.171   | 0.007   | 0.019    | 0.701   |
| 18.5 to <25.0        | Reference |          |         |          |          |         |
| ≥25.0                | −0.013   | 0.020    | 0.492   | −0.001  | 0.019    | 0.981   |
| Stem cell source     |          |          |         |          |          |         |
| Bone marrow          | Reference |          |         |          |          |         |
| Peripheral blood     | −0.081   | 0.017    | <0.001  | −0.072  | 0.017    | <0.001  |
| Cord blood           | 0.115    | 0.017    | <0.001  | 0.144   | 0.017    | <0.001  |
| Underlying disease   |          |          |         |          |          |         |
| Myeloid leukemia     | Reference |          |         |          |          |         |
| Lymphoid leukemia    | 0.032    | 0.017    | 0.006   | 0.034   | 0.016    | 0.038   |
| Myelodysplastic syndrome | 0.024   | 0.020    | 0.238   | 0.025   | 0.020    | 0.217   |
| Non-Hodgkin lymphoma | 0.002    | 0.024    | 0.920   | 0.021   | 0.023    | 0.375   |
| Multiple myeloma     | 0.132    | 0.070    | 0.059   | 0.124   | 0.068    | 0.066   |
| Hodgkin lymphoma     | 0.227    | 0.082    | 0.015   | 0.247   | 0.079    | 0.002   |
| Charlson comorbidity index |      |          |         |          |          |         |
| 0                    | 0.005    | 0.021    | 0.825   | 0.006   | 0.021    | 0.787   |
| 1                    | 0.099    | 0.026    | <0.001  | 0.078   | 0.026    | 0.002   |
| 2                    |          |          |         |          |          |         |
| Secondary disease    |          |          |         |          |          |         |
| Graft-versus-host disease | 0.110   | 0.024    | <0.001  | 0.091   | 0.024    | <0.001  |
| Cytomegalovirus infection | 0.162   | 0.032    | <0.001  | 0.127   | 0.032    | <0.001  |
| Bacterial infection  | −0.135   | 0.119    | 0.259   | −0.162  | 0.116    | 0.161   |
| Candidiasis          | −0.061   | 0.050    | 0.230   | −0.081  | 0.049    | 0.098   |
| Rehabilitation       |          |          |         |          |          |         |
| Pre-transplant rehabilitation (yes) | −0.118 | 0.019    | <0.001  | −0.134  | 0.020    | <0.001  |
| Frequency of rehabilitation | 0.029   | 0.048    | 0.544   | 0.138   | 0.050    | 0.006   |
| University hospital (yes) | 0.027   | 0.037    | 0.462   | 0.049   | 0.037    | 0.175   |

SE, standard error.
who had complete independence in ADLs, it is assumed that many subjects likely had reduced physical capacity. Moreover, pre-transplant rehabilitation might help patients understand the significance and necessity of rehabilitation even before transplantation has taken place. Pre-transplant rehabilitation could have contributed to shortening the post-transplant LOS by reducing the decline in pre-transplant physical capacity and by supporting the early start of post-transplant rehabilitation. Moreover, a shorter post-transplant hospital LOS probably contributed to a shorter total hospital LOS, which in turn likely reduced the total cost of hospitalization.

Some studies have shown that preoperative rehabilitation reduces hospital LOS in lung cancer patients.\(^{22-27}\) In the current study, we clarified the benefit of preoperative rehabilitation in patients with hematologic malignancy scheduled to undergo allo-HSCT. Despite the benefits of pre-transplant rehabilitation, the number of days available for such rehabilitation during hospitalization for HSCT is limited. Therefore, we considered it desirable to start pre-transplant rehabilitation in an outpatient setting or as a home program before hospitalization for HSCT. A previous study showed that 4–6 weeks pre-transplant rehabilitation before hospitalization for HSCT helped reduce the hospital LOS for HSCT without adverse events.\(^{19}\)

In addition to pre-transplant rehabilitation, the transplant source, higher CCI, and complications (GVHD and cytomegalovirus infection) also affected post-transplant LOS. The difference in the post-transplant course for the different transplant sources might also have influenced the post-transplant LOS. Therefore, it will be necessary to verify each transplant source in future studies. A higher CCI is known to be a poor prognostic factor\(^{29}\) and was also found to be a predictor of prolonged post-transplant hospital LOS in the current study. Both GVHD and cytomegalovirus infection are known from previous studies to be associated with longer hospital stays\(^{29,30}\) and the results of the current study are consistent with those results. It is a useful finding that pre-transplant rehabilitation was associated with shorter post-transplant LOS, even when adjusted for post-transplant complications.

The current results suggest that pre-transplant rehabilitation contributes to shorter post-transplant hospital LOS regardless of whether the hospital is a university hospital. However, the implementation of pre-transplant rehabilitation differed between academic and non-academic hospitals. This may reflect differences in facilities, size of workforce, hospital case volume, or the background of the patients undergoing HSCT. In the future, it will be necessary to examine the reasons for the differences in the implementation of pre-transplant rehabilitation at different facilities.

This study has some limitations. First, the type of pre-transplant rehabilitation implemented was not specified, and therefore the most appropriate rehabilitation strategy could not be established. Second, the type and duration of pre-transplant treatment prior to hospitalization were also unclear. The longer that a course of treatment not including rehabilitation continues, the more likely it is that a decline in physical capacity will occur, which could affect the LOS. However, we included only subjects who were fully independent in ADLs, thereby minimizing this impact on the study findings. Third, the patient’s physical condition before allo-HSCT was unknown. Although pre-transplant rehabilitation is generally provided to patients in a good physical condition, it may have also been implemented in patients with poor physical condition such that rehabilitation needed to be started before transplantation. Consequently, our results should be interpreted with caution. Adjusting for subjective symptoms (e.g., fatigue) and the results of biochemical examinations (e.g., red blood cell, hemoglobin, and albumin levels) may solve this problem. However, the DPC database does not include these data, which is another limitation of this study. Finally, limited data were collected because of the retrospective nature of the study. Therefore, we were not able to adjust for confounding factors associated with longer LOS such as psychiatric morbidity,\(^{31}\) oral mucositis,\(^{32}\) or nutritional status prior to transplantation.\(^{33}\)

However, we were able to adjust for other influencing factors, namely, hematological cancer diagnosis,\(^{31}\) transplant source,\(^{31}\) and complications.\(^{29,30}\) Future interventional studies and randomized controlled trials will be necessary to verify the effects of pre-transplant rehabilitation on post-transplant hospital LOS.

In conclusion, pre-transplant rehabilitation for patients with hematologic malignancy scheduled to undergo allo-HSCT may help shorten post-transplant hospital LOS. Consequently, it may be necessary to consider starting rehabilitation before transplantation.

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**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest.

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