

Impact of hospital length of stay on the risk of readmission and overall survival after allogeneic stem cell transplantation

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1 **ABSTRACT**

2 Patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) are
3 at high risk of readmission for complications. We sought to examine the association
4 between HSCT hospital length-of-stay and the incidence of readmission and survival
5 after discharge. We retrospectively reviewed the cases of 230 allo-HSCT recipients. The
6 cumulative incidence of readmission with non-relapse transplant-related complications
7 (including infections; acute and chronic GVHD; liver, lung, renal, or neurological
8 complications; and hematological abnormalities) two years after the first discharge was
9 49.7% in patients with length-of-stay ≤ 100 d ($n = 156$), and 66.6% in patients with
10 length-of-stay > 100 d ($n = 74$) ($P = 0.02$). The cumulative incidence of readmission with
11 infections two years after first discharge was lower in the length-of-stay ≤ 100 d group
12 than in the length-of-stay > 100 d patients (27.1% vs. 41.3%, $P = 0.04$). Length-of-stay $>$
13 100 d was the only risk factor identified that correlated positively with the rate of
14 readmission for non-relapse transplant-related complications (relative risk [RR], 1.53;
15 95% confidence interval [CI], 1.08-2.18, $P = 0.018$) or infections (RR, 1.64; [CI], 1.03-2.61;
16 $P = 0.038$). Close follow-up of patients with longer length-of-stay after allo-HSCT is
17 advised.

18 **KEYWORDS**

1 Allogeneic stem cell transplantation, Risk factors, Length-of-stay, Readmission

2

1 INTRODUCTION

2 Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the treatment of
3 choice for cure of many haematological disorders. The number of allo-HSCTs
4 performed worldwide exceeds 25 000 each year, and the total cumulative number has
5 exceeded 400 000 [1]. Progress in transplant methodology, such as better supportive
6 care, newer antimicrobial drugs, and improvements in treatment for post-transplant
7 complications, has led to a decrease in early mortality after allo-HSCT [2-5].

8 Complications influence the post-transplant clinical course and may increase
9 hospital length-of-stay. Risk factors for readmission in the first 30 d from discharge
10 include hematopoietic stem cell transplantation comorbidity index (HCT-CI), a total
11 body irradiation (TBI)-based preparative regimen, and infection during admission for
12 index admission [6]. The impact of readmission at 30 d of discharge up to d 100 after
13 HSCT on overall survival is controversial, but it significantly correlates with increased
14 hospitalisation cost [6,7]. Spring *et al.* estimated rates of readmission at 30 d of
15 discharge and by d 100 after HSCT. Readmission within 30 d of discharge and by d 100
16 after HSCT was significantly associated with poor overall survival (OS) in patients
17 receiving both myeloablative and reduced-intensity conditioning HSCT [8]. Longer
18 length-of-stay in hospitals or frequent readmissions may also bring a decline in patients'

physical strength and lead to a delay in social rehabilitation. Yokota *et al.* showed that longer length-of-stay in hospitals for HSCT positively correlated with patients' mental distress [9].

We retrospectively assessed the effect of HSCT length-of-stay on the incidence of readmissions and on overall survival after discharge among consecutive allo-HSCT recipients at a single institute. We also assessed factors influencing length-of-stay for HSCT.

METHODS

Patients and Setting

The study included 230 consecutive patients with haematological disorders who underwent their first allo-HSCT between January 2001 and December 2010 at Japanese Red Cross Nagoya First Hospital, and were discharged (first discharge after HSCT) without relapse. Exclusion criteria included multiple transplants within two years (during the hospitalisation period after first allo-HSCT [$n = 10$] or after first discharge [$n = 17$]), death ($n = 82$) or relapse or disease progression ($n = 8$) during the first allo-HSCT hospitalisation period, and loss to follow-up after first discharge ($n = 7$). The patients were divided into two groups according to length-of-stay, namely length-of-stay

1 ≤ 100 d from transplant to first discharge ($n = 156$), and length-of-stay > 100 d from
2 transplant to first discharge ($n = 74$).

3 The patients were required to fulfil the following criteria before their first
4 discharge: neutrophil engraftment achieved, ability to take oral immunosuppressive
5 drugs for GVHD prevention, and no active GVHD or infection requiring systemic
6 intravenous treatment. This study was approved by the ethical committee of Japanese
7 Red Cross Nagoya First Hospital.

8 9 Endpoints and definitions

10 The primary endpoint of the study was the cumulative incidence of readmissions with
11 non-relapse transplant-related complications at 2 y after first discharge. Other endpoints
12 included OS after discharge, and factors influencing length-of-stay. Relapse was defined
13 as hematological relapse or cytogenetic relapse requiring further treatment. OS was
14 defined as time from first discharge to death or last follow-up.

15 Indications for readmission were defined by the patient's attending physician
16 and were independently retrospectively reviewed by a single transplant physician.

17 Indications were categorised as follows: relapse; infection; acute and chronic GVHD;
18 liver, lung, renal, or neurological complications; haematological abnormality; and

1 others.

3 Statistical analysis

4 Descriptive statistical analysis was performed to assess patient baseline characteristics,
5 diagnosis, disease status at conditioning, HCT-CI, preparative regimen, and GVHD
6 prophylaxis. Medians and ranges are provided for continuous variables. The chi-squared
7 test or Mann-Whitney test was used for group comparison. We used cumulative
8 incidence curves in a competing-risks setting to calculate the probability of readmission
9 after first discharge [10]. The Kaplan-Meier method was used to estimate OS after first
10 discharge. The log-rank test was used for univariate group comparisons. An adjusted
11 comparison of the groups with regard to outcomes with competing risks, Fine and
12 Gray's proportional-hazards model for the subdistribution of a competing risk, was used
13 [11]. For readmission for non-relapse complications or for infectious complications,
14 death before readmission and relapse before readmission were the competing events;
15 and for non-relapse mortality (NRM), relapse was the competing event. A logistic
16 regression model was used to identify risk factors for longer length-of-stay before first
17 discharge.

18 Variables considered for risk factor analyses for readmission were the patient

age at transplant (≤ 40 y vs. > 40 y for adult recipients; cutoff points were around the median in each group), patient sex, diagnosis (hematological malignancy vs. benign diseases), disease status at conditioning (first or second complete remission [CR] of AML, 1CR or 2CR of ALL, first or second chronic phase of CML, refractory anaemia or refractory anaemia with ringed sideroblasts as standard-risk diseases, 1CR or 2CR of ML, and benign diseases vs. advanced for all others), conditioning regimen (reduced-intensity conditioning vs. myeloablative conditioning), HCT-CI (0 vs. 1–2 vs. 3–6) [12], HLA disparity (match [8/8 HLA matched donors at the antigen or allele levels] vs. mismatch [all others]), donor source (related peripheral blood cells vs. related bone marrow vs. unrelated bone marrow vs. unrelated cord blood), type of prophylaxis against GVHD (tacrolimus-based vs. cyclosporine-based), and transplant year (2001–2005 vs. 2006–2010). Conditioning regimens were classified as myeloablative if total-body irradiation > 10 Gy, oral busulfan ≥ 9 mg/kg, intravenous busulfan ≥ 7.2 mg/kg, or melphalan > 140 mg/m² was used. Variables were selected in a backward stepwise manner with a variable retention criterion of $P < 0.05$. All analyses were performed using commercial software (Stata® version 12.0, Stata Corporation, College Station TX, USA). All P values are two-sided.

RESULTS

Patient baseline characteristics

Patient characteristics are shown in Table 1. Median age was 41 y for all patients regardless of length-of-stay. Among the two groups, there were no statistically significant differences in terms of age at transplant, sex, diagnosis, disease status, HCT-CI, conditioning regimen, or GVHD prophylaxis. More patients with length-of-stay \leq 100 d received allo-HSCT between 2006–2010 ($P = 0.004$). The distribution of donor type or stem cell source differed among the two groups. In length-of-stay \leq 100 d patients, the numbers of recipients were 37 (24%) for recipients of peripheral blood from related donors, 33 (21%) for recipients of bone marrow from related donors, 73 (47%) for recipients of bone marrow from unrelated donors, and 13 (8%) for recipients of cord blood from unrelated donors. The corresponding numbers of recipients with length-of-stay > 100 d were 5 (7%), 16 (21%), 42 (57%), and 11 (15%), respectively ($P = 0.012$). The patients with length-of-stay ≤ 100 d were more likely to have an HLA-matched donor than those with length-of-stay > 100 d (76% vs. 57%, $P = 0.004$). The number of recipients who developed grade II to IV acute GVHD during their first HSCT hospitalization period in length-of-stay ≤ 100 d group were 18 (12%), and in length-of-stay > 100 d group were 30 (41%), respectively ($P = 0.0004$), and the proportions were

not significantly different between the two time periods (24% for 2001-2005 and 18% for 2006-2010, $P=0.323$).

Incidence of readmission and its indications

The reasons for first readmission after first discharge are described in Table 2. The total number of patients who were readmitted at least once after first discharge was 145 (63%) of 230. Infection was the most frequent indication (45%), followed by acute and chronic GVHD (15%) and relapse (13%). Less common indications were organ system complications including abnormalities of the lungs, liver, kidneys, and central nervous system.

The readmission probabilities with non-relapse transplant-related complications in the first 2 y after first discharge are shown in Fig.1. The cumulative incidence of readmission with non-relapse transplant-related complications was 49.7% in length-of-stay ≤ 100 d patients and 66.6% in length-of-stay > 100 d patients ($P = 0.02$).

The cumulative incidence of readmission with infections in the first 2 y after first discharge was 27.1% in length-of-stay ≤ 100 d patients and 41.3% in length-of-stay > 100 d patients ($P = 0.04$) (Fig. 2). Infectious complications requiring

hospitalisation included VZV infection ($n = 31$), CMV infection ($n = 9$), bacterial pneumonia ($n = 9$), haemorrhagic cystitis ($n = 5$), HSV infection ($n = 3$), and pulmonary aspergillosis ($n = 2$).

Risk factors for readmission after first discharge

In univariate analysis (Table 3), length-of-stay >100 d patients were at a significantly higher risk of being readmitted with non-relapse transplant-related complications than length-of-stay ≤ 100 d patients (hazard ratio [HR] 1.53; 95% confidence interval [CI, 1.08–2.18, $P = 0.018$). No other variables were found to be significantly associated with readmission.

Longer length-of-stay for transplant admission also significantly increased the risk of readmission for infections. In univariate analyses, compared with recipients of PB from related donors, recipients of BM from unrelated donors had a greater risk of readmission for infections (Table 4). Length-of-stay for transplant admission was the only factor retained in the final multivariate model by using the backward stepwise method, showing that only length-of-stay >100 d patients were at significantly higher risk of being readmitted with infections within 2 y after first discharge compared with length-of-stay ≤ 100 d patients (HR 1.64; CI, 1.03–2.61; $P = 0.038$).

Effect of length-of-stay on OS after first discharge

OS at 2 y and 10 y after first discharge was 78.2% and 62.5% in length-of-stay ≤ 100 d patients and 84.8% and 67.4% in length-of-stay >100 d patients, respectively ($P = 0.88$) (Fig. 3). Cumulative incidences of NRM within 2 y after first discharge were similar among the two groups, at 7.8% in length-of-stay ≤ 100 d patients and 8.2% in length-of-stay >100 d patients ($P = 0.962$) (Fig. 4).

Factors contributing to longer length-of-stay for transplant admission

In multivariable analysis, multiple factors which significantly affected length-of-stay for transplant admission were identified. Female patients had a significantly longer length-of-stay than male (odds ratio [OR] 2.14; 95% CI, 1.03–4.45; $P = 0.042$) (Table 5). HLA-mismatched recipients had a significantly longer length-of-stay than those with HLA-matched recipients (OR 2.78; 95% CI, 1.21–6.38; $P = 0.016$). Recipients of related-BMT (OR 5.78; 95% CI, 1.55–21.5; $P = 0.009$) and unrelated-BMT (OR 9.16; 95% CI, 2.50–33.6; $P = 0.001$) had a significantly longer length-of-stay than recipients of related-PBSCT. Patients who received tacrolimus for GVHD prophylaxis were at a lower risk for longer length-of-stay (OR 0.40; 95% CI, 0.17–0.93; $P = 0.034$) compared

with recipients of cyclosporine. Patients who underwent allo-HSCT between 2006 and 2010 (OR 0.26; 95% CI, 0.12–0.56; P = 0.001) compared with transplant year between 2001 and 2005 were at significantly lower risk for increased length-of-stay. CMV infection (OR 12.8; 95% CI, 2.48–66.5; P = 0.002), fungal infection (OR 12.3; 95% CI, 2.03–74.3; P = 0.006), late-onset non-infectious pulmonary complications (OR 10.8; 95% CI, 2.93–40.1; P = 0.0004), and grade II to IV acute GVHD (OR 5.58; 95% CI, 2.52–12.4; P = 0.0004), were significantly associated with longer length-of-stay.

DISCUSSION

Length-of-stay after allo-HSCT was the only factor identified throughout multivariate model building process to increase the risk of readmission with non-relapse transplant-related complications and in particular with infectious complications in the first 2 y after allo-HSCT. Length-of-stay may be a simple and easy index for patients to understand the risks for readmission, and also for medical staff in providing patient education at initial discharge. The main cause of readmission with infectious complications was viral infections, such as *Herpes zoster* and CMV infections. Other causes included bacterial infections, acute and chronic GVHD, and relapse. Early diagnosis and treatment of *Herpes zoster* infections can reduce the incidence of persistent damage, such as

1 postherpetic neuralgia. Furthermore, it is important to identify and prevent of high-risk
2 cases of VZV infection. However, in Japan there is a limit on insurance adaptation for
3 preventive administration of drugs to prevent reactivation and infection of VZV.
4 The monitoring of CMV antigenemia can prevent the development of serious CMV
5 infections [13,14]. Our present study revealed the importance of providing daily
6 guidance about infectious complications to length-of-stay >100 d patients. McKenna *et*
7 *al.* analysed the risk factors for hospital readmission following transplantation and
8 showed the necessity of enhanced education by ancillary staff before discharge in order
9 to decrease readmission rates [15]. Our findings are consistent with McKenna *et al.* 's
10 conclusions supporting the importance of patient education, especially for infection
11 prevention, before initial discharge.

12 Longer length-of-stay led to higher readmission rates after allo-HSCT, but did
13 not affect OS or NRM in our study. Close follow-up by transplant centres allows the
14 early diagnosis and treatment of complications, including infections. More than 350
15 centres perform HSCT in Japan, representing one of the highest team densities in the
16 world [1], and most of the study subjects were able to come to our hospital for post-
17 transplant outpatient follow-up bi-weekly or monthly after the first discharge. This
18 might explain why longer length-of-stay did not result in increasing NRM.

1 The median length of initial hospitalisation after first transplant was 93 d (40–
2 387 d); therefore, we were able to assess readmission within two years after first
3 discharge. The initial hospitalisation period in our report is much longer than that in
4 reports from the western countries. Ballen *et al.* report that the median time alive and
5 out of hospital within 100 d after allo-HSCT for patients with AML and ALL in CR1 or
6 CR2 was 52 d with a single umbilical cord blood transplant and 69 d with matched
7 unrelated bone marrow transplant with a myeloablative regimen [16]. In our analysis,
8 the median time alive and out of hospital in the first 100 d after first transplant for
9 hematological malignant disease was much shorter than in Barren’s report: 14 d in
10 single CBT and 18 in UMBT recipients. Japan introduced a universal healthcare system
11 in 1961, in which all citizens have a public health insurance plan. Patients can choose
12 their medical institution, and are guaranteed to receive the standard of medical care.
13 At Japanese Red Cross Nagoya First Hospital, of 868 patients who received a first allo-
14 HSCT from 1977–2014, 283 are alive and 247 patients (87%) have been followed by this
15 centre. We were therefore able to maintain a high follow-up rate. Nevertheless, several
16 limitations of our study warrant mention. The main limitation is that the results are from
17 an analysis of transplants in a single centre. Our centre started performing allo-HSCT in
18 1977, and the follow-up rate of survivors is 87%. The timing of discharge and readmission

of transplant recipients is often influenced by a centre's experience, and by other social variables, including patient preferences and their family background. However, the influence of differences in the timing of discharge and readmission in our study is minimized by its basis on a single centre's experience. A second limitation is that the study subjects were recipients of allo-HSCT over a decade, and practice changes over time may have influenced the outcome. Transplants between 2001 and 2005 were at higher risk of longer length-of-stay than those between 2006 and 2010. The medical insurance system has changed over 10 years. In Japan, the Diagnosis Procedure Combination (DPC) was started in 2003 in some advanced treatment hospitals [17,18], and our centre has since introduced this system. This change may affect length-of-stay and frequency of readmission. Additionally, treatment of infections has changed with the development of new drugs. Treatment for CMV infection, the most frequent reason for readmission in our study, was limited to intravenous ganciclovir until 2009 in Japan. Valganciclovir hydrochloride (p.o.) was approved only for CMV retinitis in HIV patients, and later approved for allo-HSCT-linked CMV infections in May, 2009. Because our study was limited to subjects who received transplants before 2010, we assume that the availability of this drug had little impact on the results. In this study, as well as CMV infection, VZV infection was commonly the reason for readmission. In Japan, acyclovir

1 is generally administered to prevent VZV infection during the study period. At this center,
2 acyclovir prevention was given to recipients from 7 days before HSCT to 35 days post-
3 HSCT during the study period. Prophylaxis against VZV during middle/late periods post
4 HSCT was not given to recipients during the study period.

5 In our study, a longer length-of-stay at first allogeneic hematopoietic
6 transplantation was associated with increased risk of readmission with non-relapse
7 transplant-related complications, particularly infections, in the first two years after first
8 discharge, but had no effect on long-term survival.

9 10 **AUTHOR CONTRIBUTIONS**

11 A.S., Y.A., K.M., and H.K. designed the study, and wrote the paper; A.S. and Y.A.
12 analysed the results and made the figures; Y.O. and N.K. submitted and cleaned the data
13 and reviewed the results.

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1 **CONFLICT OF INTEREST**

2 The authors declare that they have no conflict of interest.

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