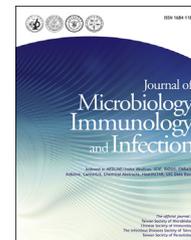




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ORIGINAL ARTICLE

# Risk factors and outcomes of cytomegalovirus viremia in pediatric hematopoietic stem cell transplantation patients



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Risk factors

**Abstract** *Background:* Cytomegalovirus (CMV) is a major pathogen causing significant mortality and morbidity in immunocompromised hosts. It is important to find risk factors associated with CMV viremia and its outcome.

*Methods:* We investigated the incidence, time of onset, risk factors for CMV viremia, and characteristics of CMV diseases in 57 pediatric patients receiving hematopoietic stem cell transplantation (HSCT). Between August 2011 and March 2014, cases of pediatric HSCT patients at the National Taiwan University Children's Hospital were reviewed. Viremia was identified by plasma CMV real-time polymerase chain reaction (RT-PCR) assay.

*Results:* Eighteen (32%) of the 57 patients developed CMV viremia at a median of 23 days post-HSCT (range -3 to +721 days). Eighty-nine percent (16/18) of CMV viremia occurred within 100 days posttransplantation. Four patients finally had CMV diseases (1 with CMV colitis and 3 with CMV pneumonitis) and one patient died of CMV pneumonitis complicated with pulmonary hemorrhage and sepsis. Significant risk factors associated with CMV viremia via univariate analysis include older age ( $p = 0.03$ ), leukemic patients [odds ratio (OR): 5.2, 95% confidence interval (CI): 1.52~17.7,  $p = 0.008$ ], allogeneic HSCT (OR: 14.57, 95% CI: 1.76~120.5,

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$p = 0.002$ ), antithymoglobulin (ATG) use before transplantation (OR: 5.09, 95% CI: 1.52~16.9,  $p = 0.007$ ), graft-versus-host disease (GvHD) (OR: 10.1, 95% CI: 2.7~38.7,  $p < 0.001$ ), and gastrointestinal GvHD (OR: 10.9, 95% CI: 2.72~43.9,  $p = 0.001$ ).

**Conclusion:** In pediatric posttransplantation patients, CMV viremia mostly occurred within 100 days after transplantation. Risk factors associated with CMV viremia include older diagnostic age, leukemic patients, unrelated donor HSCT, pretransplant ATG use, GvHD, and gastrointestinal GvHD.

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## Introduction

Cytomegalovirus (CMV), is a virus which belongs to the human herpesviruses, betaherpesviruses. It is a major pathogen causing significant mortality in immunocompromised hosts, such as prematurity and posttransplantation patients.<sup>1,2</sup> From previous studies, the incidence of CMV viremia in pediatric post bone marrow transplantation patients was variable, from 12.8% to 41%.<sup>2–5</sup> The clinical manifestations of CMV infection range from asymptomatic infection, that is, active CMV replication in the blood in the absence of clinical symptoms or organ failure, to CMV disease, characterized by CMV infection with systemic end-organ involvement.<sup>5</sup>

Previous known risk factors of CMV reactivation were CMV serostatus, transplantation type, T-cell depletion regimen, and graft-versus-host-disease (GvHD) development.<sup>3,4,6,7</sup> The objective of this retrospective study was to evaluate the incidence and timing of CMV viremia in a pediatric population who had received hematopoietic stem cell transplantation (HSCT). The risk factors for CMV viremia were studied and characteristics of CMV disease are described.

## Patients and methods

### Study design and data collection

This study was approved by the ethics committee of National Taiwan University Hospital, Taiwan. We retrospectively reviewed 57 pediatric patients receiving HSCT at the National Taiwan University Hospital during August 2011 to March 2014. No intervention or clinical specimen was collected from patients. All of the information of the patients in this study was obtained from medical records. We collected their demographics, underlying diseases, serostatus, HSCT type and post-HSCT condition, antithymoglobulin (ATG) use, medications, and outcomes.

### Identifications and definitions

Currently, quantitative polymerase chain reaction (PCR) assays of plasma samples have become the most common way in the determination of viral load during CMV infection of transplant patients. In this study, CMV real-time PCR (RT-PCR) was performed for quantitation of plasma CMV viremia

and bronchoalveolar lavage fluid using COBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Molecular Systems, Inc., Branchburg, NJ, USA), the first U.S. Food and Drug Administration (FDA)-approved assay. The quantitated cut-off level of this method was 150 copies/mL. CMV viremia was defined by positive CMV-specific RT-PCR in plasma. Since conditioning chemotherapy of these patients, plasma CMV PCR was checked by weekly surveillance, which would continue until patients were discharged or had a negative plasma CMV PCR result.

Diagnosis of CMV disease was based on positive CMV viremia and either one of the following: the presence of appropriate symptoms (fever, and/or organ associated symptoms, such as cough/diarrhea, etc.) combined with a positive CMV RT-PCR from the coherent specimen (e.g., pneumonia with positive CMV RT-PCR from bronchoalveolar lavage fluid), or a tissue biopsy specimen that was CMV-positive by either culture or immunohistochemical staining.<sup>2,8,9</sup>

### Statistical analysis

All analyses were performed using PASW version 18.0 (SPSS, Chicago, IL, USA). Comparisons between the CMV viremia group and nonviremia group were performed using the Mantel-Haenszel chi-square test for categorical variables to calculate odds ratio (OR) and 95% confidence interval (CI) and using the Mann-Whitney  $U$  test and Wilcoxon signed rank test for continuous variables. Multivariate analysis was performed using multiple logistic regression. A  $p$  value  $< 0.05$  was considered to be statistically significant. All results of significance are reported as two-tailed.

## Results

### Demographics

From August 2011 to March 2014, 60 patients who received HSCT were initially reviewed in the pediatric department of National Taiwan University Hospital. However, three patients were excluded: one patient had disease relapse on posttransplantation Day +27 and finally expired due to Gram-negative bacteria sepsis, and the other two patients experienced severe sepsis immediately after HSCT and expired on posttransplantation Day +9 and Day +28, respectively. Therefore, a total of 57 patients were

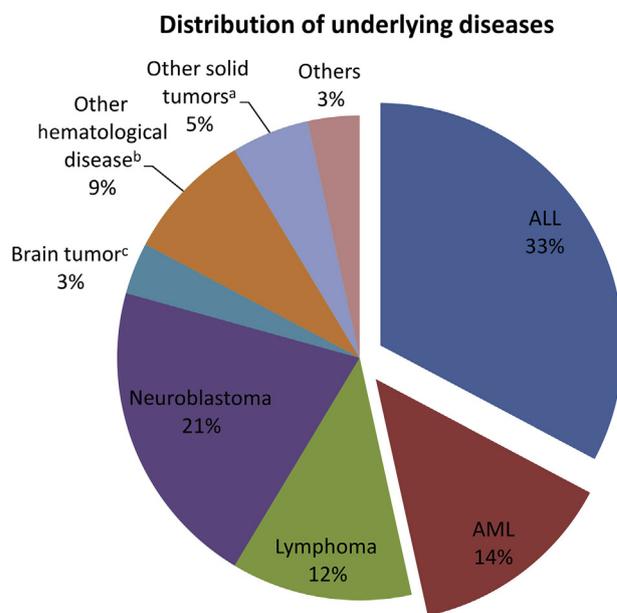
retrospectively reviewed and included in this study, and their age ranged from 0 years to 20 years at disease diagnosis in the pediatric hemato-oncological ward of National Taiwan University Hospital. The mean age ± standard deviation of patients was 8.1 ± 5.9 years (range 0–20 years). The male to female ratio was 1.2 (31 men, 26 women). Patients’ demographic data are shown in Table 1.

Patients’ underlying diseases are shown in Figure 1. The majority (56%) of patients had hematological diseases, including acute lymphoblastic leukemia (33%), acute myeloid leukemia (14%), and other hematological diseases, such as aplastic anemia, red cell aplasia, myelodysplasia, and thalassemia (9%). In addition, other diagnoses included two (3%) of brain tumor, three (5%) of other solid tumors (retinoblastoma, mediastinal tumor, and rhabdomyosarcoma), and two (3%) of others, including severe combined immunodeficiency and osteopetrosis.

**CMV viremia**

Thirty-two percent (18/57) of patients developed CMV viremia at a median of 23 days post-HSCT (range from Day –3 to Day +721). Eighty-nine percent (16/18) of the CMV viremia occurred in the early posttransplantation period (<100 days). In viremia patients, the initial viral load ranged from 1.5 × 10<sup>2</sup> copies/mL to 2.2 × 10<sup>6</sup> copies/mL. One patient developed late-onset CMV viremia on post-transplantation Day +721 and he had the highest initial viral load (2.2 × 10<sup>6</sup> copies/mL) among viremia patients.

Of these 18 viremia patients, 44% (8/18) did not receive antiviral treatment and 56% (10/18) did: 17% (3/18) received ganciclovir treatment, 6% (1/18) had ganciclovir plus foscarnet, 22% (4/18) received ganciclovir plus CMV immunoglobulin, and 11% (2/18) received intravenous immunoglobulin treatment. Only one patient received foscarnet because of marked myelosuppression after ganciclovir use and there was no clinical evidence of ganciclovir-resistant CMV in these 10 patients. After the anti-CMV



**Figure 1.** Distributions of underlying diseases. <sup>a</sup> Retinoblastoma, mediastinal tumor, rhabdomyosarcoma. <sup>b</sup> Thalassemia, anaplastic anemia, red cell aplasia, myelodysplasia. <sup>c</sup> Severe combined immunodeficiency, osteopetrosis. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia.

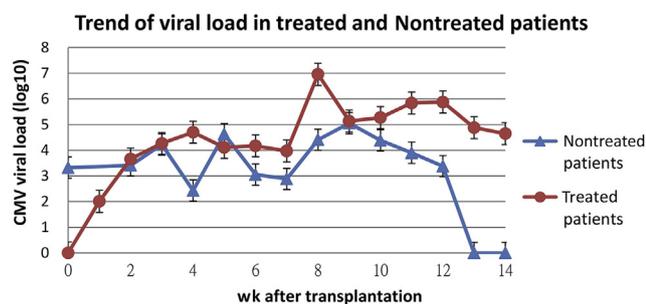
treatment, their CMV viral load decreased significantly (*p* = 0.037 using the Wilcoxon signed rank test).

Figure 2 demonstrates the trend of average CMV viral load in treated and nontreated patients. Due to PCR equipment limits, viral load <150 copies/mL or undetectable was defined as 0 copies/mL in the figure. In these two groups, high viral load was most frequently found within 3 months after transplantation. In Figure 2, a total of eight treated patients and eight nontreated patients were recorded. Data of two treated patients were not shown in the figure due to late-onset of CMV viremia. In the treated

**Table 1** Baseline characteristics and distribution of risk factors

	Viremia ( <i>n</i> = 18)	Nonviremia ( <i>n</i> = 39)	OR	95% CI	<i>p</i>
Mean age of diagnosis (y)	10.9 ± 6.3	6.8 ± 5.3			0.03
Mean HSCT age (y)	12.6 ± 6.9	8.7 ± 5.8			0.08
Sex (%)					0.57
	Female	18 (46)			
	Male	10 (56)			
Diagnosis (%)			5.2	1.52 ~ 17.7	0.008
	Leukemia	13 (72)			
	Others	5 (28)			
HSCT type (%)			14.57	1.76 ~ 120.5	0.002
	Allo-PBSCT <sup>a</sup>	17 (95)			
	Auto-PBSCT	1 (5)			
Antithymoglobulin (ATG) use (%)			5.09	1.52 ~ 16.9	0.007
	Yes	12 (67)			
GvHD (%)	14 (78)	11 (28)	10.1	2.7 ~ 38.7	< 0.001
GI aGvHD (%)	10 (56)	4 (10)	10.9	2.72 ~ 43.9	0.001

<sup>a</sup> acute.  
aGvHD = acute graft versus host disease; CI = confidence interval; GI aGvHD = gastrointestinal acute graft versus host disease; GvHD = graft-versus-host-disease; OR = odds ratio; PBSCT = peripheral blood stem cell transplantation.



**Figure 2.** Viral load in treated and nontreated patients after transplantation. Numbers of each point in the figure were recorded in the following:

Number of patients in each point of treated and nontreated patients

Weeks after HSCT	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Treated (n)	8	8	8	8	8	8	7	6	6	5	5	4	4	2	2
Nontreated (n)	8	0	8	8	7	6	6	5	6	6	6	6	8	4	4

HSCT = hematopoietic stem cell transplantation.

and nontreated groups, patient numbers of each point are cited in the figure legend. Patient numbers fluctuated for reasons such as patient's death or some interrupted data. The average initial viral loads in the treated and nontreated groups were  $2 \times 10^4$  copies/mL (range, 315–120,000 copies/mL) and  $2.6 \times 10^4$  copies/mL (range, 152–150,000 copies/mL), respectively. The average highest viral loads in treated and nontreated groups were  $3.8 \times 10^6$  copies/mL (range, 550–27,000,000 copies/mL) and  $1.2 \times 10^5$  copies/mL (range, 356–620,000 copies/mL), respectively. There was no significant difference in the initial and highest viral load between these two groups ( $p = 0.85$  and  $p = 0.72$ , respectively).

Of 18 viremia patients, nine patients expired: two patients died of disease progression with complications such as sepsis and gastrointestinal bleeding, three died of sepsis (2 with documented pathogens), two died of disease progression, one died of progressive lung GvHD with respiratory failure, and one died of CMV pneumonia complicated with pulmonary hemorrhage and sepsis.

In this study, a high prevalence of pretransplant CMV seropositivity was found in recipients, overall up to 82% (47/57), with 86% (19/22) in 0–6-year-olds, 83% (10/12) in 6–12-year-olds, and 87% (20/23) in >12-year-olds. A total of 17 (17/18, 94%) recipients with CMV viremia were initially CMV-seropositive. Only one (1/18, 6%) seronegative recipient in viremic patients received autologous transplantation.

### Risk factors associated with CMV viremia

CMV serostatus and viral load of 18 viremic patients are shown in Table 2. Only one patient was CMV serologically negative who had undergone autologous HSCT. The other two groups of CMV serostatus, D–/R+ (donor-seronegative/recipient-seropositive) and D+/R+ (donor-seropositive/recipient-seropositive), consisted of seven patients and 10

**Table 2** Cytomegalovirus (CMV) serostatus and viral load of 18 viremic patients

CMV serostatus	Initial viral load [median, range (copies/mL)]	<i>p</i>
D–/R– (n = 1)	2700	
D–/R+ (n = 7)	$3.9 \times 10^2$ , 283–150,000	0.24
D+/R+ (n = 10)	$5.8 \times 10^3$ , 152–120,000	
CMV serostatus	Highest viral load [median, range (copies/mL)]	<i>p</i>
D–/R– (n = 1)	7500	
D–/R+ (n = 7)	$1.39 \times 10^5$ , 4450–3,000,000	0.11
D+/R+ (n = 10)	$1.9 \times 10^4$ , 356–27,000,000	

D– = donor seronegative; D+ = donor seropositive; R– = recipient seronegative; R+ = recipient seropositive.

patients, respectively. There was no statistical influence by donor or recipient serostatus on the initial and highest viral load ( $p = 0.24$  and  $p = 0.11$ , respectively). Risk factors associated with CMV viremia are summarized in Table 1. Sex distribution in the two groups was similar, with 44% female in the viremia group and 46% female in the nonviremia group. The mean age of diagnosis of the viremia and the nonviremia group was  $10.9 \pm 6.3$  years and  $6.8 \pm 5.3$  years, respectively ( $p = 0.03$ ). As for diagnosis, leukemia patients carried a greater risk of CMV viremia (OR = 5.2, 95% CI 1.52–17.7,  $p = 0.008$ ). Ninety-five percent (17/18) of patients of the viremia group received allo-peripheral blood stem cell transplantation (PBSCT), which increased the risk of CMV viremia (OR = 14.57, 95% CI 1.76–120.5;  $p = 0.002$ ). Sixty-seven percent (12/18) of patients of the viremia group had pretransplantation ATG use which was also a risk factor (OR = 5.09, 95% CI 1.52–16.9,  $p = 0.007$ ). Seventy-eight percent (14/18) of patients of the viremia group had more than one kind of GvHD (OR = 10.1, 95% CI 2.7–38.7,  $p < 0.001$ ). Gastrointestinal GvHD was another risk factor (OR = 10.9, 95% CI 1.72–43.9,  $p = 0.001$ ), whereas skin GvHD showed no statistical significance. Multivariate analyses were also performed, but did not show statistical evidence for these factors.

### CMV disease

Clinical features of the four patients with CMV disease are shown in Table 3. One patient developed CMV colitis and the other three developed CMV pneumonia, which accounted for 7% (4/57) in post-HSCT patients. Initial viral load of these four patients ranged from  $3.1 \times 10^2$  copies/mL to  $3.6 \times 10^3$  copies/mL, similar to the other 14 asymptomatic CMV viremia patients ( $p = 0.67$ ). As for the highest CMV viral load, it ranged from  $3.6 \times 10^3$  copies/mL to  $3 \times 10^6$  copies/mL in CMV disease patients; from the 14 patients with only viremia, the highest CMV viral load ranged from  $3.5 \times 10^2$  copies/mL to  $2.7 \times 10^7$  copies/mL ( $p = 0.67$ ). Three patients with CMV disease were diagnosed with hematological malignancy. All of these four patients were allogeneic HSCT recipients, had positive CMV serology before transplantation, and experienced acute GvHD.

**Table 3** Characteristics of four cytomegalovirus (CMV) disease patients

	Patient 1	Patient 2	Patient 3	Patient 4
Diagnosis	Hodgkin lymphoma	ALL	AML	MDS
Diagnostic age (y)	18	10	0.3	20
Age at BMT (y)	22.08	11.75	0.95	24.36
Conditioning regimen	Carmustine, etoposide, Ara-C, melphalan <sup>a</sup>	Busulfan, cyclophosphamide <sup>b</sup>	Busulfan, cyclophosphamide	Busulfan, cyclophosphamide
BMT type	allo	allo	allo	allo
ATG use	Yes	Yes	Yes	No
D/R CMV serology	D+/R+	D-/R+	D-/R+	D-/R+
Onset of viremia(d)	49	34	11	126
CMV disease	Colitis	Pneumonitis	Pneumonitis	Pneumonitis
GvHD	GI Grade I	GI Grade I Skin Grade I Liver Grade I	GI Grade I Skin Grade II Liver Grade I	Skin Grade I Suspicious GI GvHD
Treatment	Ganciclovir Foscarnet	Ganciclovir CMV-Ig	Ganciclovir CMV-Ig	Ganciclovir
Outcome	Expired	Alive	Expired	Alive
Cause of death	PDRAB sepsis		Pulmonary hemorrhage, sepsis	

<sup>a</sup> Carmustine 300 mg/m<sup>2</sup>/dose QD for 1 day; etoposide 200 mg/m<sup>2</sup>/dose QD for 4 days; Ara-C 200 mg/m<sup>2</sup>/dose bid for 4 days; melphalan 140 mg/m<sup>2</sup>/dose for 1 day.

<sup>b</sup> Busulfan 4 mg/kg/day for 4 days (5 mg/kg/day if patient <6 years old); cyclophosphamide 60 mg/kg/day for 2 days.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; Ara-C = cytarabine; ATG = antithymoglobulin; BMT = bone marrow transplantation; CMV = cytomegalovirus; CMV-Ig = cytomegalovirus immune globulin; D = donor; GI = gastrointestinal; GvHD = graft versus host disease; MDS = myelodysplastic syndrome; MUD = matched unrelated donor; PDRAB = pan-drug resistant *Acinetobacter baumannii*; QD = daily; R = recipient.

Three of these patients received myeloablative conditioning chemotherapy with busulfan and cyclophosphamide, pretransplantation ATG, and developed acute gastrointestinal GvHD. All received ganciclovir treatment. Two of them died: one died of CMV pneumonitis complicated with pulmonary hemorrhage and sepsis, and the other died of pan-drug resistant *Acinetobacter baumannii* sepsis. As for the other 14 asymptomatic patients with viremia, eight of them (43%) received treatment.

With regards to risk factors of developing CMV disease, there was no statistically significant difference between hematological malignancy, HSCT type, ATG usage, and GvHD.

## Discussion

Infection is always a major issue for post-HSCT patients and CMV plays a major role in viral infection in pediatric post-HSCT patients. Among the 57 pediatric post-HSCT patients involved in this study, from August 2011 to March 2014, a high incidence (32%) of CMV viremia was found. Eighty-nine percent of CMV viremia occurred within the early post-transplantation period (<100 days), compatible with the previous report by Sousa et al.<sup>10</sup> Four patients (4/57, 7%) finally developed CMV disease, and one of them died of CMV pneumonia with pulmonary hemorrhage and concurrent sepsis.

Comparisons between the viremia group and the non-viremia group revealed that older diagnostic age, leukemia, allo-PBSCT, ATG use, GvHD, and gastrointestinal GvHD were possible significant risk factors for CMV viremia (Table 1). The results were compatible with those of previous

reports.<sup>3,6,7</sup> The allo-PBSCT regimen and ATG use were both related to T-cell immunity destruction and delayed recovery in transplantation patients.

As regards CMV serostatus, in previous studies<sup>11</sup>, donor and recipient serostatus played a major role in post-transplantation CMV infection. In addition, recipient seropositivity carries a higher risk for mortality and morbidity.<sup>12–14</sup> Ljungman et al<sup>15</sup> found that approximately 80% of CMV seropositive recipients may experience CMV infection after allogeneic bone marrow transplantation without prophylaxis. In our study, we found a high prevalence of CMV seropositive recipients of up to 82% (47/57). CMV viremia incidence was 32%, which was much lower than the results of previous studies.<sup>15</sup> In our study, pre-HSCT acyclovir prophylaxis may be one reason for this phenomenon.

Allogeneic-HSCT accounts for 94% (17/18) in viremia patients. Allogeneic-HSCT can cause marked immunosuppression, which interferes with T-cell reconstruction after transplantation. The immune reconstruction process is correlated strongly with different kinds of opportunistic infections. Innate immunity restores rapidly after allogeneic HSCT, however, adaptive immunity takes much longer. Prior to reconstruction of adaptive immunity, there is an increased susceptibility to fungal and viral infection, such as candida, *Aspergillus*, and herpes group virus.<sup>16</sup> In a recent review, cytotoxic pretransplantation conditioning and posttransplantation alloreactivity are risk factors for T-cell immune deficiency because they independently interfere with normal thymus function.<sup>17</sup> In addition, the intensity of conditioning constitutes the most important parameters influencing T-cell expansion.<sup>18</sup> In comparison

with mini-myeloablative chemotherapy which has a reduced risk of early CMV disease, myeloablative chemotherapy would prolong the duration of recovery of adaptive T-cell immunity.<sup>19</sup> For adaptive immunity or so-called cellular immunity, much more time is needed for recovery than for innate immunity. In patients who received managements associated with T-cell or thymic damage, such as a myeloablative regimen, total body irradiation, ATG, or cyclosporine, the cellular immunity reconstruction would be delayed.<sup>20</sup> Total body irradiation was analyzed in this study without a statistically significant difference, so the data was not shown.

Other known risk factors, like cord blood transplantation, chemotherapy with fludarabine-containing regimens, transplantation of T-cell-depleted stem cells (with either graft manipulation *ex vivo* or use of anti-T-cell antibodies *in vivo* with alemtuzumab) and a low CD4 count, and undetectable CMV-specific T-cell immunity have all been reported previously, however, the above were not found in this study due to no available data for these patients.<sup>15</sup>

With regards to CMV disease in posttransplantation patients, pneumonia is the most common and serious.<sup>19,21</sup> The incidence of CMV pneumonia ranges from 1% to 6% in autologous bone marrow transplantation recipients and from 10% to 30% in allogeneic bone marrow transplantation recipients.<sup>22</sup> Konoplev et al<sup>21</sup> stated that the incidence of CMV pneumonia was significantly higher among patients with hematological malignancies than those with solid tumors (5% vs. 1%,  $p = 0.019$ ). In our study, three of four patients with CMV diseases had hematological malignancies. Jang et al<sup>23</sup> identified several risk factors for developing CMV diseases, including high initial viral load, leukopenia, and neutropenia at the time of detection of CMV viremia, and leukopenia remains an independent predictor ( $p = 0.045$ ) on multivariate analysis. In our study, the difference in initial viral load between the viremia-only group and the CMV diseases group was not significant [median, 3900 copies/mL (range, 152–15,000 copies/mL) vs. 2025 copies/mL (range, 315–53800 copies/mL),  $p = 0.67$ , Mann-Whitney  $U$  test]. In addition, the highest viral load during anti-CMV treatment in the CMV disease group and non-CMV disease group was  $3 \times 10^6$ /mL and  $2.7 \times 10^7$ /mL, respectively ( $p = 0.67$ ).

According to a previous definition of conditioning regimens,<sup>24,25</sup> three of these four patients received myeloablative conditioning chemotherapy in this study. Myeloablative conditioning chemotherapy uses very high doses of chemotherapy or radiation prior to transplant, to kill nearly all of the cancer cells and normal cells in the bone marrow, predisposing recipients to infectious complications that may contribute to a poor outcome.

From Figure 2, it can be seen that the viral load of the treated group seemed higher than that of the nontreated group, however, it is not comparative in the figure due to the different treatment timing of these patients. In the nontreated group, viral load gradually decreased approximately 3 months after HSCT, which could be explained by T-cell recovery. For the treated group, viral load several weeks after treatment significantly decreased ( $p = 0.037$ ).

In this study, all patients received acyclovir as prophylaxis regimen and weekly monitoring of plasma CMV viral

load, which is a routine program in our pediatric hematological transplant patients. Current efforts have gone from treatment of CMV to its prevention or preemptive treatment. Some reports supported the benefit of prophylactic ganciclovir or high dose acyclovir use,<sup>26,27</sup> however, rare evidence was shown in pediatric patients. In addition to prophylaxis, preemptive therapy has been discussed for a long time, with several documented benefits. However, it remains controversial as to whether prophylaxis or preemptive therapy is the optimal strategy for preventing CMV disease.

There are several limitations in this study. First, this is a retrospective chart review, and all of the information was collected from medical records. Second, a relatively small sample size was included with an even smaller number of CMV disease patients. Third, posttransplantation patients had variable diversity of disease severity and clinical condition with different immunosuppressant use. All of the above factors could interfere with the susceptibility and severity of opportunistic infection in these patients and further statistical results.

In conclusion, the incidences of CMV viremia and CMV disease were high, 32% and 7%, respectively, in this study. Viremia occurred mostly during the early posttransplantation period (89%), usually within 100 days after transplantation. Risk factors associated with CMV viremia include older diagnostic age, leukemic patients, unrelated donor HSCT, pretransplant ATG use, GvHD, and gastrointestinal GvHD. Monitoring of CMV viremia and early preemptive therapy are recommended to reduce morbidity and mortality in the high-risk HSCT patients.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

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