

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

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4 Running title: effect of acute GVHD on physical function

5 Ryota Hamada(P. T.)¹, Tadakazu Kondo(MD, Ph.D.)², Masanobu Murao(P. T.)¹, Jyunsuke
6 Miyasaka(P. T.)¹, Michiko Yoshida(P. T.)¹, Manabu Nankaku(P. T, Ph.D.)¹, Junya Kanda(MD,
7 Ph.D.)², Akifumi Takaori-Kondo (MD, Ph.D.)², Ryosuke Ikeguchi (MD, Ph.D.)¹, Shuichi
8 Matsuda(MD, Ph.D.)¹

9 ¹ Rehabilitation Unit, Kyoto University Hospital, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto
10 606-8507, Japan

11 ² Department of Hematology and Oncology, Graduate of School of Medicine, Kyoto University,
12 Shogoin, 54 Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

13

14 Corresponding author: Tadakazu Kondo

15 Department of Hematology and Oncology , Graduate of School of Medicine, Kyoto University
16 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto city, Kyoto 606-8507, Japan

17 TEL: +81-75-751-3111 FAX: +81-75-751-3201

18 Email: tadakazu@kuhp.kyoto-u.ac.jp

19

20 **Abstract**

21 **Purpose**

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

25 **Methods**

26 76 patients were included as subjects of this study. Severity of acute GVHD was classified
27 according to the method defined by Grucksberg. To evaluate physical function, the knee extensor
28 strength and six-minute walk distance (6MWD) were performed.

29 **Results**

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

36 **Conclusion**

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

39 **Keywords**

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

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

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58 **Introduction**

59 Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative therapeutic measure
60 for hematopoietic neoplastic diseases such as leukemia and malignant lymphoma, and

61 non-neoplastic diseases such as aplastic anemia. Advancement in supportive care including
62 conditioning regimens, antibiotics, and immunosuppressant agents have significantly reduced
63 transplantation-related mortality and improved survival rate after transplantation [1]. On the other
64 hand, a decline in physical function after allo-HSCT has been recently recognized as a new concern,
65 and complications after allo-HSCT are considered as one of the factors responsible [2]. The major
66 complication after allo-HSCT is acute graft-versus-host disease (GVHD). Acute GVHD is caused
67 by lymphocytes derived from donors recognizing the normal organ of the recipient as foreign.
68 Acute GVHD is characterized by selective damage to the skin, liver, and the gastrointestinal tract.
69 Currently, it has been reported that moderate to severe acute GVHD develops in about 20% of
70 patients after allo-HSCT, regardless of the Human leukocyte Antigen (HLA) disparity, conditioning
71 regimen, or the use of immunosuppressive agents [3-4]. High-dose corticosteroid is the standard
72 first-line therapeutic drug in acute GVHD. The use of corticosteroid is designed to suppress the
73 donor lymphocyte-mediated immune insult on the recipient tissues. However, high doses of
74 corticosteroids are associated with the occurrence of various serious side effects, one of which is
75 skeletal muscle atrophy [5-9]. In previous reports, it has been shown that corticosteroid-induced
76 muscle atrophy develops in 40% of patients who receive high doses of corticosteroids [2].
77 Severity of acute GVHD has been classified according to the method defined by Grucksberg [10].
78 Clinical situations in which implementation of rehabilitation becomes difficult due to severe acute
79 GVHD is common. However, the effect of the severity of acute GVHD on the physical function
80 after allo-HSCT remains to be elucidated. The purpose of this study was to investigate the effect of

81 the severity of acute GVHD on physical function after allo-HSCT retrospectively.

82

83 **Patients and Methods**

84 A total of 147 patients who received allo-HSCT at the Kyoto University Hospital between 2010 and
85 2017 were included in this study. 16 patients who died during the hospitalization period and 55
86 patients whose physical functions could not be evaluated were excluded, and eventually 76 patients
87 were included in this study. There was no significant difference in the patient characteristics and
88 physical function before transplantation between enrolled and excluded patients (data not shown).
89 Severity of acute GVHD was classified according to the method defined by Grucksberg [10].

90 There were 35 patients who did not have acute GVHD during the hospital stay and 41 patients who
91 developed acute GVHD (Grade I: 13, Grade II: 22, Grade III-IV: 6) (Figure I). This study was
92 approved by the Institutional Review Board of Kyoto University Hospital (Approval number:
93 R0715). All patients were informed about the study procedures before the tests and written
94 informed consent was obtained.

95

96 **Variables**

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

101 medical record system.

102

103 **Evaluation of physical functions**

104 An evaluation of physical function was conducted based on the knee extensor strength and
105 six-minute walk distance (6MWD) test. Knee extensor strength was measured using the IsoForce
106 GT-330 (OG Giken Co., Ltd., Okayama, Japan) during isometric contraction for 3 seconds. With
107 the patient in a sitting position with the hip and knee at an angle of 90°, the force sensor was placed
108 5 cm above the lateral malleolus. The better of two trials was used as the score. Torque was
109 calculated by multiplying strength by the lever arm and was expressed as a percentage of body
110 weight (Nm/kg) [11]. The 6MWD test was conducted according to the protocol recommended by
111 the American Thoracic Society [12]. The course set a straight course of 30 m in the corridor and
112 6MWD was measured under maximum effort.

113

114 **Time of Evaluation**

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

120

121 **Statistical analysis**

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

127

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

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

138

139 **Diagnosis of acute GVHD**

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

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

149

150 **Results**

151 **Patient background and treatment characteristics**

152 Among the patients, 54% developed acute GVHD. The mean age of the patients without acute
153 GVHD was 45.5(21-66) years, and that of patients with acute GVHD was 45.5(19-66) years.

154 Among patients who did not develop acute GVHD, 23 were in complete remission, while 12 were
155 in non-remission at transplantation. Among patients who developed acute GVHD, 24 were in
156 complete remission, while 17 were in non-remission at transplantation. Characteristics of the
157 patients and treatment contents according to the severity of acute GVHD are shown in Table 1.

158 Among patients with acute GVHD, 32% had grade I, 54% had grade II, and 15% had grade III-IV
159 disease. There was no significant difference in the patient background characteristics and treatment

160 contents at transplantation. There was no significant difference in number of engraftment days
161 between the groups. However, length of hospital days after transplantation was significantly longer
162 in Grade II and Grade III-IV groups than that in the non-GVHD group (Grade II, $p<0.01$; Grade
163 III-IV, $p<0.01$) (Figure III). Total protein did not show any significant change in any of the groups
164 (Figure IV).

165

166 **Changes in physical function and rehabilitation implementation rate**

167 In the non-GVHD and Grade I groups, the 6MWD significantly decreased from before
168 transplantation to after transplantation (non-GVHD, $p<0.01$; Grade I, $p<0.01$), and it recovered
169 significantly at the time of discharge (non-GVHD, $p<0.01$; Grade I, $p<0.01$). In the Grade II group,
170 the knee extensor strength and 6MWD significantly decreased from before transplantation to after
171 transplantation ($p<0.01$), and it recovered significantly at the time of discharge ($p<0.01$) (Figure IV).

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

177 In the Grade III-IV groups, the rehabilitation implementation rate significantly decreased from pre-
178 HSCT period to post-HSCT discharge ($p<0.01$). In the Grade III-IV groups, the rehabilitation
179 implementation rate during post-HSCT discharge significantly decreased compared to the

180 non-GVHD groups, Grade I and II groups (non-GVHD, $p<0.01$; Grade I, $p<0.01$; Grade II, $p<0.01$).
181 Additionally, total rehabilitation implementation rate also significantly decreased in Grade III-IV
182 group compared to the non-GVHD and Grade II groups (non-GVHD, $p<0.01$; Grade II, $p<0.01$)
183 (Figure V).

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

190

191 Discussion

192 Acute GVHD after allogeneic HSCT has been reported to suppress physical function after
193 transplantation [2,15,16]. However, there is no report that examines the influence of differences in
194 the severity of acute GVHD on the clinical courses and physical function after transplantation in
195 detail. In this study, 54% of patients developed acute GVHD with 32% Grade I, 54% Grade II, and
196 15% Grade III-IV based on severity. Grucksberg's classification focuses mainly on the symptoms of
197 skin, liver, and intestinal tract, and its grade increases as the symptoms become severe. In this study,
198 there was no significant difference in the number of engraftment days between groups regardless of
199 the degree of severity of acute GVHD. However, the number of hospital days prolonged with the

200 increase in acute GVHD grade level, requiring hospitalization for about 80 days in Grade III-IV
201 group. When acute GVHD develops, the treatment method changes depending on THE severity. In
202 case of mild acute GVHD, concentration of cyclosporine or tacrolimus in the blood is measured and
203 adjusted to an appropriate concentration [17]. On the other hand, in case of moderate or more acute
204 GVHD, corticosteroid therapy is usually selected as the initial treatment. If it becomes severe,
205 corticosteroid treatment may be insufficient and secondary therapies (anti-thymocyte globulin,
206 mesenchymal stem cell, etc.) are required [18-21]. Therefore, in the Grade III-IV group, the number
207 of hospital days increases due to prolonged therapeutic intervention for acute GVHD after
208 transplantation.

209 Studies focusing on changes in physical functions after allo-HSCT have shown that exercise
210 tolerance and lower limb muscle strength decrease in the early stage of transplantation [22-26]. In
211 the early stages after transplantation, the amount of physical activity decreases due to environmental
212 restrictions specific to transplantation, such as clean room management besides transplant-related
213 complications. On the other hand, it has been reported that the amount of physical activity increases
214 and physical function improves when the transplanted donor stem cells engraft and the clean room
215 management ends [27]. In the non-GVHD and the grade I-II groups, the rehabilitation
216 implementation rate was maintained at a high level throughout the transplantation treatment process.
217 Furthermore, since there was little therapeutic intervention for acute GVHD at the early stage of
218 transplantation, it was considered that physical function was suppressed due to the decrease in the
219 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

240 strength. High dose corticosteroid therapy is selected as a treatment option when acute GVHD
241 becomes severe [18-21]. Corticosteroid-induced muscle atrophy, which affects Type II fiber
242 (fast-twitch muscle fiber), is a complication of corticosteroid administration [30-31]. Knee extensor
243 strength is a method of evaluating muscular strength which occupies a large amount of Type II fiber
244 [32]. Therefore, it was considered that the knee extensor strength significantly decreases due to the
245 influence of high dose corticosteroid administration. In addition, it is suggested that in the group
246 requiring a high dose of corticosteroid, the lower limb muscular strength may not sufficiently
247 recover even at discharge. Our results showed significantly reduced 6MWD after transplantation
248 regardless of the severity of acute GVHD, supporting the results from previous reports [33-34].
249 However, the knee extensor strength and the 6MWD did not show the same change in each group.
250 The 6MWD is a method of evaluating the entire endurance performance, which includes various
251 other factors apart from the lower limb muscular strength. In this study, the rehabilitation
252 implementation rate and the rate of change of the 6MWD were found to have a significant
253 correlation. The 6MWD recovered significantly due to successful implementation of rehabilitation
254 in patients with mild acute GVHD and those who did not develop acute GVHD. In the Grade III-IV
255 group, reduction of lower limb muscle strength due to corticosteroid administration was also
256 considered as a factor to inhibit recovery of 6MWD, in addition to factors such as difficulty in
257 rehabilitation accompanied by severe GVHD. As a result, we concluded that continued
258 rehabilitation is necessary to restore endurance performance. The limitation of this study is that we
259 were unable to examine physical activity after transplantation in further detail. Furthermore, there is

260 a possibility of selection bias since 55 patients were not evaluated for physical function.

261

262 **Conclusion**

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

271

272 **Acknowledgements**

273 We are grateful to the medical, nursing, and laboratory staff of the participating departments for
274 their contributions to this study.

275 **Funding information**

276 none

277

278 **Compliance with ethical standards**

279 **Conflict of interest**

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

281 **Ethical approval**

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

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390

391 **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 (<i>Men/Female</i>) ^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, <i>kg/m²</i> ^b	21.7±3.7	21.8±3.6	21.3±3.9	22.3±2.5
Diagnosis (<i>Leukemia/MDS/Lymphoma</i>) ^a	24/6/5	8/2/3	12/6/4	4/1/1
Transplantation type (<i>Bone marrow/Cord blood/Peripheral blood</i>) ^a	19/11/5	8/2/3	10/11/1	3/1/2
HLA (<i>Matched relative/Matched unrelative</i>) ^a	22/13	6/7	9/13	4/2
Complete remission (<i>CR/non-CR</i>) ^a	23/12	10/3	10/12	4/2
Conditioning (<i>Myeloablative/Reduced intensity</i>) ^a	20/15	9/4	18/4	4/2

392 MDS : myelodysplastic syndrome

393 HLA : Human Leukocyte Antigen

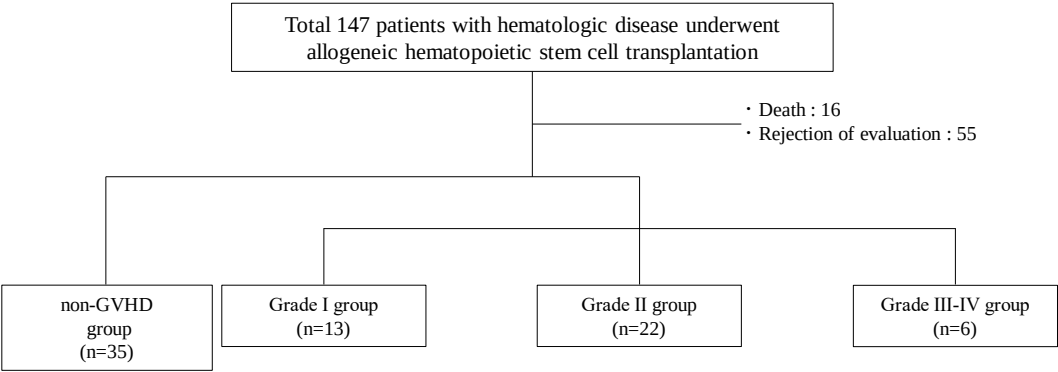
394 ^a Values represents the number of patients in each category

395 ^b Values represents the mean ± SD

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398 **Figure I.** Study flow chart



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

Protocol	Before transplantation		Transplantation	After transplantation		
	Two weeks before transplantation	Previous treatment		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		

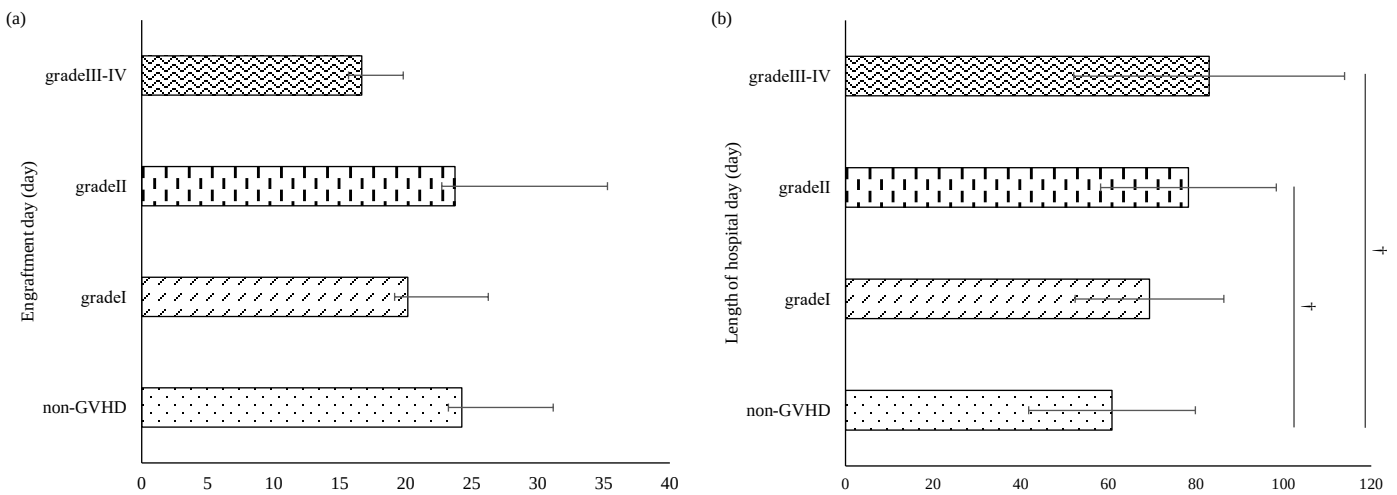
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410 **Figure III.** Days of engraftment day and length of hospital days of the non-GVHD and acute
411 GVHD groups.

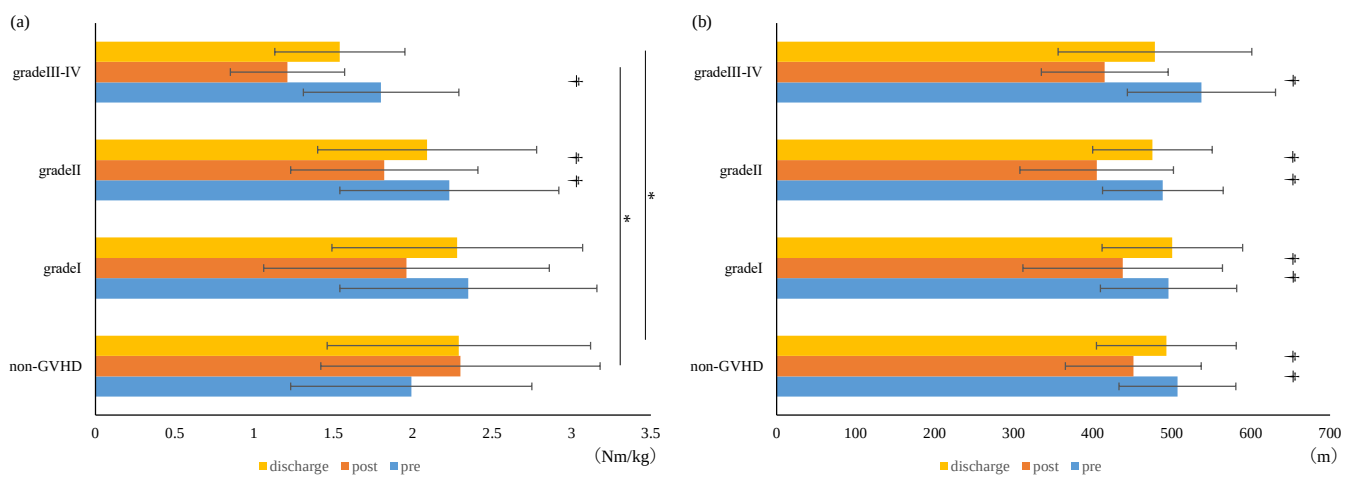


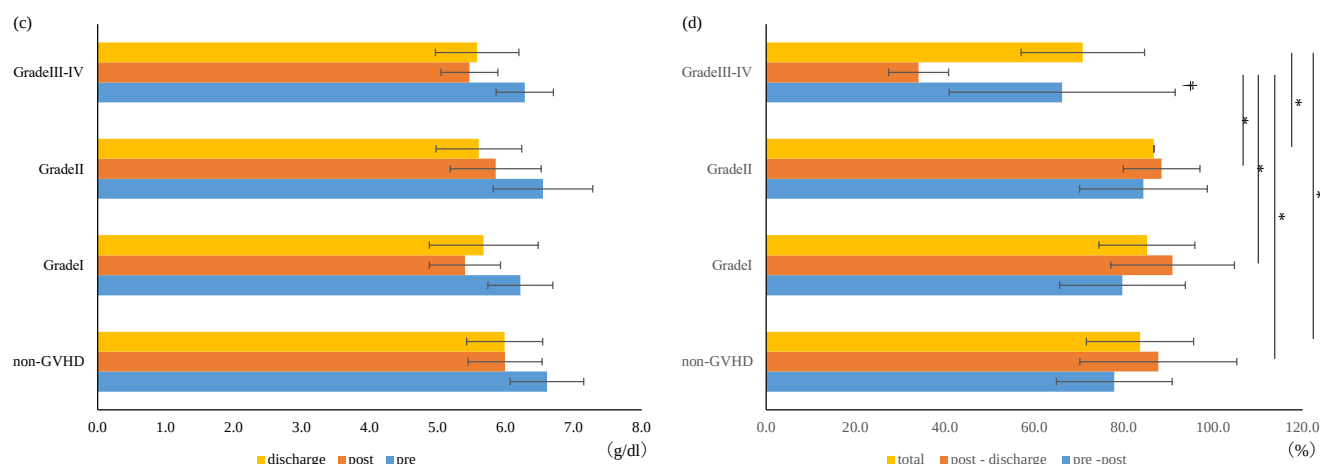
(a) Engraftment days of non-GVHD group and acute GVHD group.

(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.

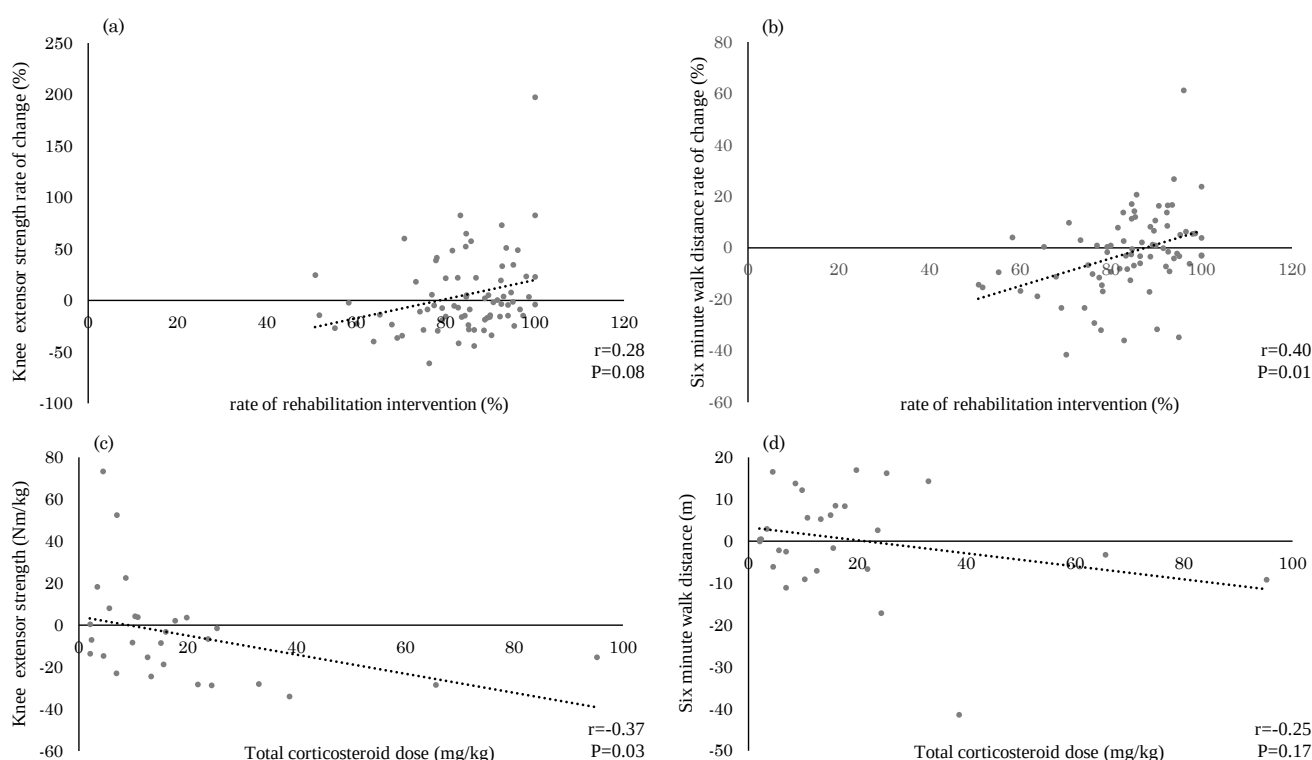
(c) Total protein of non-GVHD group and acute GVHD group.

(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.