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Factors Affecting Day-to-Day Variations in Tacrolimus Concentration among Children and Young Adults Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Tacrolimus is widely used as prophylaxis for graft versus host disease (GVHD) in allogeneic stem cell transplantation (allo HSCT). It has a narrow therapeutic index range; high tacrolimus concentrations are associated with toxicity, whereas low concentrations are associated with an increased risk of GVHD. Although dose adjustments based on therapeutic drug monitoring are performed, unexpected large variations in tacrolimus concentration are sometimes encountered. The available evidence suggests that the factors affecting tacrolimus concentration are not fully understood. This study was aimed primarily at investigating the factors affecting day to day variations in tacrolimus concentration in children and young adults who received continuous tacrolimus infusion after allo HSCT. The secondary objective was to identify the factors causing large variations (>20%) in tacrolimus concentrations. This retrospective cohort study comprised 123 consecutive pediatric and young adult patients (age <25 years) who received continuous i.v. tacrolimus infusion after allo HSCT at Shinshu University Hospital, Matsumoto, Japan, between January 2009 and December 2021. To compare day to day variations in tacrolimus concentration without consideration of the tacrolimus dose, 2 consecutive days when the tacrolimus dose was not changed were selected from between the first post allo HSCT day of a tacrolimus concentration >7 ng/mL and day 28 post allo HSCT. Subsequently, information for the subsequent 24 hours was collected along with the tacrolimus concentrations and hematocrit values. Tacrolimus concentration was determined using whole blood samples. Tacrolimus concentrations were significantly higher in patients who received red blood cell concentrate (RCC) transfusions ($P < .0001$) and methotrexate (P .0162), patients with persistent fever (P .0056), and patients with a decline in fever (P .0003). In contrast, tacrolimus concentrations were significantly lower in patients who received platelet concentrate (PC) transfusions ($P < .0001$), who redeveloped fever (P .0261), and who had a replaced tacrolimus administration route set (P .0008). Variations in tacrolimus concentration were significantly correlated with variations in hematocrit (r .556; $P < .0001$). Body weight ($P < .0001$), RCC transfusion ($P < .0001$), methotrexate use (P .0333), persistent fever (P .0150), and decline in fever (P .0073) were associated with a sharp increase in tacrolimus concentration. In contrast, body weight ($P < .0001$), PC transfusion (P .0025), and replacement of the tacrolimus administration route set (P .0025) were associated with a sharp decrease in tacrolimus concentration. RCC and PC transfusions, fever, methotrexate administration, and replacement of the tacrolimus administration route set were independent factors affecting day to day variations in tacrolimus concentration. In addition to these factors, low body weight was a risk factor for both sharp increases and decreases in tacrolimus concentration. These findings suggest the need for better control of tacrolimus concentration using whole blood samples.

INTRODUCTION

Effective prevention of graft versus host disease (GVHD) is critical for successful allogeneic stem cell transplantation (allo HSCT), because GVHD is associated with nonrelapse mortality [1,2]. Tacrolimus and a short course of methotrexate are standard regimens used for GVHD prevention [3–6]; however, tacrolimus has a narrow therapeutic index. Although high concentrations are associated with toxicity [7,8], low

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concentrations are linked to an increased risk of acute GVHD [9,10]. Common adverse effects of tacrolimus include hypomagnesemia, hyperkalemia, hypertension, and nephrotoxicity. Nevertheless, tacrolimus has rarely been associated with life threatening complications, such as transplantation associated thrombotic microangiopathy and neurotoxicity. The pharmacokinetic characteristics of tacrolimus show wide intraindividual and interindividual variability [11], proposed to be secondary to multiple factors, including food, drug drug interactions, and drug disease interactions [12–16]. Therefore, tacrolimus dose adjustments based on therapeutic drug monitoring (TDM) are required.

Tacrolimus is generally administered by continuous i.v. infusion beginning on the day before allo HSCT at a dose of .03 mg/kg/day [11,17,18]. The reported target range of tacrolimus concentration is 10 to 20 ng/mL in adults; however, only a few studies have evaluated tacrolimus concentration targets in children undergoing allo HSCT [19]. According to Watanabe et al. [9], the mean whole blood level of tacrolimus as a continuous infusion should be maintained between 7 and 12 ng/mL in pediatric patients. A tacrolimus level >15 ng/mL may be associated with an increased risk of toxicity [10]. Based on these reports, the target range for tacrolimus level in our department during the first 4 weeks after allo HSCT is 7 to 15 ng/mL; to the greatest extent possible, we ensure that tacrolimus levels remain within the 10 to 12 ng/mL range.

To strictly control tacrolimus concentration, we monitor tacrolimus concentration daily for at least the first 28 consecutive days after allo HSCT and adjust the tacrolimus dose to the target concentration. Nevertheless, unexpected significant variations in tacrolimus concentration are sometimes encountered. These findings suggest that the factors affecting tacrolimus concentration are not fully understood.

The pharmacokinetics of tacrolimus is unique. After systemic administration, tacrolimus is distributed mainly in RBCs. Because tacrolimus concentration is commonly measured in whole blood, variations in hematocrit level affect tacrolimus concentration [20–22]. Uchida et al. [23] recently reported that transfusion of RBC concentrate (RCC) is associated with an increase in tacrolimus concentration [23]. However, confounding factors that affect tacrolimus concentration, such as other concomitant drugs related to CYP3A4, immunosuppressive agents (eg, steroids, methotrexate), and patient status, have not been fully considered in previous studies, and the effect of transfusions on tacrolimus concentration is not fully understood. Therefore, in the present study, we investigated the factors that affect day to day variations in tacrolimus concentration in children and young adults who received a continuous tacrolimus infusion after allo HSCT.

METHODS

Study Design and Settings

This was a retrospective cohort study of 123 consecutive pediatric and young adult patients age < 25 years who received a continuous infusion of tacrolimus after allo HSCT at Shinshu University Hospital, Matsumoto, Japan, between January 2009 and December 2021. Data were collected retrospectively from the patients' electronic medical records at Shinshu University Hospital. Patient characteristics and transplantation related data collected included age, sex, primary diagnosis, height, weight, date of transplantation, stem cell source, and donor type.

To compare day to day variations in tacrolimus concentration without considering the tacrolimus dose administered, 2 consecutive days when the tacrolimus dose was not changed (day X − 1 and day X) were selected from between the first day of a tacrolimus concentration >7 ng/mL post allo HSCT to day 28 post allo HSCT (Figure 1). Information was collected during the subsequent 24 hour period (from blood analysis on day X to blood analysis on day X + 1). Specifically, the following information was collected: development of fever, persistence of fever, decline of fever, initiation of CYP3A4 related drug treatment (eg, azole antifungals [voriconazole, itraconazole], calcium blockers, proton pump inhibitors), initiation of immunosuppressive agents (eg, steroids, mycophenolate mofetil), administration of methotrexate, transfusion (RCC, platelet concentrate [PC], or fresh frozen plasma [FFP]), and replacement of the tacrolimus administration route set. Fever was defined as body temperature ≥38.0 °C. "Persistence of fever" started at least before blood examination on day X and continued until after blood examination on day X + 1. "Decline in fever" was defined as fever subsiding to <38.0 °C from the blood analysis on day X to the blood analysis on day X + 1 and remaining below 38.0 °C. Tacrolimus concentrations and hematocrit values on days X and X + 1 were recorded as well. To prevent

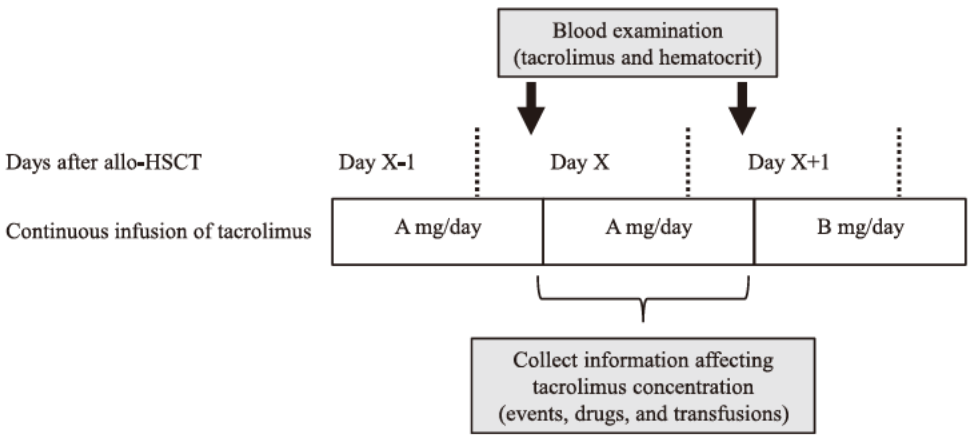

Figure 1. Outline of data collection. To compare the day-to-day variations in tacrolimus concentration without considering the tacrolimus dose, 2 consecutive days when the tacrolimus dose was not changed (days X − 1 and X) were selected from between the first day when tacrolimus concentration was >7 ng/mL post-allo-HSCT to day 28 post-allo-HSCT. Information for the subsequent 24 hours (from blood examination on day X to blood examination on day X + 1) was collected in addition to the tacrolimus concentration and hematocrit value.

catheter infection, we changed the tacrolimus administration route set every 1 to 2 weeks.

This study was approved by the Research Ethics Committee of Shinshu University School of Medicine (approval 5144). The requirement for informed consent was waived because of the study's retrospective nature, in which we analyzed existing data with no identifiable private information.

Tacrolimus Dose and Monitoring

Tacrolimus was administered as a continuous i.v. infusion at .03 mg/kg/day over a 24 hour period starting 1 day before allo HSCT. The target blood concentration of tacrolimus was 7 to 15 ng/mL and, to the greatest possible extent, the concen tration was controlled in the range of 10 to 12 ng/mL. Because all patients received tacrolimus by continuous i.v. infusion until at least day 28 post allo HSCT, all data were collected at the time of continuous i.v. infusion. Whole blood concentra tions of tacrolimus were analyzed using the Elecsys tacrolimus assay kit on a Cobas e411 analyzer (Roche Diagnostics, Indian apolis, IN), which is based on an electrochemiluminescence immunoassay, between October 2020 and December 2021 [24]. The ARCHITECT tacrolimus immunoassay (Abbott, Abbott Park, IL), which is based on a chemiluminescent microparticle immunoassay, was used from January 2009 to September 2020 [25].

Study Objective

The primary objective of this study was to investigate the factors affecting day to day variations in tacrolimus concen trations among children and young adults who received a con tinuous i.v. infusion of tacrolimus after allo HSCT. The secondary objectives were to identify the factors that led to sharp variations (≥20%) in tacrolimus concentration and to assess the effects of transfusions on variations in tacrolimus concentration.

Statistical Analysis

Patient and disease characteristics in all cohorts were sum marized using descriptive statistics. Univariate analyses were conducted using an unpaired *t* test to analyze the factors influ encing tacrolimus concentration. Next, multivariate analyses were conducted using multiple linear regression to identify the independent factors affecting tacrolimus concentration. The following variables were considered in these analyses: body weight, sex, administration of RCC, administration of PC, the start of steroid therapy, administration of methotrexate, initiation of CYP3A4 related drug treatment, development of fever, decline of fever, persistence of fever, and replacement of the tacrolimus administration route set. Multivariate analyses were conducted using logistic regression to identify indepen dent risk factors that led to sharp variations in tacrolimus con centration. The following variables were considered in the multivariate analysis of factors influencing a sharp increase in tacrolimus concentration: body weight, sex, administration of RCC, initiation of steroid therapy, administration of methotrex ate, initiation of CYP3A4 related drug treatment, persistence of fever, and decline of fever. The following variables were con sidered in the multivariate analysis of factors influencing sharp decreases in tacrolimus concentration: body weight, sex, administration of PC, development of fever, and replacement of the tacrolimus administration route set. Simple linear regression was used to assess the correlation between the 2 continuous variables (variations in tacrolimus concentration versus variations in hematocrit, variations in hematocrit ver sus body weight, and variations in tacrolimus concentration versus body weight). All statistical analyses were performed using EZR [26] and Prism version 9.4.1 (GraphPad Software, San Diego, CA). All reported *P* values were 2 sided, and statisti cal significance was set at $P < .05$.

RESULTS

Patient Characteristics

Patient demographic and clinical characteristics are pre sented in Table 1. One hundred twenty three patients who underwent allo HSCT were included in this study. Twenty five (20.3%) allo HSCT cases were second or subsequent allo HSCT. The median patient age at the time of transplantation was 9.2 years (range, 1.7 months to 24 years). Our cohort included 69 male patients (56.1%) and 89 patients with a malignant dis ease (72.4%). Cord blood was the most common source of stem cells (n = 78; 63.4%). Eighty one allo HSCTs (65.9%) were per formed after a myeloablative conditioning regimen.

Factors Influencing Tacrolimus Concentration

A total of 1315 points for 2 consecutive days when the tacrolimus dose was not changed were extracted from the cohort for analysis. Univariate analysis using an unpaired *t* test showed significantly higher tacrolimus concentrations in patients who received RCC transfusion (percent variation: 24.90 versus .73; $P < .0001$) and steroid initiated patients (percent variation: 9.45 versus 1.36; $P = .0401$) than in those who did not receive these interventions. Tacrolimus concen trations also were significantly higher in patients with

Table 1
Patient Characteristics (N = 123)

Characteristic	Value
Age at allo-HSCT, yr, median (range)	9.2 (0-24)
Age group, n (%)	
0-5 yr	40 (32.5)
6-10 yr	30 (24.4)
11-15 yr	28 (22.8)
>15 yr	25 (20.3)
Sex, n (%)	
Male	69 (56.1)
Female	54 (43.9)
Diagnosis, n (%)	
Acute leukemia	66 (53.7)
Lymphoma	9 (7.3)
Myelodysplastic syndrome	9 (7.3)
Solid tumor	5 (4.1)
Chronic active Epstein-Barr virus infection and related disease	2 (1.6)
Primary immune deficiency syndrome	11 (8.9)
Hemophagocytic lymphohistiocytosis	3 (2.4)
Aplastic anemia/bone marrow failure	14 (11.4)
Metabolic disease	4 (3.3)
Stem cell source, n (%)	
Bone marrow	35 (28.5)
Cord blood	78 (63.4)
Peripheral blood	10 (8.1)
Related donor, n (%)	
Yes	29 (23.6)
No	94 (76.4)
Conditioning regimen, n (%)	
Myeloablative	81 (65.9)
Nonmyeloablative	42 (34.1)

Table 2
Univariate and Multivariate Analysis of Factors Influencing Tacrolimus Concentration

Variables	Univariate Analysis			Multivariate Analysis				
	% variation in tacrolimus concentration		*P* Value	B	95% CI		*β*	*P* Value
	With	Without			Lower	Upper		
Body weight, per 1-kg increase	NA	NA	NA	-0.003	-0.05	0.05	-0.003	0.8942
Female sex	2.23	0.81	0.1010	0.881	-0.62	2.38	0.028	0.2483
Administration of RCC	24.90	-0.73	< 0.0001	25.403	22.75	28.06	0.452	< 0.0001
Administration of PC	-1.26	3.27	< 0.0001	-4.094	-5.63	-2.56	-0.128	< 0.0001
Start of steroid administration	9.45	1.36	0.0401	6.005	-0.76	12.77	0.042	0.0819
Administration of methotrexate	3.85	1.29	0.1510	3.732	0.69	6.77	0.058	0.0162
Initiation of CYP3A4-related drug treatment	2.22	1.45	0.8590	1.572	-5.89	9.04	0.010	0.6797
Development of fever	1.52	-0.35	0.4180	-4.674	-8.79	-0.56	-0.056	0.0261
Decline of fever	8.30	1.18	0.0016	7.500	3.47	11.53	0.092	0.0003
Persistence of fever	6.67	1.26	0.0189	5.594	1.64	9.55	0.067	0.0056
Replacement of the tacrolimus administration route set	-14.89	1.53	0.0104	-18.845	-29.81	-7.88	0.028	0.0008

B indicate partial regression coefficient; *β*, standardized partial regression coefficient; NA, not applicable.

persistent fever (percent variation: 6.67 versus 1.26; $P = .0189$) and in those whose fever declined (percent variation: 8.30 versus 1.18; $P = .0016$) than in those who did not experience these events. On the other hand, tacrolimus concentrations were significantly lower in patients who received PC transfusion (−1.26 versus 3.27; $P < .0001$) and in whom the tacrolimus administration route set was replaced (−14.89 versus 1.53; $P = .0104$) compared with those who did not receive these interventions (Table 2). Multivariate analysis using multiple linear regression showed significantly higher tacrolimus concentrations in patients who received RCC transfusion (partial regression coefficient [B], 25.403; 95% confidence interval [CI], 22.75 to 28.06; $P < .0001$) and methotrexate (B, 3.732; 95% CI, .69 to 6.77; $P = .0162$) compared with those who did not. Tacrolimus concentrations also were significantly higher in patients with persistent fever (B, 5.594; 95% CI, 1.64 to 9.55; $P = .0056$) and in those whose fever declined (B, 7.500; 95% CI, 3.47 to 11.53; $P = .0003$). In contrast, tacrolimus concentration was significantly lower in patients who received PC transfusion (B, −4.094; 95% CI, −5.63 to −2.56; $P < .0001$), developed fever (B, −4.674; 95% CI, −8.79 to −.56; $P = .0261$), and had a replaced tacrolimus administration route set (B, −18.845; 95% CI, −29.81 to −7.88; $P = .0008$) (Table 2). The standardized partial regression coefficient (β) for RCC transfusion was the highest among the variables ($\beta = .452$).

Correlation between Variations in Tacrolimus Concentration and Hematocrit Variation

Figure 2 shows that the percent variation in tacrolimus concentration was significantly correlated with the percent variation in hematocrit ($r = .556$; $P < .0001$).

Hematocrit Variations after PC Transfusion

Hematocrit was significantly lower in patients who received PC transfusion compared with those who did not (−1.15% versus 1.23%; $P = .0005$) (Supplementary Figure S1).

Factors Influencing Sharp Variations in Tacrolimus Concentrations

A multivariate logistic regression model was then developed. The independent predictors of sharp variations (≥20%) in tacrolimus concentration and the corresponding odds ratios (ORs) and 95% CIs are shown in Figures 3 and 4. Body weight (OR, .97; 95% CI, .95 to .98; $P < .0001$), administration of RCC (OR, 27.60; 95% CI, 17.10 to 44.70; $P < .0001$), methotrexate (OR, 2.23; 95% CI, 1.07 to 4.69; $P = .0333$), persistent fever (OR, 2.95; 95% CI, 1.23 to 7.04; $P = .0150$), and decline in fever (OR, 3.18; 95% CI, 1.36 to 7.40; $P = .0073$) were associated with sharp increases in tacrolimus concentration (Figure 3). On the other hand, body weight (OR, .96; 95% CI, .94 to .98; $P < .0001$), administration of PC (OR, 2.19; 95% CI, 1.32 to 3.65; $P = .0025$), and replacement of the tacrolimus administration route set (OR, 16.50; 95% CI, 2.69 to 101.00; $P = .0025$) were associated with sharp decreases in tacrolimus concentration (Figure 4).

Effects of Body Weight on Variations in Hematocrit and Tacrolimus Concentration after RCC Transfusion

The percent variation in hematocrit was weakly correlated with body weight during RCC transfusions ($r = .376$; $P < .0001$) (Figure 5A). However, the percent variation in hematocrit in patients weighing <20 kg did not correlate with body weight ($r = .010$; $P = .4567$) (Figure 5B), whereas that in patients weighing ≥20 kg was significantly correlated with body weight ($r = .605$; $P < .0001$) (Figure 5C). Likewise, the percent variation in tacrolimus concentration among patients

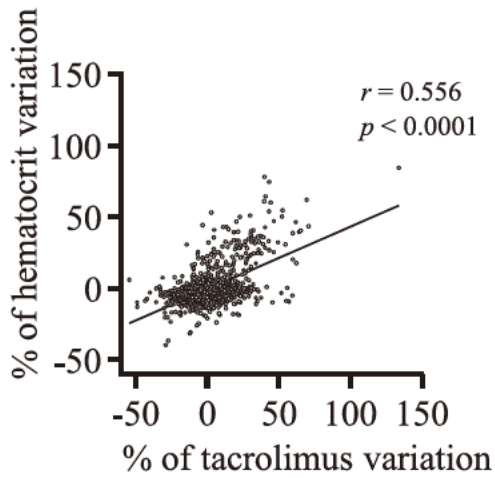

Figure 2. Correlation between tacrolimus concentration and hematocrit value.

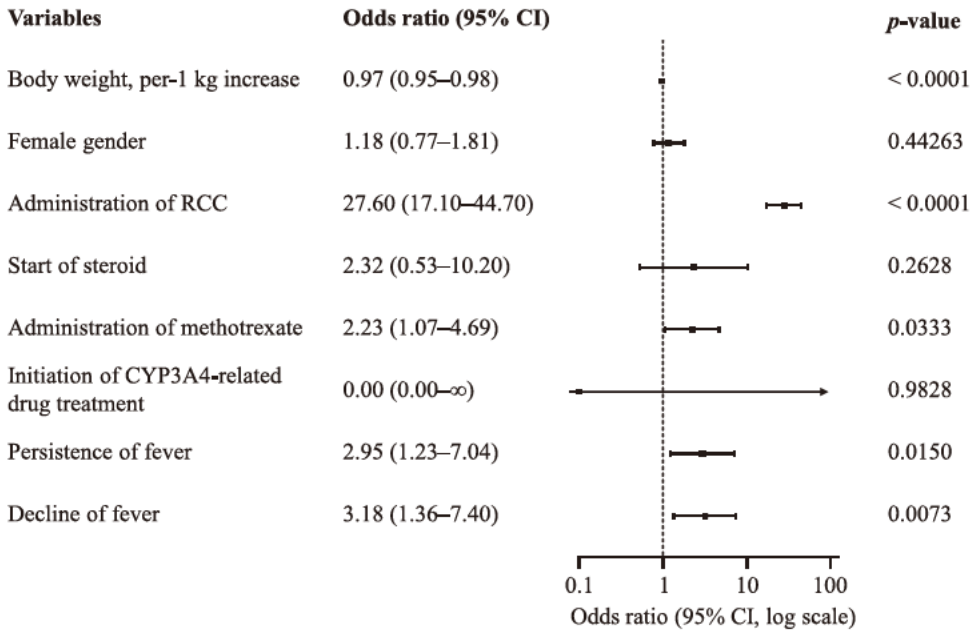

Figure 3. Multivariate analysis of factors influencing sharp increases in tacrolimus concentration.

who received RCC transfusion was weakly correlated with body weight (r = .391; P < .0001) (Figure 5D). However, the percent variation in tacrolimus concentration among patients weighing <20 kg did not correlate with body weight (r = .080; P = .5672) (Figure 5E), whereas that in patients weighing ≥20 kg was significantly correlated with body weight (r = .444; P = .0004) (Figure 5F).

DISCUSSION

In this study, we identified RCC and PC transfusions, fever, administration of methotrexate, and replacement of the tacrolimus administration route set as independent factors affecting day to day variations in tacrolimus concentration. Previous studies have shown that the hematocrit value affects tacrolimus concentration in whole blood because tacrolimus is mainly associated with erythrocytes (approximately 85%), followed by diluted plasma proteins and lymphocytes (approximately 14% and 0.5%, respectively) [20 23,27]. Our results confirm these findings, in that an increase in hematocrit and RCC transfusion correlated with an increase in tacrolimus concentration. In addition, in this study, PC transfusion correlated with a decrease in tacrolimus concentration, a finding that has not been reported previously. The decrease in tacrolimus concentration after PC transfusion may be due to a decrease in hematocrit (Supplementary Figure S1). The concentration of RBCs may be diluted by PC transfusion, and anemia may progress owing to inadequate recovery of hematopoietic ability after allo HSCT.

The occurrence of sharp variations (≥20%) in tacrolimus concentration is a major issue in clinical settings, and we investigated the factors leading to these sharp variations. We identified low body weight as an independent risk factor, in addition to transfusions, fever, administration of methotrexate, and replacement of the tacrolimus administration route set. Remarkably, low body weight is a risk factor for both sharp increases and decreases in tacrolimus concentration, suggesting that large variations in tacrolimus concentration tend to occur in patients with low body weight. We hypothesized that one of the reasons why low body weight is a risk factor for a sharp increase in tacrolimus concentration is the difference in the impact of RCC transfusion on body weight. Specifically, we expected that body weight would correlate with hematocrit

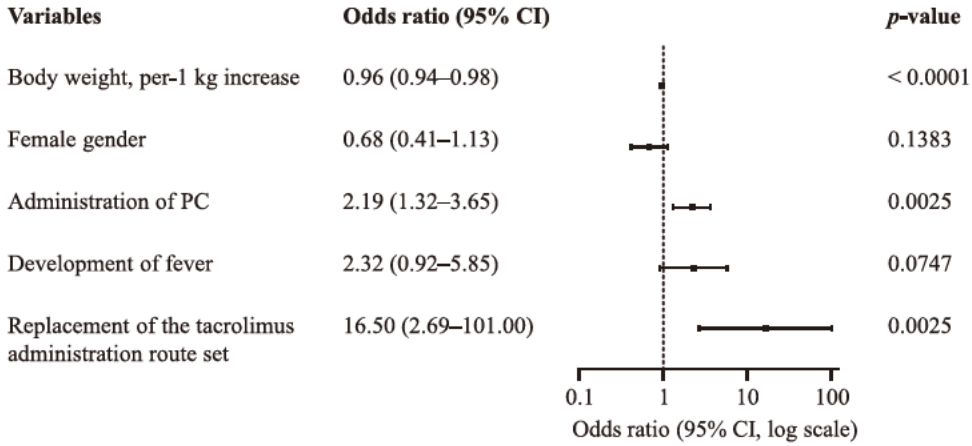

Figure 4. Multivariate analysis of factors influencing sharp decreases in tacrolimus concentration.

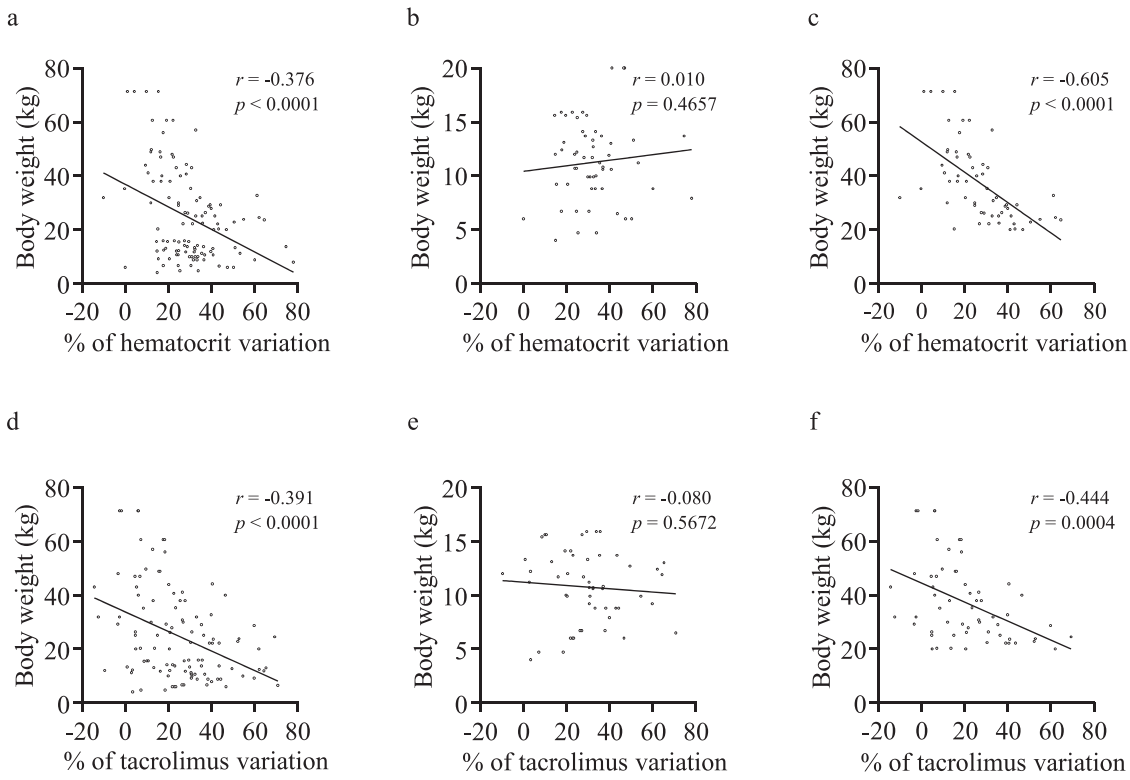

Figure 5. Effect of body weight on variations in hematocrit and tacrolimus concentration after RCC transfusion. (A) Correlation between percent variation in hematocrit and body weight. (B) Correlation between percent variation in hematocrit and body weight in patients weighing <20 kg. (C) Correlation between percent variation in hematocrit and body weight in patients weighing ≥20 kg. (D) Correlation between percent variation in tacrolimus concentration and body weight. (E) Correlation between percent variation in tacrolimus concentration and body weight in patients weighing <20 kg. (F) Correlation between percent variation in tacrolimus concentration and body weight in patients weighing ≥20 kg.

variation after RCC transfusion and, consequently, would also correlate with tacrolimus variation. This seems to be partially true. The percent variation in hematocrit in patients weighing ≥20 kg was significantly correlated with body weight (Figure 5C), whereas that in patients weighing <20 kg was not (Figure 5B). Likewise, the percent variation in tacrolimus con centration in patients weighing ≥20 kg was significantly corre lated with body weight (Figure 5F), whereas that in patients weighing <20 kg was not (Figure 5E). This result may be due to the amount of RCC transfusions in our department; almost all patients weighing ≥20 kg received 2 units of RCC, whereas those weighing <20 kg received an amount corresponding to their body weight.

The other reasons why low body weight is a risk factor for the sharp variations in tacrolimus concentration remain unclear, however. One possible explanation is the difference in tacrolimus clearance according to age. Because younger age has been associated with greater tacrolimus clearance [28], tacrolimus concentrations in younger patients may change readily. To test this hypothesis, we analyzed the factors affect ing sharp variations in tacrolimus concentrations using age instead of body weight for multivariate analysis (Supplemen tary Tables S1 and S2). Similar to low body weight, younger age was associated with sharp increases and decreases in tacrolimus concentration ($P < .0001$). These results show that younger age tends to induce a sharp variation in tacrolimus concentration. Therefore, because low body weight and young age are risk factors for sharp variations in tacrolimus concen tration, more careful monitoring is needed for these patients.

Because tacrolimus is metabolized mainly via CYP3A4, con comitant use of drugs metabolized via CYP3A4 or those that inhibit CYP3A4 could increase tacrolimus concentration [19,29,30]. In this study, initiating drugs related to CYP3A4 within 24 hours did not affect tacrolimus concentration (Table 2 and Figure 3). These results indicate that 24 hours is too early to analyze the effect of drugs metabolized via CYP3A4 on tacrolimus concentration. Extending the data col lection period is difficult, however. Although extending the period may be useful for accurately evaluating CYP3A4 related drugs against tacrolimus concentration, other factors influenc ing tacrolimus concentration, such as transfusions and fever, may become obscure. Determining the proper data collection period and duration of collection is also difficult. A limitation of this study is that some factors that gradually influence tacrolimus concentration were not fully considered. When analyzing the factors that gradually influence tacrolimus con centration and metabolism, the assessment of sequential tacrolimus dosing and the ratio of tacrolimus concentration to dosage (C/D) would be better than day to day variations in tacrolimus concentration.

Polymorphisms in CYP3A5, CYP3A4, and ABCB1 also have been frequently reported to influence tacrolimus metabolism [19,31,32]. For example, transplantation recipients with the CYP3A5*3/*3 genotype exhibit twice the tacrolimus C/D as recipients with CYP3A5*1/*1 and *1/*3. It would have been better to include these polymorphism data when analyzing factors influencing tacrolimus concentration (especially in the range of fluctuation of tacrolimus concentration). One limita tion of this study was that we did not include these polymor phism data in the statistical analysis.

An increase in tacrolimus concentration after immunosup pressant administration has been noted occasionally. In this

study, we evaluated the impact of immunosuppressants, (ie, steroids and methotrexate) on tacrolimus concentration immediately after starting immunosuppressants. Administration of methotrexate was an independent factor affecting tacrolimus concentration, whereas the start of steroid administration was not. The reason for the different impacts of methotrexate and steroids on tacrolimus concentration is unclear; however, one possibility might be the difference in the time from administration to the emergence of effects against lymphocytes for each immunosuppressant. Similar to CYP3A4 related drugs, the assessment of sequential tacrolimus dosing and C/D after immunosuppressant administration will be useful to clarify this issue.

In this study, we attempted to classify the impact of fever on tacrolimus concentration. Both a decline in fever and persistence of fever were associated with an increase in tacrolimus concentration, whereas the occurrence of fever was associated with a decrease in tacrolimus concentration (Table 2). Yanagisawa et al. [28] reported that engraftment syndrome increased tacrolimus clearance. As the main symptom of engraftment syndrome is fever, variations in tacrolimus concentration could be associated with fever related to engraftment syndrome.

Tacrolimus exerts its pharmacologic activity via T lymphocytes [33], and thus the most useful TDM information is derived from intracellular quantification in lymphocytes [34–37]. However, the current standard and recommended matrix for tacrolimus TDM is whole blood owing to its ease of withdrawal, higher concentration compared with plasma, and, consequently, simpler management in terms of sensitivity [19,38]. Therefore, variations in tacrolimus concentrations determined using whole blood associated with variations in hematocrit could be “superficial” and may result in incorrect tacrolimus dose adjustments. These “superficial” variations in tacrolimus concentrations may be reduced in 2 ways: (1) by using the formula to correct the tacrolimus level at the hematocrit level [39] and (2) by minimizing day to day variations in hematocrit specifically, reducing the volume of transfusion (especially that of RCC) during the early post transplantation period compared with that in the other periods. In clinical settings, minimization of day to day variations in hematocrit would be more acceptable than using the correction formula.

In conclusion, this study demonstrates that RCC and PC transfusions, fever, methotrexate administration, and replacements of the tacrolimus administration route set are independent factors affecting day to day variations in tacrolimus concentration. Low body weight and younger age are also risk factors for both sharp increases and decreases in tacrolimus concentration, in addition to the aforementioned factors. By considering these factors, better control of tacrolimus concentration could be achieved.

Supplementary Figure S1. Variations in hematocrit after PC transfusion.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.01.014.

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