Recovery of physical function, muscle mass and quality of life in patients undergoing allogeneic hematopoietic stem cell transplantation

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Research Article

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Abstract

Purpose

This study aimed to investigate the recovery of physical function, muscle mass, and quality of life (QOL) in allogeneic hematopoietic stem cell transplantation (allo-HSCT) patients 1 year after the procedure.

Methods

A total of 71 patients who underwent allo-HSCT at our institution between February 2010 and June 2020, for whom a physical therapy assessment could be performed before allo-HSCT, at discharge, and 1 year after allo-HSCT, were included. Exercise therapy during hospitalization was provided individually by a physical therapist, and exercise was self-administered after discharge.

Results

One year after allo-HSCT, handgrip strength and results of the 6-minute walk test (6 MWT) recovered to pre-HSCT levels. Muscle mass 1 year after allo-HSCT showed slight improvement after discharge from the hospital but did not reach the pre-HSCT level. All subscales of QOL, 1 year after allo-HSCT, recovered to pre-HSCT levels, but only two of the eight subscales recovered to the national norm of 50. Multivariate analysis revealed factors associated with the recovery of physical function and QOL, including improved hemoglobin levels, albumin levels, and adherence to exercise therapy. In contrast, factors that negatively affected recovery were steroid administration and pre-HSCT intensity conditioning.

Conclusion

The results suggest that continued exercise therapy may contribute to the recovery of muscle strength, endurance, and QOL 1 year after allo-HSCT.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a useful treatment for hematopoietic malignancies, and improved transplant outcomes have increased survival rates [1, 2]. However, patients' physical function is impaired prior to allo-HSCT due to inactivity caused by remission induction and consolidation therapy initiated after diagnosis [3]. In addition, pre-transplant treatment with high-dose chemotherapy, infections associated with allo-HSCT, and graft-versus-host disease (GvHD) can lead to a decline in physical activity [4, 5]. Therefore, rehabilitation is important to prevent a decline in physical function and quality of life (QOL).6,7 Exercise therapy is beneficial in maintaining physical function, QOL, and lower extremity muscle mass after allo-HSCT [4]. In addition to physical function and QOL assessment, muscle mass measurement is essential for preventing sarcopenia and frailty [8, 9]. Recently, it has been suggested that early rehabilitation after diagnosis of a hematological disease is helpful for early recovery of physical function. The safety and feasibility of starting rehabilitation before hospitalization for transplantation have also been reported [10, 11]. In addition, most patients are independent in activities of daily living (ADL) but have limited outdoor activities when discharged from the hospital. Therefore, a post-discharge approach aimed at early recovery of physical function is particularly important.

Numerous reports on QOL recovery in allo-HSCT patients have been published, with the recovery time ranging from 6 months to 1 year [12, 13]. With regard to recovery of physical function, Wiskemann et al. reported that results of the 6-min walk test (6 MWT) at 6– 8 weeks after discharge recovered compared to at the time of discharge, but not to pre-HSCT levels [14]. Hayakawa et al. reported that results of the 6 MWT at 1 year after allo-HSCT recovered to pre-HSCT levels, but handgrip strength and knee extension muscle strength did not improve [15]. Most reports on the recovery of physical function are from the early post-discharge period [14, 16, 17], and very few studies report the recovery over more than six months after allo-HSCT. In addition, there are no reports on the recovery at 1 year after allo-HSCT with respect to changes in muscle mass. This study aimed to investigate the recovery of physical function, muscle mass, and QOL 1 year after allo-HSCT. We also examined several factors that affect the recovery of physical function, muscle mass, and QOL.

Patients And Methods

The inclusion criteria for this study included patients with hematologic diseases who underwent their first allo-HSCT at our institution, and whose physical function, muscle mass, and QOL could be assessed prior to allo-HSCT. Exclusion criteria included patients with bone and joint disorders, cardiac dysfunction, or bone metastasis. Of the 327 patients who underwent allo-HSCT between February 2010 and June 2020, 286 met the inclusion criteria. We have provided online information regarding this retrospective study. This study was approved by the ethics committee (NCR21-45).

Exercise intervention

Our institution provides rehabilitation to all patients undergoing allo-HSCT. Physiotherapy assessments are performed routinely before allo-HSCT, at discharge, and during the long-term follow-up (LTFU) outpatient visits.

Exercise therapy during hospitalization began approximately 2 weeks before allo-HSCT and was conducted individually by the physical therapist five times a week for 20 to 40 minutes per session until discharge. The exercise therapy consisted of stretching, strength, balance, and endurance training. The target intensity for strength training was "somewhat hard" (10–13) based on the Borg scale [18]. Exercise intensity for endurance training was determined using the Karvonen method [19], with 60% of predicted maximal heart rate. If patients had vomiting/nausea, fever, or fatigue symptoms, exercise intensity was reduced. Exercise therapy was self-administered after discharge from the hospital. Before discharge, rehabilitation guidance was provided, and patients were instructed to continue the exercises they had performed during hospitalization. In particular, continuing lower- extremity strength training and walking exercises was recommended.

Our HSCT ward has an International Organization for Standardization of class 7 and an International Organization for Standardization of class 5 for patient rooms. Exercise therapy was performed in patient rooms, wards, and rehabilitation rooms. During the myelosuppression period, it was performed in the rehabilitation space of the ward and patient rooms.

Assessment

Physical function, muscle mass, and QOL assessments were performed approximately 2 weeks prior to allo-HSCT, at the time of discharge, and 1 year after allo-HSCT during LTFU outpatient visits.

Physical function tests

The 6 MWT and handgrip strength were measured as physical function tests. The 6 MWT was based on the American Thoracic Society guidelines [20] and performed in a straight corridor with cones at 20 m intervals.

Handgrip strength was measured in a standing position with mild shoulder joint abduction using an adjustable-handle dynamometer (TKK 5101; TAKEI Scientific Instruments Co. Ltd., Niigata, Japan). The average of the left and right handgrip strength measurements was used as the handgrip strength index.

Body composition

Muscle mass and body weight were used to evaluate body composition. Muscle mass was measured by bioelectrical impedance analysis using Physion MD (Physion Ltd., Kyoto, Japan) in a resting supine position, with mild shoulder and hip abduction.

Health-related QOL

Health-related QOL was assessed using the Medical Outcome Study 36-item Short Form Health Survey (SF-36) [21, 22]. SF-36 consists of eight subscales: physical functioning (PF), role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Each subscale was calculated on a 0 to 100-point scale. A score of zero indicated the worst health status, and a score of 100 indicated the best health status for the subscale. The calculated score based on the national standard was 50, with higher values indicating a better QOL. In addition, summary scores were calculated for each of the following three components: physical, mental, and role/social.

Clinical factors

Blood tests (albumin [Alb], total protein [TP], and hemoglobin [Hb]), fever, GvHD, and total steroid dose were selected as clinical factors. Acute GvHD was graded according to the following guidelines [23]. It was defined as "mild" in grades I–II and "severe" in grades III–IV. The total steroid dose was expressed as milligrams of prednisolone (1 mg of hydrocortisone = 0.25 prednisolone, 1 mg of methylprednisolone = 1.25 prednisolone) per kilogram.

Statistical Analysis

The results for each index are presented as mean or median. Normality was tested using the Kolmogorov– Smirnov method. Changes in physical function, muscle mass, QOL, and clinical factors over time were analyzed using the one-way analysis of variance (Bonferroni's correction for multiple comparisons) or the Friedman test (Scheffe's test). Multiple regression analysis was used to examine the factors associated with physical function, muscle mass, and QOL recovery 1 year after allo-HSCT. The independent variables were the rate of change in clinical factors (pre-HSCT to 1-year post-HSCT), change in physical function (pre-HSCT to 1-year post-HSCT), steroid dosage, adherence to exercise therapy during hospitalization, pre-HSCT intensity conditioning, age, and GvHD. These were used to perform single regression analysis, and factors with $P < 0.15$ were used for multiple regression analysis. The percentage change in each indicator from pre-HSCT to 1 year after HSCT was expressed as a percentage. Adherence to exercise therapy was calculated as the percentage of days in which exercise therapy was performed relative to the scheduled days of exercise therapy. Statistical analysis was performed using EZR version 1.55 [24], and a P-value of < 0.05 was considered statistically significant.

Results

A flow diagram of the study population is shown in Fig. 1. Of the 286 patients, 103 could not be evaluated at discharge because of death. Analysis was performed on 71 of the remaining 183 patients who were discharged after excluding another 112 patients (54 patients who died within 1 year of allo-HSCT, 16 patients who were in inpatient care 1 year after allo-HSCT, 32 patients who were absent during the 1-year LTFU, four patients who skipped assessment due to physical problems, and six patients who followed-up at other hospitals).

Patient characteristics are shown in Table 1. Sex was almost equally distributed between men and women, with adult T-cell leukemia being the most common disease. The most common transplant source was cord blood, and the most common pre-HSCT intensity conditioning was myeloablative conditioning. The mean time from allo-HSCT to discharge assessment was relatively short, 60.1 days. Acute GvHD was observed in 25 patients (severe GvHD in nine patients) during hospitalization. Chronic GvHD was observed in 19 patients but was limited to mild skin issues, mucous membrane disorders, dry eyes, and joint symptoms (joint contractures and joint pain), and the median total steroid dose after discharge was only 1.3 mg/kg. Adherence to exercise therapy during hospitalization was high (90.3%).

Physical function and Body Composition change before and after allo-HSCT

Table 2. shows changes in physical function and body composition before and after allo-HSCT.

Handgrip strength decreased significantly at the time of discharge assessment (-12.7%, $P < 0.001$) but improved considerably during the one year after allo-HSCT (18.6%, $P < 0.001$), reaching the pre-HSCT level 1 year after allo-HSCT. Likewise, results of the 6 MWT decreased significantly at discharge (-6.9%, $P < 0.001$) but markedly improved during the 1 year after allo-HSCT (19 .8%, $P < 0.001$) and recovered to pre-HSCT levels 1 year after HSCT.

Regarding changes in muscle mass, whole-body muscle mass significantly decreased at discharge (-6.8%, $P < 0.001$) and showed a slight improvement during the 1 year after allo-HSCT; however, the pre-HSCT level was not achieved. Similar outcomes were noted in the body weight and upper extremity, lower extremity, and trunk muscle mass.

Changes in the QOL before and after allo-HSCT

Table 3. shows the changes in the QOL before and after allo-HSCT.

Six of the eight subscales, excluding general health and social functioning, decreased significantly at discharge. However, all eight subscales improved substantially from the time of discharge to 1 year after allo-HSCT, reaching the pre-HSCT level one year after allo-HSCT. Of the eight subscales, only vitality and mental health were above the national norm of 50 at 1 year after allo-HSCT.

Changes in clinical factors before and after allo-HSCT

Table 4. shows the changes in the clinical factors before and after allo-HSCT.

Alb, TP, and Hb levels decreased significantly after allo-HSCT ($P < 0.001$) but showed significant recovery from discharge to 1 year after allo-HSCT. In addition, Alb values at 1-year post-HSCT showed better results than pre-transplant levels.

Factors associated with recovery to pre-HSCT revels

A multivariate analysis of factors related to the recovery of physical function, muscle mass, and QOL to the pre-HSCT level 1 year after HSCT is presented in Table 5.

An improvement in Alb levels was positively associated, while the total steroid dose during hospitalization was negatively associated with recovery of handgrip strength at 1-year post-HSCT ($R2 = 0.104$, $p < 0.009$). An improvement in Hb levels was positively associated with improvement in the results of the 6 MWT ($R2 = 0.187$, $p < 0.005$). The rate of change in body weight was positively associated with the recovery of whole-body muscle mass ($R2 = 0.184$, $P < 0.008$), and the rate of change in Alb was positively associated with the recovery of trunk muscle mass ($R2 = 0.096$, $P < 0.030$).

Adherence to exercise therapy and improvement in 6 MWT results were positively associated with QOL, and pre-HSCT intensity conditioning was negatively associated with recovery of PF at 1-year post-HSCT ($R2 = 0.225$, $p < 0.002$).

Total steroid dose, age, acute GvHD, and pre-HSCT intensity conditioning were negatively associated, while adherence to exercise during hospitalization and the change rate of handgrip strength were positively associated with other subscales.

Discussion

We investigated the recovery of physical function, muscle mass, and QOL 1 year after allo-HSCT in patients undergoing initial allo-HSCT. One year after allo-HSCT, physical function and QOL scores had reached pre-HSCT levels.

Handgrip strength, results of the 6 MWT, and muscle mass all decreased significantly at the time of discharge but improved considerably during the one year after allo-HSCT. In addition, the 6 MWT at 1-year post-HSCT improved considerably compared with the pre-HSCT level. In this study, exercise therapy was initiated before allo-HSCT and continued until discharge, with an implementation rate of 90.3%, similar to other reports (74–90% [14, 25, 26]). Continuation of exercise therapy seemed to contribute to maintaining patients' activities and ADL abilities, enabling discharge at the ambulatory level. At the time of discharge, the patient was instructed to perform the exercises at home. In addition, we advised the patients to continue stretching, strength training, and walking. Patients were also guided on how to maintain and improve their activities during the daytime. Most patients could lead active daily lives in the first few months after discharge from the hospital, although some had decreased activity due to fatigue. By maintaining moderate activity after discharge from the hospital, handgrip strength and results of the 6 MWT appeared to have recovered to pre-HSCT levels one year after allo-HSCT.

Multivariate analysis showed that the recovery of 6 MWT results was associated with improvement in hemoglobin level, and recovery of handgrip strength was associated with improvement in Alb level, which were factors for recovery of physical function to the pre-HSCT level at 1-year post-allo-HSCT. A low Hb status is a hypoxic risk to tissues throughout the body due to decreased oxygen-carrying capacity concerning physical function and hemoglobin levels [27]. Therefore, a low Hb level is an independent risk factor for decreased physical function (especially decreased endurance) [28, 29]. In allo-HSCT patients, there is also a negative association between pre-HSCT Hb levels and results of the 6 MWT [3]. In this study, Hb improved compared to the pre-HSCT level 1 year after allo-HSCT. Increased activity and improved Hb level after discharge from the hospital may have contributed to the recovery in results of the 6 MWT. In relation to muscle strength and nutritional status, low nutritional status caused muscle weakness [30, 31]. In this study, taste disturbance and anorexia persisted initially but gradually improved after discharge. One year after allo-HSCT, Alb levels recovered to above the pre-HSCT levels. Improvements in nutritional status were considered to have contributed to the recovery of handgrip strength.

Steroid administration during hospitalization was considered a factor that negatively affected the recovery of handgrip strength. In allo-HSCT, steroids are administered as a treatment for acute GvHD and chronic GvHD. Steroids for acute GvHD are usually prescribed in high doses, while for chronic GvHD, they are administered for long periods after discharge from the hospital. In allo-HSCT patients, steroid administration is associated with decreased physical function during hospitalization [32]. In the present study, chronic GvHD was observed in 26.8% of cases. Symptoms of chronic GvHD include mild skin issues, mucous membrane disorders, and dry eyes, many of which can be treated with topical medication. Therefore, the median steroid dose after discharge from the hospital was very low, 1.3 mg/kg.

Changes in body composition, muscle mass, and body weight at 1-year post-HSCT improved slightly during the 1-year post-HSCT but did not reach pre-HSCT levels. Loss of appetite in long-term post-HSCT survivors is reported to persist after discharge from the hospital [13, 33]. In the present study, taste disturbance and loss of appetite seen during hospitalization persisted after discharge in many cases, and improvement in food intake was slow. In the hematological data, TP and Alb reached pre-HSCT levels one year after allo-HSCT. In this study, improvements in TP and Alb were associated with recovery of physical function. However, muscle mass and body weight recovery required more time. In multivariate analysis, an association was found between body weight and muscle mass recovery. Therefore, a delay in the improvement of body weight during the 1 year after allo-HSCT was thought to affect muscle mass recovery.

Improvement in the QOL after allo-HSCT is generally reported to be 1 year [12, 13]. In this study, all SF-36 subscales one year after allo-HSCT reached the pre-HSCT level. QOL in long-term post-HSCT survivors has been reported to be affected by chronic GvHD [34, 35]. In the present study, most patients with chronic GvHD had relatively mild symptoms, including skin issues, dry eyes, and dry mouth. Chronic GvHD was observed in 26.8% of the patients, and it was relatively mild in most cases and thus had little impact on the QOL. At 1-year post-HSCT, scores on six of the eight subscales of SF-36 were below the national norm of 50; Gifford et al. reported the QOL equivalent to the national norm 2 years after allo-HSCT [36]. Therefore, QOL scores at 1-year post-HSCT recovered to pre-HSCT levels but not to the national norm; as indicated in previous studies, recovery to the national standard level may take more than 1 year after allo-HSCT.

The results of the multivariate analysis showed that the rate of change in 6 MWT and adherence to exercise therapy during hospitalization contributed to the improvement of QOL to pre-HSCT level 1 year after HSCT.

It has been reported that physical function is associated with QOL in allo-HSCT recipients,3 and there is a positive correlation between handgrip strength/6 MWT and the subscale SF-36 (PF) [37]. In long-term post-HSCT survivors, those with higher physical function have a better QOL [38]. Continuous exercise therapy during hospitalization leads to establishing exercise habits, and maintenance of activity after discharge from the hospital is associated with improvement in QOL. Therefore, activity maintenance after discharge may have contributed to the improved QOL.

The American College of Sports Medicine promotes exercise therapy to restore physical function in cancer survivors [39]. Continuation of exercise therapy during allo-HSCT hospitalization positively impacts physical function and QOL during and after discharge. Therefore, for the early recovery of physical function, muscle mass, and QOL in allo-HSCT recipients, it is important to implement exercise therapy during hospitalization, continue exercise at home after discharge, and conduct regular assessments in the outpatient setting.

This study has some limitations. First, this was a single-center, retrospective study involving only 71 cases. Second, exercise therapy after discharge was self-administered, and quantitative activity levels could not be assessed because no progress records were kept. However, at the 1-year post-HSCT assessment, we confirmed that the patients had gradually expanded their ADL and activity by interviewing them about their activity level at home, complications, and dietary intake. Third, many patients dropped out at the 1-year post-HSCT assessment. Of the 32 patients attending our hospital who could not be evaluated one year after allo-HSCT, there were eight cases of relapse, but the performance status was maintained. Furthermore, among these patients, only a very small number had severely limited muscle strength or endurance; however, these results may be biased and require further investigation. Future large-scale studies that include post-discharge activity assessments are needed to clarify the time necessary for the recovery of physical function, muscle mass, and QOL after allo-HSCT.

Conclusion

In conclusion, muscle strength, endurance, and QOL of allo-HSCT recipients reached pre-HSCT levels one year after allo-HSCT, but muscle mass and body weight did not reach pre-HSCT levels. Factors associated with the recovery of physical function and QOL were adherence to exercise therapy during hospitalization and nutritional status. Continuous exercise therapy initiated before allo-HSCT may increase patient activity after discharge from the hospital and contribute to the recovery of physical function and QOL.

Declarations

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Author contribution

Takahiro Takekiyo, Koichiro Dozono, Atae Utsunomiya, and Nobuaki Nakano designed the study, reviewed and analyzed the data, and wrote the paper. The clinical data collection was performed by Takahiro Takekiyo, Nozomi Mori, Norihisa Nakashima, and Toshiyuki Okamura, who critically reviewed the previous versions of the manuscript. All the authors approved the final manuscript.

Ethics approval

The study was performed in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later amendments. This study was approved by the Ethics Committee of Imamura General Hospital (approval number: NCR21-45).

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Competing Interests

The authors declare no conflict of interest.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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Tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

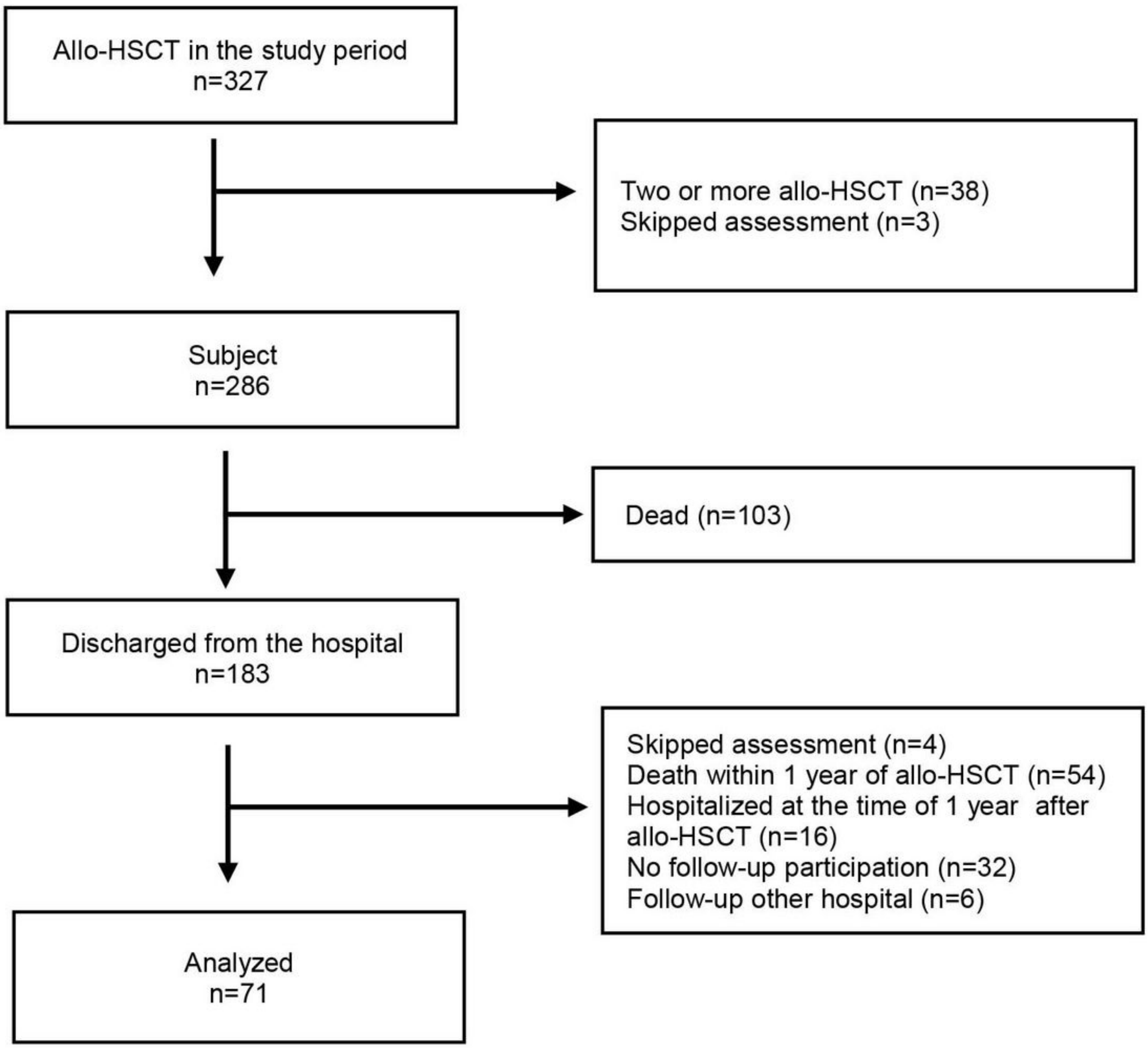

Figure 1

Study flow diagram

allo-HSCT=allogeneic hematopoietic stem cell transplantation

Supplementary Files

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- Table1.xlsx
- Table2.xlsx
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