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Evaluation of Platelet Parameters in Patients With Secondary Failure of Platelet Recovery and Cytomegalovirus Infection After Hematopoietic Stem Cell Transplantation

Yujian Zhao, B.S.[1†], Shuo An, BS.[1†], Hongchen Bi, B.S.[1], Xiaoli Luo, B.S.[1], Mingyang Wang, MM[2], Aiming Pang, MD[2], Erlie Jiang, MD[2], Yigeng Cao, MD[2], and Yujie Cui, MD[1]

Abstract

Objective: To investigate the clinical significance of changes in platelet parameters in patients with secondary failure of platelet recovery (SFPR) and cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation (HSCT).

Methods: In this retrospective study, 79 patients who had undergone allogeneic HSCT (allo-HSCT), including 40 patients with SFPR and 39 patients without SFPR, were recruited. The evaluated parameters were platelet count (PLT), plateletcrit (PCT), platelet-large cell ratio (P-LCR), mean platelet volume (MPV), platelet distribution width (PDW), the incidence of CMV infection after allo-HSCT, and the correlation of SFPR and CMV infection in patients who had undergone allo-HSCT. The control group included 107 healthy donors.

Results: The SFPR group had significantly lower megakaryocyte counts, PLT, and PCT and significantly higher P-LCR, MPV, and PDW than the healthy donor and non-SFPR groups. The incidence of CMV infection was higher in SFPR patients than in non-SFPR patients. Among the patients with SFPR, P-LCR, MPV, and PDW were lower in those with CMV DNA >8000 copies/mL than in those with CMV DNA <8000 copies/mL ($P < .05$ for all); the CMV viral load was slightly negatively correlated with MPV ($P = .0297$) and P-LCR ($P = .0280$).

Conclusion: We demonstrate for the first time that the level of platelet activation in SFPR patients, which was closely related to CMV infection, was higher than that in that in non-SFPR patients, and higher CMV load was associated with the inhibition of platelet activation.

Keywords

secondary failure of platelet recovery, platelet parameters, cytomegalovirus infection

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[1] School of Medical Laboratory, Tianjin Medical University, Tianjin, China
[2] State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Hematopoietic Stem Cell Transplantation Center, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China

[†] These authors contributed equally to this work.

Corresponding Author:
*Yujie Cui, School of Medical Laboratory, Tianjin Medical University, No. 1 Guangdong Road, Hexi District, Tianjin 300203, China.
Email:yujiecui1@126.com

Yigeng Cao, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences; Peking Union Medical College, No.288, Nanjing Road, Heping District, Tianjin, 300020, China.
Email: caoyigeng@ihcams.ac.cn

Introduction

Secondary failure of platelet recovery (SFPR) is a serious complication after hematopoietic stem cell transplantation (HSCT) and is defined as the achievement of a platelet count (PLT) of $\geq 50 \times 10^9$/L for 7 consecutive days without transfusion support after HSCT followed by a decline in PLT to $\leq 20 \times 10^9$/L for more than 7 consecutive days or the need for platelet transfusion .[1] A previous study reported that SFPR was significantly associated with the following risk factors: transplant from an unrelated donor, development of grade 2 to 4 acute graft-versus-host disease (GVHD), impaired renal or liver function, and cytomegalovirus (CMV) infection after engraftment.[2] Platelet parameters, such as PLT, platelet-large cell ratio (P-LCR), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), reflect the development, prognosis, and severity of various diseases .[3–5] Wang et al[4] have reported that patients with immune thrombocytopenic purpura had significantly lower PLT and PCT and higher P-LCR, P-LCR, and PDW than healthy individuals. However, the significance of platelet parameters in SFPR remains unclear. Importantly, studies have shown that patients with CMV infection after HSCT are at increased risk of SFPR. CMV-platelet interactions lead to proinflammatory and proangiogenic responses that exacerbate tissue damage.[6,7] However, the role of CMV infection in SFPR is unclear and the correlation between platelet parameters and CMV infection in patients with SFPR is unknown. Therefore, in this study, we aimed to explore the changes in the number and activity of platelets in patients with SFPR and the correlation of these changes with CMV infection.

Patients and Methods

Patients

The present study included 79 patients who underwent allogeneic HSCT (allo-HSCT) between January 2017 and September 2019 in the Stem Cell Transplantation Center at the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. SFPR was defined as a PLT of $\geq 50 \times 10^9$/L for 7 consecutive days without transfusion support after HSCT followed by a decline in PLT to $\leq 20 \times 10^9$/L for more than 7 consecutive days or the need for platelet transfusion. Non-SFPR was defined as a PLT of $\geq 20 \times 10^9$/L for 7 consecutive days without transfusion support after HSCT with no further dependance on platelet transfusion. The exclusion criteria were as follows: primary platelet engraftment failure after HSCT, death within 6 months after HSCT, recurrence of primary disease after transplantation, and incomplete or unavailable patient data. In addition, 107 healthy donors (HDs) were included as the control group.

Methods

Venous blood samples were analyzed using an XN-9000 or XE-2100 hematology analyzer (Sysmex) to determine PLT, P-LCR, PCT, MPV, and PDW. The bone marrow was aspirated by trained individuals following a standard operating procedure. The bone marrow samples from the posterior iliac crest were collected and placed on a glass slide. After drying and staining these samples, they were observed under a microscope and the number of megakaryocytes was counted by senior experts in blood cell morphology. All instruments were operated strictly in accordance with the standard operating procedures.

Timeline of Data Collection

In the HD group, the platelet parameters were evaluated at the time of physical examination. In the SFPR group, the bone marrow megakaryocyte counts were determined using the first bone marrow puncture after the decline in PLT to $\leq 20 \times 10^9$/L whereas the platelet parameters were evaluated after the SFPR diagnosis. In the non-SFPR group, the bone marrow megakaryocyte counts and platelet parameters were determined approximately 45 days after the allo-HSCT.

CMV Detection and Grouping

In the present study, the detection of CMV DNA copy number in venous blood by fluorescent PCR. The highest CMV DNA copy number after the diagnosis of CMV infection was used. We grouped by platelet activity indices, calculated and determined using the receiver operating characteristic curve that the cut off value of the CMV DNA copy number is 8000 copies/mL, meanwhile, CMV DNA copy number = 1000 copies/mL is the limit of detection. Therefore, we divided SFPR patients into 3 groups(CMV negative group, CMV<8000 copies/mL group and CMV>8000 copies/mL group) for research.

Statistical Analysis

All clinical data were analyzed using GraphPad Prism version 8 (GraphPad Software). Categorical data were presented as proportions and assessed using the χ^2 test. The Pearson's chi-square test or Fisher's exact test was performed for the general characteristics of the patient, such as comparing the differences in the effects of aGVHD (I-IV grade GVHD) on non-SFPR group and SFPR group. Continuous data were presented as means with standard deviation or medians with interquartile range. The Mann–Whitney test used to compare nonparametric quantitative variables between 2 groups, whereas the Kruskal–Wallis test and Brown–Forsythe and Welch analysis of variance were used to compare more than 2 groups. Correlation was evaluated by Pearson rank correlation coefficients. A P value of $<.05$ was considered to indicate statistical significance.

Results

General Characteristics of the Study Subjects

A total of 79 patients who had undergone allogeneic HSCT (allo-HSCT) between January 2017 and September 2019 at the

Table 1. Characteristics of the Study Cohort.

	Non-SFPR	SFPR	*P*
N	39	40	
Age(years)	36(22.00,45.00)	42(30.75,48.25)	.0412
Donor age(years)	35(30.00,45.50)	40(28.50,47.50)	.8634
Donor gender			.5000
Male to male	11	15	
Male to female	12	10	
Female to male	11	7	
Female to female	5	8	
Blood type match			.2672
Matched	24	16	
Major mismatched	6	11	
Minor mismatched	7	11	
Bidirectional mismatched	2	2	
Graft cell dose infused			.5379
MNC,108/kg	8.00(7.36,10.00)	10.16(8.31,12.68)	
CD34,106/kg	3.56(2.71,4.73)	2.97(2.34,3.44)	
HSCT classification			.4623
Unrelated donor HSCT	2	3	
Compatriots all together HSCT	22	17	
Haploid HSCT	15	20	
Diagnosis			.4605
AML	14	17	
ALL	7	5	
MAL	0	1	
CML	1	2	
MDS	9	12	
BMF	8	3	
GVHD preventive drug use			.0335
Tacrolimus/MMF/MTX	14	19	
Ciclosporin/MTX	16	6	
Ciclosporin/MMF/MTX	9	15	
100 days I-IV grade GVHD			.2022
0	25	19	
I	6	8	
II	6	4	
III	1	4	
IV	1	5	
GVHD in number of days	32(27.75,43.50)	38(31.00,59.00)	.2065

AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MAL, acute mixed lineage leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; BMF, bone marrow failure; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; SFPR, secondary failure of platelet recovery; HSCT, hematopoietic stem cell transplantation.

Stem Cell Transplantation Center at the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College were recruited. Of these 79 patients, 39 were non-SFPR patients and 40 were SFPR patients. The characteristics of SFPR and non-SFPR patients are presented in Table 1.

Platelet Parameters and Megakaryocyte Count in the HD, non-SFPR, and SFPR Groups

The PLT and PCT were significantly different among the HD, non-SFPR, and SFPR groups. Specifically, these 2 parameters, which were lowest in the SFPR group, were higher in the non-SFPR group ($P < .0001$) and the highest in the HD group ($P < .0001$) (Figure 1A and B). P-LCR, MPV, and PDW were not significantly different between the non-SFPR and HD groups ($P > .05$). However, the P-LCR, PDW, and MPV of the SFPR group were significantly higher than those of the non-SFPR group (P-LCR, $P < .0001$; PDW, $P < .01$; MPV, $P < .01$) and those of the HD group (P-LCR, $P < .0001$; PDW, $P < .01$; MPV, $P < .0001$) (Figure 1C to E). Finally, the number of megakaryocytes was significantly lower in the SFPR group than in the non-SFPR group ($P < .0001$, Supplemental Figure S1).

Comparison of the CMV Infection Status After Allo-HSCT Between the non-SFPR and SFPR Groups

After allo-HSCT, CMV infection occurred in 7 of the 39 patients (17.9%) in the non-SFPR group and in 29 of the 40 patients (72.5%) in the SFPR group (Table 2). The CMV infection rate was significantly higher in the SFPR group than in the SFPR group ($P < .0001$). The average CMV DNA copy number was higher in the SFPR group than in the non-SFPR group, although the difference was not statistically significant.

Comparison of Platelet Parameters According to the Severity of CMV Infection After Allo-HSCT and Their Correlation with CMV DNA Viral Load

We next evaluated the association of specific CMV viral load levels with platelet parameters after allo-HSCT. In patients who underwent allo-HSCT, CMV infection (<8000 CMV DNA copies/mL) was associated with significantly decreased PLT and PCT ($P < .01$ for both, Supplemental Figure S2) and with significantly increased P-LCR, MPV, and PDW ($P < .01$ for all, Figure 2A to C). Conversely, CMV infection (>8000 CMV DNA copies/mL) was associated with decreased PLT, PCT, P-LCR, MPV, and PDW (Supplemental Figure S2 and Figure 2A to C), but the difference was not statistically significant.

In the SFPR group, mild CMV infection (<8000 CMV DNA copies/mL) was associated with increased PLT, PCT, P-LCR, MPV, and PDW (Supplemental Figure S3 and Figure 2D to F) whereas severe CMV infection (>8000 CMV DNA copies/mL) was associated with decreased PLT, PCT, P-LCR, MPV, and PDW; the changes were statistically significant for P-LCR and MPV (Figure S3 and Figure 2D to F, $P < .05$). The PLT, PCT, and PDW also tended to decrease, but the difference was not statistically significant. Moreover, in the SFPR group, the P-LCR ($r = 0.3884$, $P = .028$) and MPV ($r = 0.3846$,

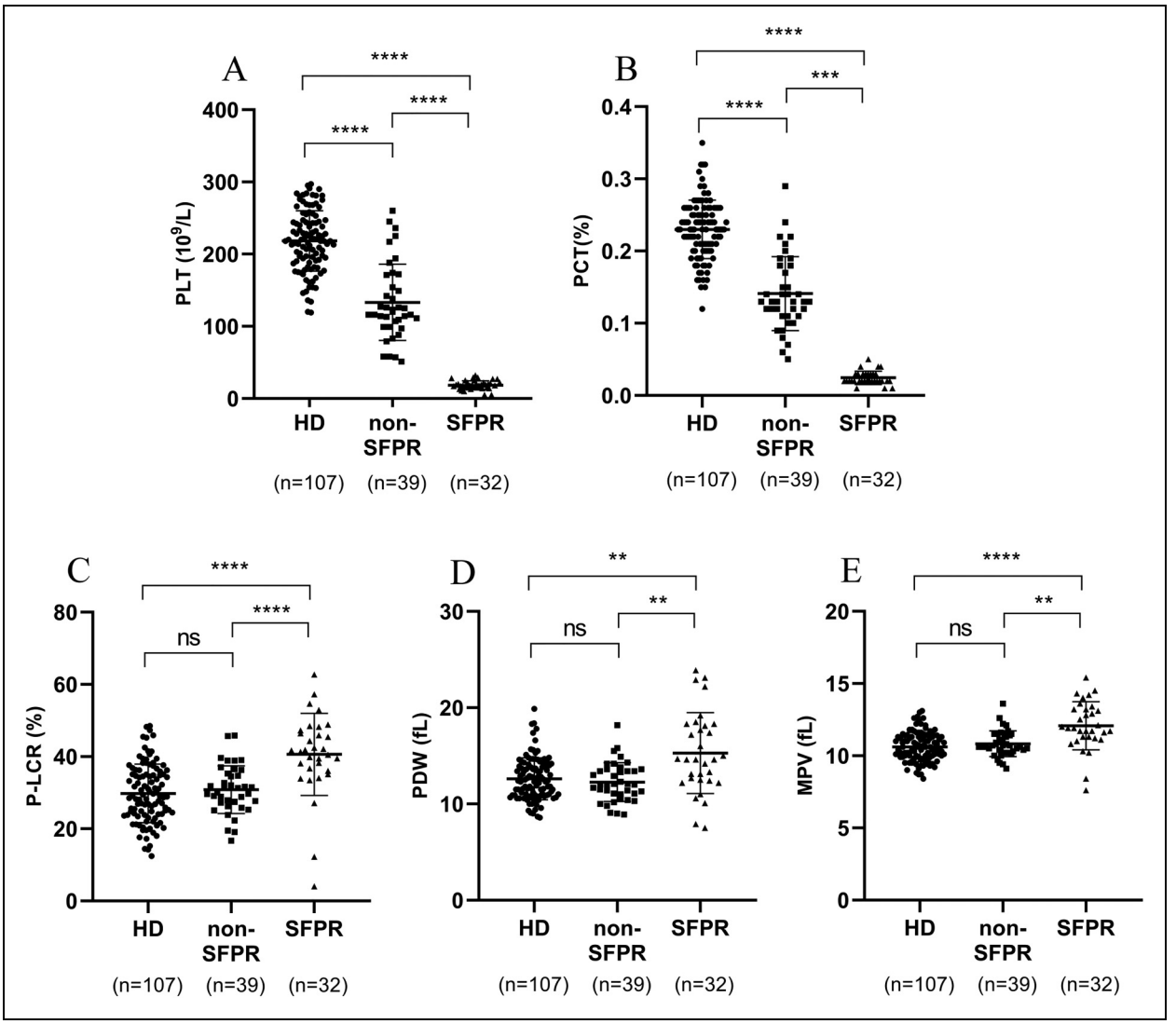

Figure 1. Comparison of platelet parameters between the HD, non-SFPR, and SFPR groups. (A) PLT, (B) PCT, (C) P-LCR, (D) PDW, and (E) MPV. Abbreviations: PLT, platelet count; ns, not significant; HD, healthy donors; SFPR, secondary failure of platelet recovery; PCT, plateletcrit; P-LCR, platelet-large cell ratio; MPV, mean platelet volume; PDW, platelet distribution width. $^{**}P < .01$, $^{***}P < .001$, $^{****}P < .0001$.

Table 2. CMV Infection in non-SFPR Group and SFPR Group.

CMV infection	Non-SFPR (n = 39)	SFPR(n = 40)	*P* value
No CMV infection/case	32	11	
CMV infection/case	7	29	
CMV <8000(copies/mL)/case	6	24	
CMV >8000(copies/mL)/case	1	5	
CMV >8000(copies/mL)proportion(%)	14.2	17.2	
The incidence of CMV infection （%）	17.9	72.5	$P < .0001$
Average copy number($x \pm s$) （copies/mL）	5452 ± 6875.74	7024.21 ± 9109.32	$P = .2022$

Abbreviations: CMV, cytomegalovirus; SFPR, secondary failure of platelet recovery.

$p = .0297$) were weakly and negatively correlated with CMV viral load (Figure 2G and H). However, the PLT, PCT, and PDW were not correlated with CMV viral load (Supplemental Figure S4). Different CMV viral loads did not exhibit significant associations with platelet parameters in the non-SFPR group (Supplemental Figure S5).

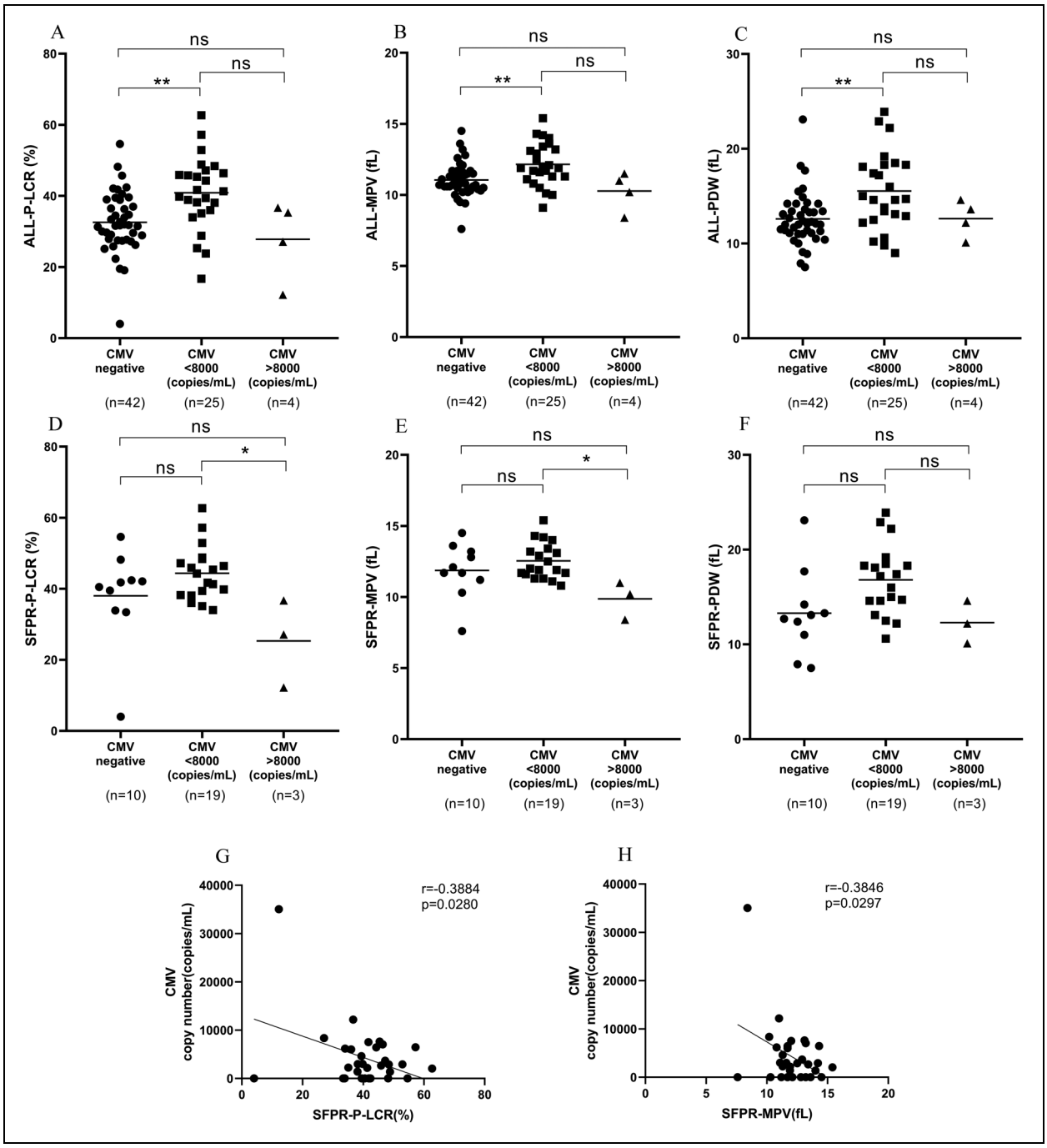

Figure 2. Comparison of platelet parameters according to the severity of CMV infection after allo-HSCT and their correlation with CMV DNA viral load. (A) P-LCR in all patients who underwent allo-HSCT, (B) MPV in all patients who underwent allo-HSCT, (C) PDW in all patients who underwent allo-HSCT, (D) P-LCR in patients with SFPR, (E) MPV in patients with SFPR, (F) PDW in patients with SFPR, (G) correlation between P-LCR in patients with SFPR and CMV copy number and (H) correlation between MPV in patients with SFPR and CMV copy number. ns, not significant. Abbreviations: CMV, cytomegalovirus; SFPR, secondary failure of platelet recovery; allo-HSCT, allogeneic hematopoietic stem cell transplantation; P-LCR, platelet-large cell ratio; MPV, mean platelet volume; PDW, platelet distribution width. *$P < .05$, **$P < .01$

Discussion

SFPR is one of the main causes of thrombocytopenia after allo-HSCT ,[1] which often causes fatal bleeding and is associated with poor prognosis. In the present study, in addition to the PLT, the PCT was significantly lower and the indices of platelet activation (PDW, P-LCR, and MPV) were significantly higher in patients with SFPR than in those without SFPR. The incidence of SFPR after allo-HSCT is 10% to 20%, and grade II to IV acute GVHD, liver and kidney dysfunction, CMV infection, and other factors can increase the risk of SFPR.[1]

Consistently, in the current study, we found that the CMV infection rate was significantly higher in the SFPR group than in the non-SFPR group and that higher CMV load may inhibit platelet activation specifically in the SFPR group.

Platelet activation is a key process in which platelets exert physiological hemostatic function.[8] It has been reported that platelet activation is closely related to the prethrombotic state of patients with coronavirus disease,[9] which indicate that platelet activation plays an important role in maintaining normal homeostasis. Therefore, proper evaluation of platelet activation is critical. Specific indicators of platelet activation mainly include the expression levels of P-selectin and CD40L of platelet surface and platelet aggregation.[10] General indicators of platelet activation mainly involve platelet-related parameters. Because specific indicators of platelet activation, however, are not widely used clinically while general indicators of platelet activation are common clinical detection methods and we collected data on general indicators of platelet activity in HDs and patients for statistical analysis. Platelet-related parameters, such as PLT, PCT, P-LCR, MPV, and PDW, indicate megakaryocyte proliferation and platelet activity. PCT is positively correlated with PLT and MPV,[4] and changes in the PCT are generally consistent with changes in PLT. We found that the PLT and PCT were lower in the SFPR group than in the HD and non-SFPR groups. We also found that the number of bone marrow megakaryocytes was significantly reduced in patients with SFPR, some of whom did not have any detectable megakaryocytes in the bone marrow. These results suggest that the proliferation and differentiation ability of bone marrow megakaryocytes was weaker in patients with SFPR than in those without SFPR and in HD. Therefore, therapies that stimulate the proliferation and differentiation of bone marrow megakaryocytes to platelets might be considered in patients with SFPR. Platelet activation usually shows larger size. MPV is a measure of platelet size, which indirectly reflects the activity of platelets.[11] In coronary artery disease, preeclampsia and primary immune thrombocytopenia, an elevated MPV is a marker of platelet activation.[12–14]

However, there are also articles reporting activated platelets leading to decreased MPV by secreting microvesiculation and platelet apoptosis and membrane integrity in resting platelets can be influenced with intensive physical stress induced by abnormal shear force in atherosclerotic vessels, mechanical artificial valve and microangiopathic conditions.[15,16] So the use of MPV alone to evaluate platelet activation is an inaccurate method. P-LCR is an index for the number of large platelets newly released from the bone marrow and PDW is used as an index reflecting the difference in platelet size and volume.[17,18] In primary open-angle glaucoma, the combined use of MPV, PDW, and P-LCR has been reported to evaluate platelet activation.[19] Therefore, we selected 3 platelet indices, PDW, MPV, and P-LCR, to jointly assess platelet activation. In the present study, the significantly higher P-LCR, MPV, and PDW detected in the SFPR group compared with the HD and non-SFPR groups suggest either an actively occurring reactive hyperplasia of megakaryocytes or enhanced platelet activation in patients with SFPR. However, we found that the proliferation and differentiation ability of bone marrow megakaryocytes were decreased in patients with SFPR. Therefore, the detected increases in P-LCR, MPV, and PDW might be primarily due to the significant increase in platelet activation aimed at maintaining normal coagulation. These results suggest that there may not be a need to rush administering platelet transfusion after thrombocytopenia in patients with SFPR and that enhanced platelet activity might partially reduce the risk of bleeding caused by thrombocytopenia. Therefore, we elucidate the hematological features of decreased PLT, increased platelet activity, and weak proliferation and differentiation ability of bone marrow megakaryocytes in patients with SFPR. There was no significant difference in P-LCR, MPV, and PDW between the non-SFPR and HD groups, indicating that the platelets were engrafted successfully.

CMV infection is the most common infectious complication after HSCT, with an incidence of 30% to 50% .[20] Studies have shown that CMV infection can damage hematopoietic progenitor cells and the hematopoietic microenvironment, leading to myelosuppression and altered hematopoietic reconstitution.[21] At the same time, anti-CMV therapeutics such as ganciclovir and valganciclovir inhibit bone marrow hematopoiesis, resulting in an increased risk of SFPR.[5] Indeed, in the present study, the incidence of CMV infection was significantly higher in the SFPR group than in the non-SFPR group. The 7 patients with CMV in the non-SFPR group had an average of 5452 ± 6875.74 CMV DNA copies/mL in the serum, which was lower than the average of 7024.21 ± 9109.32 CMV DNA copies/mL in the 29 patients with CMV infection in the SFPR group. There were significant differences in the incidence and severity of CMV infection between the non-SFPR and SFPR groups, suggesting that higher CMV load was closely associated with SFPR and that CMV infection or reactivation should be strictly prevented in patients after allo-HSCT. CMV viral load correlates with infection severity .[22] In a clinical study involving 321 patients with CMV infection after HSCT, patients with >10 000 CMV DNA copies/mL had lower serum viral clearance after 21 days of treatment compared to those with <10 000 CMV DNA copies/mL. Patients with higher viral loads in venous blood often require longer treatment duration and experience higher rates of recurrence .[23] In the current study, our analyses of 36 patients who received allo-HSCT and were infected or reactivation with CMV revealed that the PLT and PCT of CMV infection group (<8000 CMV DNA copies/mL) were lower than CMV negative group ($p < .01$ for both, Suplemental Figure S2). It may be because CMV directly infect megakaryocytes and platelet associate directly with circulating leukocytes. Above all, the P-LCR, MPV, and PDW were higher in those with <8000 CMV DNA copies/mL than in those without CMV infection. However, compared to the patients with <8000 CMV DNA copies/mL, those with >8000 CMV DNA copies/mL had lower P-LCR, MPV, and PDW. These findings that we discovered for the first time suggested that mild CMV infection directly activated platelets, which were inhibited in the presence

of severe CMV infection. Specifically, among the patients with SFPR, P-LCR, MPV, and PDW were lower in patients with >8000 CMV DNA copies/mL than in those with <8000 CMV DNA copies/mL; the difference between the subgroups was statistically significant for P-LCR and MPV. In addition, the P-LCR and MPV were negatively correlated with the CMV copy number in the SFPR group. These novel findings indicated that the P-LCR and MPV were more sensitive in reflecting the severity of CMV infection in patients with SFPR.

The present study had several limitations. First, since this was not a prospective, randomized, controlled study, it was difficult to determine cause-and-effect relationships between SFPR and CMV infection in patients after allo-HSCT, meanwhile, CMV infection can occur in patients without SFPR. Second, we only used the general indicators of platelet activation (such as MPV, P-LCR, and PDW) for research, because the recruited HDs and patients did not detect the specific indicators of platelet activation at the time of admission. Third, the number of SFPR patients and non-SFPR patients was small, and there were only 4 SFPR patients with >8000 CMV DNA copies/mL. Future studies with more SFPR and non-SFPR patients are required to overcome these limitations and validate the conclusions of this study.

In conclusion, we herein demonstrated for the first time that the presence of platelet dysfunction, as evidenced by decreased PLT, increased platelet activity, and altered megakaryocyte hematopoiesis in patients with SFPR after allo-HSCT, by comparing platelet-related parameters among patients with SFPR, non-SFPR, and HD. At the same time, we also reported a novel finding that patients with CMV infection after allo-HSCT were more likely to progress to SFPR and that mild CMV infection enhances platelet activity in SFPR patients, whereas severe CMV infection inhibits platelet activity in SFPR patients. P-LCR and MPV might be considered as reliable markers to determine the severity of CMV infection in such patients.

Declaration of Conflicting Interests

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ORCID iDs

Shuo An https://orcid.org/0000-0002-8434-9212
Mingyang Wang https://orcid.org/0000-0001-7201-5090

Supplemental Material

Supplemental material for this article is available online.

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