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Effect of the severity of acute graft-versus-host disease on physical function after allogeneic hematopoietic stem cell transplantation

Running title: effect of acute GVHD on physical function

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Abstract

Purpose

The purpose of this study was to retrospectively investigate the effect of the severity of acute graft-versus-host disease (acute GVHD) on physical function after allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods

76 patients were included as subjects of this study. Severity of acute GVHD was classified according to the method defined by Grucksberg. To evaluate physical function, the knee extensor strength and six-minute walk distance (6MWD) were performed.

Results

Among these patients, 54% developed acute GVHD; of these 32%, 54%, and 15% of patients had Grade I, Grade II, and Grade III-IV GVHD, respectively. In the Grade I- II groups, mild acute GVHD following allo-HSCT, resulted in a gradual decline in physical function, which improved at discharge. However, in cases of severe acute GVHD, physical function deteriorated, implementation of rehabilitation became difficult, and the decline in physical function persisted even at discharge.

Conclusion

These results indicate that severe acute GVHD negatively affects physical function leading to longer hospital days because of inadequate rehabilitation interventions.

Keywords

allogeneic hematopoietic stem cell transplantation (allo-HSCT)・acute graft-versus-host disease

(acute GVHD)・six-minute walk distance (6MWD)・knee extensor strength

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative therapeutic measure for hematopoietic neoplastic diseases such as leukemia and malignant lymphoma, and non-neoplastic diseases such as aplastic anemia. Advancement in supportive care including conditioning regimens, antibiotics, and immunosuppressant agents have significantly reduced transplantation-related mortality and improved survival rate after transplantation [1]. On the other hand, a decline in physical function after allo-HSCT has been recently recognized as a new concern, and complications after allo-HSCT are considered as one of the factors responsible [2]. The major complication after allo-HSCT is acute graft-versus-host disease (GVHD). Acute GVHD is caused by lymphocytes derived from donors recognizing the normal organ of the recipient as foreign. Acute GVHD is characterized by selective damage to the skin, liver, and the gastrointestinal tract. Currently, it has been reported that moderate to severe acute GVHD develops in about 20% of patients after allo-HSCT, regardless of the Human leukocyte Antigen (HLA) disparity, conditioning regimen, or the use of immunosuppressive agents [3-4]. High-dose corticosteroid is the standard first-line therapeutic drug in acute GVHD. The use of corticosteroid is designed to suppress the donor lymphocyte-mediated immune insult on the recipient tissues. However, high doses of corticosteroids are associated with the occurrence of various serious side effects, one of which is skeletal muscle atrophy [5-9]. In previous reports, it has been shown that corticosteroid-induced muscle atrophy develops in 40% of patients who receive high doses of corticosteroids [2].

Severity of acute GVHD has been classified according to the method defined by Grucksberg [10]. Clinical situations in which implementation of rehabilitation becomes difficult due to severe acute GVHD is common. However, the effect of the severity of acute GVHD on the physical function after allo-HSCT remains to be elucidated. The purpose of this study was to investigate the effect of the severity of acute GVHD on physical function after allo-HSCT retrospectively.

Patients and Methods

A total of 147 patients who received allo-HSCT at the Kyoto University Hospital between 2010 and 2017 were included in this study. 16 patients who died during the hospitalization period and 55 patients whose physical functions could not be evaluated were excluded, and eventually 76 patients were included in this study. There was no significant difference in the patient characteristics and physical function before transplantation between enrolled and excluded patients (data not shown). Severity of acute GVHD was classified according to the method defined by Grucksberg [10]. There were 35 patients who did not have acute GVHD during the hospital stay and 41 patients who developed acute GVHD (Grade I: 13, Grade II: 22, Grade III-IV: 6) (Figure I). This study was approved by the Institutional Review Board of Kyoto University Hospital (Approval number: R0715). All patients were informed about the study procedures before the tests and written informed consent was obtained.

Variables

Clinical data pertaining to the following variables were obtained for all patients: gender, age, BMI, type of disease, transplantation stem cell source, degree of HLA incompatibility, disease status before transplantation, conditioning regimen, total dose of corticosteroid, total protein, total cholesterol, and rate of rehabilitation implementation. Data were obtained from the electronic medical record system.

Evaluation of physical functions

An evaluation of physical function was conducted based on the knee extensor strength and six-minute walk distance (6MWD) test. Knee extensor strength was measured using the IsoForce GT-330 (OG Giken Co., Ltd., Okayama, Japan) during isometric contraction for 3 seconds. With the patient in a sitting position with the hip and knee at an angle of 90°, the force sensor was placed 5 cm above the lateral malleolus. The better of two trials was used as the score. Torque was calculated by multiplying strength by the lever arm and was expressed as a percentage of body weight (Nm/kg) [11]. The 6MWD test was conducted according to the protocol recommended by the American Thoracic Society [12]. The course set a straight course of 30 m in the corridor and 6MWD was measured under maximum effort.

Time of Evaluation

Evaluation of each physical function was carried out before transplantation (i.e. before conditioning), after transplantation (i.e. after engraftment of transplanted stem cells), and at discharge (i.e. final intervention day of rehabilitation). As a criterion for the engraftment, the number of neutrophils exceeding 0.5×10^{10} / μL for three consecutive days was confirmed, and the chimerism analysis in bone marrow examination was performed.

Statistical analysis

SPSS software ver18.0 was used for statistical analysis. We considered two-sided p-values <0.05 as statistically significant. Statistical analysis used iterative measurement variance analysis to compare each item, and one-way ANOVA for comparison between groups at one time, and was corrected by Bonferroni method. The relevance between each physical function, rate of rehabilitation, and total corticosteroid dose was examined using Pearson's moment correlation analysis.

Exercise therapy program for allo-HSCT patients at Kyoto university hospital (Figure II)

The subjects of this study were undergoing rehabilitation interventions prior to transplantation. The contents of exercise therapy are carried out five times a week with 20 to 40 minutes of stretching, strength training, walking, and using bicycle ergometer. Exercise intensity is set to be "somewhat strong" in the Borg scale [13]. The bicycle ergometer calculates the target heart rate using the Karvonen Formula and sets it to 40% of the maximum intensity [14]. The clean room is a single room (ISO standard: class 5-6) with a toilet and a shower installed. In addition, hospital has clean management (ISO standard: class 8) for the entire ward and it is possible to exercise inside the ward at times outside of visiting hours. Exercise therapy during the aseptic management period is carried out during the hours when patients can exercise inside the ward.

Diagnosis of acute GVHD

The diagnosis of acute GVHD can be made on clinical grounds in patients presenting with a rash, diarrhea, and elevation of bilirubin within the first several weeks of transplantation. However, the diagnosis was frequently not straightforward. Skin, gastrointestinal tract, and liver biopsies were performed for proper diagnosis, when competing causes for isolated abnormalities had to be considered and excluded.

Acute GVHD is clinically graded and staged in severity (grades I to IV) depending on the extent of skin, liver, upper GI tract, and gut involvement according to the classification by Glucksberg's taxonomy. The final determination of severity was taken as the highest severity during the clinical course.

Results

Patient background and treatment characteristics

Among the patients, 54% developed acute GVHD. The mean age of the patients without acute GVHD was 45.5(21-66) years, and that of patients with acute GVHD was 45.5(19-66) years. Among patients who did not develop acute GVHD, 23 were in complete remission, while 12 were in non-remission at transplantation. Among patients who developed acute GVHD, 24 were in complete remission, while 17 were in non-remission at transplantation. Characteristics of the patients and treatment contents according to the severity of acute GVHD are shown in Table 1. Among patients with acute GVHD, 32% had grade I, 54% had grade II, and 15% had grade III-IV disease. There was no significant difference in the patient background characteristics and treatment contents at transplantation. There was no significant difference in number of engraftment days between the groups. However, length of hospital days after transplantation was significantly longer in Grade II and Grade III-IV groups than that in the non-GVHD group (Grade II, $p<0.01$; Grade III-IV, $p<0.01$) (Figure III). Total protein did not show any significant change in any of the groups (Figure IV).

Changes in physical function and rehabilitation implementation rate

In the non-GVHD and Grade I groups, the 6MWD significantly decreased from before transplantation to after transplantation (non-GVHD, $p<0.01$; Grade I, $p<0.01$), and it recovered significantly at the time of discharge (non-GVHD, $p<0.01$; Grade I, $p<0.01$). In the Grade II group, the knee extensor strength and 6MWD significantly decreased from before transplantation to after transplantation ($p<0.01$), and it recovered significantly at the time of discharge ($p<0.01$) (Figure IV). In the Grade III-IV groups, the knee extensor strength significantly decreased from before transplantation to after transplantation ($p<0.01$), and it did not recover significantly at the time of discharge. On the other hand, 6MWD significantly decreased from before transplantation to after transplantation, and it recovered significantly at the time of discharge. The decrease in 6MWD at the time of discharge remained significant compared to that at admission ($p<0.01$).

In the Grade III-IV groups, the rehabilitation implementation rate significantly decreased from pre-HSCT period to post-HSCT discharge ($p<0.01$). In the Grade III-IV groups, the rehabilitation implementation rate during post-HSCT discharge significantly decreased compared to the non-GVHD groups, Grade I and II groups (non-GVHD, $p<0.01$; Grade I, $p<0.01$; Grade II, $p<0.01$). Additionally, total rehabilitation implementation rate also significantly decreased in Grade III-IV group compared to the non-GVHD and Grade II groups (non-GVHD, $p<0.01$; Grade II, $p<0.01$) (Figure V).

There was no significant correlation between knee extensor strength and the rehabilitation implementation rate (r=0.28, $p<0.08$). However, 6MWD showed a significant correlation with the rehabilitation implementation rate (r=0.40, $p<0.01$). There was a negative correlation between rate of change of knee extensor strength and total corticosteroid dose (r=-0.37, $p<0.03$). On the other hand, there was no correlation between the rate of change of 6MWD and total corticosteroid dose (r=-0.25, $p<0.17$) (Figure V).

Discussion

Acute GVHD after allogeneic HSCT has been reported to suppress physical function after transplantation [2,15,16]. However, there is no report that examines the influence of differences in the severity of acute GVHD on the clinical courses and physical function after transplantation in detail. In this study, 54% of patients developed acute GVHD with 32% Grade I, 54% Grade II, and 15% Grade III-IV based on severity. Grucksberg's classification focuses mainly on the symptoms of skin, liver, and intestinal tract, and its grade increases as the symptoms become severe. In this study, there was no significant difference in the number of engraftment days between groups regardless of the degree of severity of acute GVHD. However, the number of hospital days prolonged with the increase in acute GVHD grade level, requiring hospitalization for about 80 days in Grade III-IV group. When acute GVHD develops, the treatment method changes depending on THE severity. In case of mild acute GVHD, concentration of cyclosporine or tacrolimus in the blood is measured and adjusted to an appropriate concentration [17]. On the other hand, in case of moderate or more acute GVHD, corticosteroid therapy is usually selected as the initial treatment. If it becomes severe, corticosteroid treatment may be insufficient and secondary therapies (anti-thymocyte globulin, mesenchymal stem cell, etc.) are required [18-21]. Therefore, in the Grade III-IV group, the number of hospital days increases due to prolonged therapeutic intervention for acute GVHD after transplantation.

Studies focusing on changes in physical functions after allo-HSCT have shown that exercise tolerance and lower limb muscle strength decrease in the early stage of transplantation [22-26]. In the early stages after transplantation, the amount of physical activity decreases due to environmental restrictions specific to transplantation, such as clean room management besides transplant-related complications. On the other hand, it has been reported that the amount of physical activity increases and physical function improves when the transplanted donor stem cells engraft and the clean room management ends [27]. In the non-GVHD and the grade I-II groups, the rehabilitation implementation rate was maintained at a high level throughout the transplantation treatment process. Furthermore, since there was little therapeutic intervention for acute GVHD at the early stage of transplantation, it was considered that physical function was suppressed due to the decrease in the amount of physical activity associated with clean room management at the early stage of transplantation. We predicted that the physical function after engraftment improved by rehabilitation intervention. On the other hand, in Grade III-IV group, physical function decreased significantly after transplantation similar to grade I-II group. Additionally, at the time of discharge, the patients did not show sufficient recovery of physical function compared to before transplantation. In other words, even if the hospitalization period is extended, it is difficult to restore physical function in Grade III-IV group. Grade III-IV group showed significantly lower values of rehabilitation implementation rate compared to the other groups, which inhibited the recovery of physical function. As acute GVHD becomes severe, gastrointestinal symptoms appear in addition to skin symptoms. From a nutritional point of view, when acute GVHD becomes severe, oral nutrition intake decreases and central venous nutrition is forced to prevent weight loss [28]. Especially when the intestinal tract GVHD becomes severe, nutrient absorption from the intestinal tract is inhibited. Hence, the lower nutritional intake accompanying severe acute GVHD may have influenced the recovery of the physical function.

Regarding the change in each physical function depending on the severity of acute GVHD, knee extensor strength of Grade II and III-IV groups decreased significantly after transplantation. One of the factors that reduced knee extensor strength is disuse muscle atrophy associated with an increase in bed rest. It has been reported that the muscular strength and cross-sectional area of the quadriceps muscle decreases as bed rest increases [29]. Hence, an increase in bedtime due to severe acute GVHD was considered as one of the factors that affected knee extensor strength weakness. In addition, corticosteroid administration is also conceivable as a factor that reduces knee extensor strength. High dose corticosteroid therapy is selected as a treatment option when acute GVHD becomes severe [18-21]. Corticosteroid-induced muscle atrophy, which affects Type II fiber (fast-twitch muscle fiber), is a complication of corticosteroid administration [30-31]. Knee extensor strength is a method of evaluating muscular strength which occupies a large amount of Type II fiber [32]. Therefore, it was considered that the knee extensor strength significantly decreases due to the influence of high dose corticosteroid administration. In addition, it is suggested that in the group requiring a high dose of corticosteroid, the lower limb muscular strength may not sufficiently recover even at discharge. Our results showed significantly reduced 6MWD after transplantation regardless of the severity of acute GVHD, supporting the results from previous reports [33-34]. However, the knee extensor strength and the 6MWD did not show the same change in each group. The 6MWD is a method of evaluating the entire endurance performance, which includes various other factors apart from the lower limb muscular strength. In this study, the rehabilitation implementation rate and the rate of change of the 6MWD were found to have a significant correlation. The 6MWD recovered significantly due to successful implementation of rehabilitation in patients with mild acute GVHD and those who did not develop acute GVHD. In the Grade III-IV group, reduction of lower limb muscle strength due to corticosteroid administration was also considered as a factor to inhibit recovery of 6MWD, in addition to factors such as difficulty in rehabilitation accompanied by severe GVHD. As a result, we concluded that continued rehabilitation is necessary to restore endurance performance. The limitation of this study is that we were unable to examine physical activity after transplantation in further detail. Furthermore, there is a possibility of selection bias since 55 patients were not evaluated for physical function.

Conclusion

We retrospectively investigated the effect of the severity of acute GVHD on physical function after allo-HSCT in detail for the first time. The results indicate that if the severity is mild even after developing an acute GVHD following allo-HSCT, there is a gradual decline in physical function, which improves at discharge. However, if it becomes severe, it is difficult to implement rehabilitation and the deterioration of physical function becomes prominent. Therefore, physical function declines even at discharge. If acute GVHD becomes severe, physical function may further deteriorate, hence, it is imperative to rethink the rehabilitation approach for patients with severe GVHD.

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Funding information

none

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study was approved by the Institutional Review Board of Kyoto University Hospital conducted in accordance with the international ethical recommendations stated in the Japanese Good Clinical Practice Guidelines.

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Table I. Patient background by severity of acute graft versus host disease.

	non-GVHD (n=35)	Grade I (n=13)	Grade II (n=22)	Grade III-IV (n=6)
Gender *(Men/Female)* [a]	25/10	10/3	13/9	3/3
Age [b]	45.5±14.1	44.8±12.4	45.8±15.2	46.3±14.2
Body mass index, *kg/m²* [b]	21.7±3.7	21.8±3.6	21.3±3.9	22.3±2.5
Diagnosis *(Leukemia/MDS/Lymphoma)* [a]	24/6/5	8/2/3	12/6/4	4/1/1
Transplantation type *(Bone marrow/Cord blood/Peripheral blood)* [a]	19/11/5	8/2/3	10/11/1	3/1/2
HLA *(Matched relative/Matched unrelative)* [a]	22/13	6/7	9/13	4/2
Complete remission *(CR/non-CR)* [a]	23/12	10/3	10/12	4/2
Conditioning *(Myeloablative/Reduced intensity)* [a]	20/15	9/4	18/4	4/2

MDS：myelodysplastic syndrome

HLA：Human Leukocyte Antigen

[a] Values represents the number of patients in each category

[b] Values represents the mean ± SD

Figure I. Study flow chart

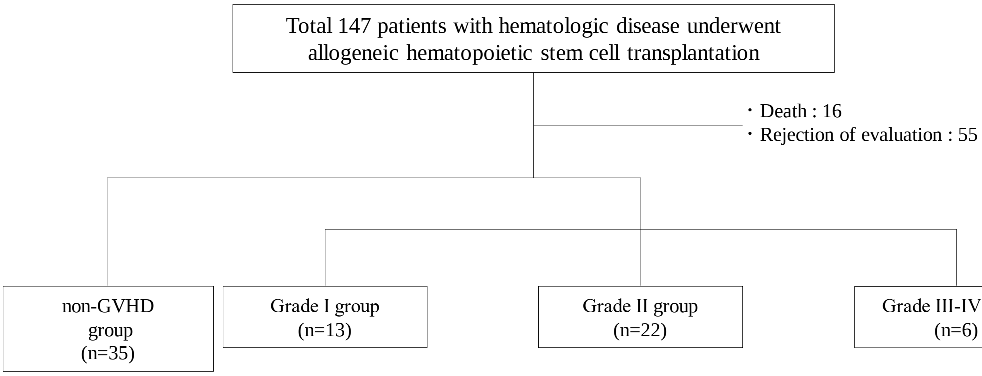
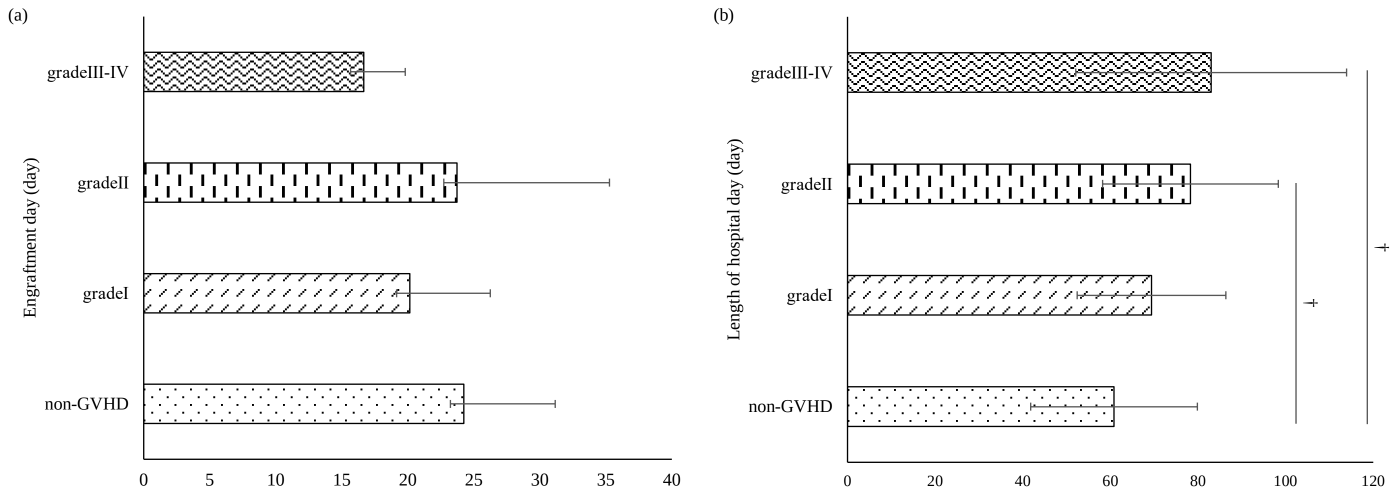


Figure II. Physical therapy program before and after hematopoietic stem cell transplantation.

	Before transplantation			After transplantation	
Protocol	Two weeks before transplantation	Previous treatment	Transplantation	Engraftment	Engraftment-Discharge
Intervention place	Rehabilitation room	Clean floor			Rehabilitation room
Program	Physical function tests (pre) ‣Stretching ‣Muscle strength exercise ‣Endurance training	‣Stretching ‣Muscle strength exercise ‣Endurance training ‣Walking training			Physical function tests (post/discharge) ‣Stretching ‣Muscle strength exercise ‣Endurance training
	Hospital	Hospital ward			Hospital

Figure III. Days of engraftment day and length of hospital days of the non-GVHD and acute GVHD groups.

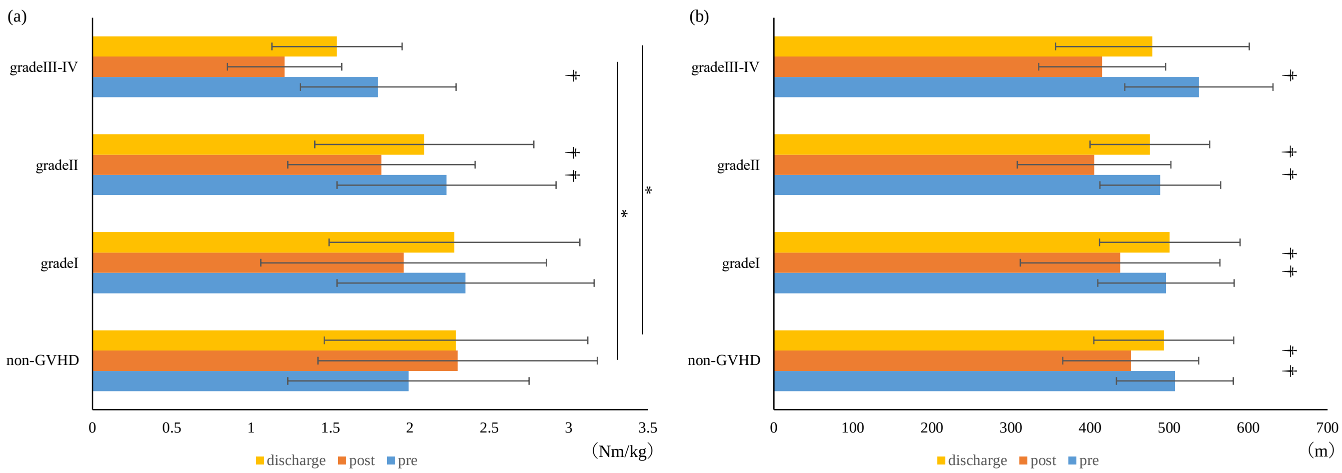


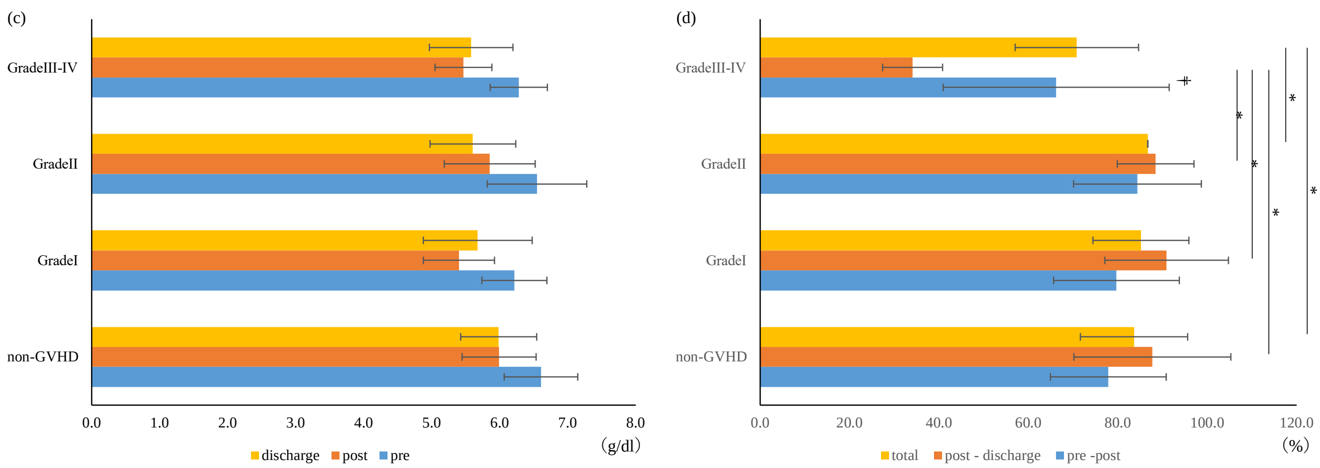
(a)Engraftment days of non-GVHD group and acute GVHD group.

(b)Length of hospital days of non-GVHD group and acute GVHD group.

† : Significant difference was recognized($p<0.01$)

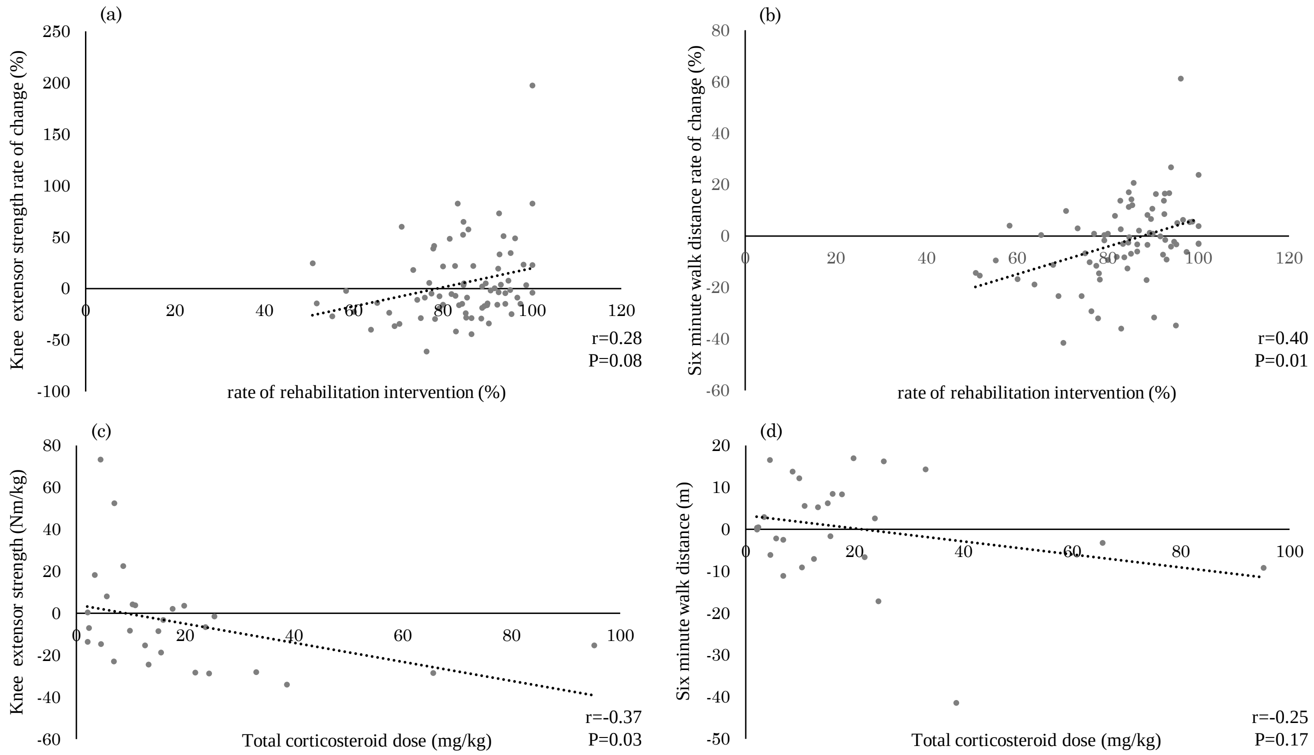
Figure IV. Physical function evaluation for the non-GVHD and acute GVHD groups.





(a) Knee extensor strength of non-GVHD group and acute GVHD group.
(b) Six-minute walk distance of non-GVHD group and acute GVHD group.
(c) Total protein of non-GVHD group and acute GVHD group.
(d) Rate of rehabilitation of non-GVHD group and acute GVHD group.
* : Significant difference between groups(p<0.01)
† : Significant difference at each time(p<0.01)

Figure V. Relationship between each physical function and total corticosteroid administration, executing rate of rehabilitation.



(a)(b): Scatterplots illustrating the relationship between total corticosteroid dose and physical function change.
(c)(d): Scatterplots illustrating the relationship between executing rate of rehabilitation and physical function change.