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Pulmonary Infection Within 100 Days After Transplantation Impaired Platelet Recovery in Patients with Hematologic Malignancies: A Propensity-Score-Matched Analysis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Pulmonary infection is one of the life-threatening complications occurring during allogeneic hematopoietic stem cell transplantation (alloHSCT), even when prophylactic measures have been employed. Few studies have investigated whether pulmonary infection affects platelet recovery during alloHSCT.

Material/Methods: We retrospectively reviewed 253 consecutive patients with hematologic diseases who received alloHSCT in our institute. Among them, 62 patients (25%) had pulmonary infection within 100 days after alloHSCT. Using the one-to-two propensity-score matching logistic model, 50 patients with pulmonary infection and 100 patients without were included based on age, disease and stage, time from diagnosis to transplantation, infused $CD34^+$ cells, and mononuclear cells.

Results: The incidences of prolonged thrombocytopenia in patients with pulmonary infection were 44% (22/50) and 9% (9/100) in the corresponding matched group ($P<0.001$). The mean time for platelet engraftment in patients with and without pulmonary infection were 19.29±13.96 days and 13.94±4.12 days ($P=0.012$), respectively. Multivariable logistic regression showed that pulmonary infection was an independent risk factor for impaired platelet recovery (OR: 5.335, 95% CI: 2.735–10.407, $P<0.001$). Impaired platelet recovery was associated with shorter survival and higher treatment-related mortality.

Conclusions: Our results indicate that patients with pulmonary infection within 100 days after alloHSCT are more likely to suffer from impaired platelet recovery and have inferior long-term survival.

MeSH Keywords: Hematopoietic Stem Cell Transplantation • Platelet Count • Pneumonia

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Background

Impaired platelet recovery occurs in 5–37% of patients who received allogeneic hematopoietic stem cell transplantation (alloHSCT) [1,2]. Several possible mechanisms may contribute to impaired platelet recovery, including impaired thrombopoiesis and increased platelet consumption [3]. Complications of alloHSCT, such as graft versus host disease (GvHD), hepatic venous sinus obstruction syndrome, thrombotic microangiopathy, and infections (bacterial, virus, and fungal), and their corresponding therapies are associated with impaired platelet recovery, even in the presence of full recovery of neutrophils [4–10].

Alterations in platelet counts during acute lung injury have been studies by several groups. Schneider and colleagues studied the fate of platelets in 15 patients with severe acute respiratory failure; among them, 10 patients developed thrombocytopenia (<100 000 platelets/microliters) [11]. In another study, Carvalho et al. studied platelet function in 13 acute respiratory failure patients admitted for intensive care, 6 acutely ill intensive care patients without evidence of acute lung injury, and 10 normal subjects [12,13], showing that patients with acute respiratory failure had quantitative and qualitative platelet defects that may contribute to thrombotic and hemorrhagic complications compared with those without acute respiratory failure.

Pulmonary infection occurs in 40–60% of alloHSCT recipients, and has been reported to be an important predictor of survival [14–16]. Previous studies have reported that the incidence rate of early-stage infections ranges from 15% [17] to 64.3% [14], and pulmonary infection is a common problem [15]. The reasons why pulmonary infection is associated with decreased survival of alloHSCT recipients mostly involve treatment-related complications [18], but few studies have focused on platelet recovery in patients with pulmonary complications during the alloHSCT procedure. The aim of the present study was to evaluate the effect of pulmonary infection on platelet recovery within the first 100 days after alloHSCT.

Material and Methods

Patients

From January 2011 to December 2018, 319 patients received alloHSCT at the Institute of Hematology, Changhai Hospital; 66 patients relapsed (21%), and 253 patients without relapse were included in the present study. Among these 253 patients, 62 patients (25%) developed pulmonary infection within 100 days. For each pulmonary infection case, a set of 2 patients was chosen as control from the remaining patients who were without pulmonary infection after matching for age (<20 y, 20–40 y, 41–60 y, or >60 y), disease and stage, time from diagnosis to transplantation, median $CD34^+$ cells, and mononucleated cells transplanted. Fifty patients with pulmonary infection who had 2 matched controls were enrolled in a propensity score-matched study, and the remaining 12 patients who did not have matched controls were not included in propensity analysis. All procedures complied with the Helsinki Declaration standards and were approved by the Institutional Review Board of Changhai Hospital, Shanghai, China. The requirement for written informed consent was waived because the study used retrospective data from medical records, and there were no interventions performed in patients.

Transplant procedure

The transplant procedure was described previously [19] Forty patients (40/50, 80%) received a busulfan and cyclophosphamide (BuCy)-based conditioning regimen that consisted of cytarabine (4 g/m^2/d) intravenously on days –10 to –9; and Bu (3.2 mg/kg/d) intravenously on days –8 to –6; CTX (1.8 g/m^2/d), intravenously on days –5 to –4; Me-CCNU (250 mg/m^2/d), orally once on day –3, and intravenously on days –5 to –2. Ten patients (10/50, 20%) were treated with an FBA conditioning regimen that included fludarabine, 30 mg/m^2/day on days –10 to –6; Bu, 0.8 mg/kg every 6 h on days –5 to –3; and cytosine arabinoside, 1.5 g/m^2/day on days –10 to –6). Antithymoglobulin (ATG) was used in patients who underwent alloHSCT from a human leukocyte antigen (HLA)-mismatched donor. The acute graft versus host disease (aGvHD) prophylaxis regimen was as previously reported [20].

Infection prophylaxis and monitoring

Pulmonary high-resolution computed tomography (HRCT) was performed before alloHSCT. Patients were assigned to the horizontal laminar flow unit before conditioning. Sulfamethoxazole/trimethoprim was used to prevent prophylaxis *Pneumocystis jiroveci*. The preemptive treatment for CMV reactivation consisted of ganciclovir or valganciclovir. All patients received oral levofloxacin and fluconazole, unless they were receiving other medications for a previous infection. For secondary prevention, patients with history of invasive fungal disease (IFD) before alloHSCT received intravenous voriconazole or corresponding effective antifungal drugs. Within the first 3 months after alloHSCT, sulfamethoxazole/trimethoprim, fluconazole, and ganciclovir were administrated alternatively. CMV DNA, Epstein-Barr virus (EBV), procalcitonin (PCT), C-reactive protein (CRP), 1, 3-β-D-glucan assay (G assay), and galactomannan test (GM assay) were measured once a week until 3 months after alloHSCT.

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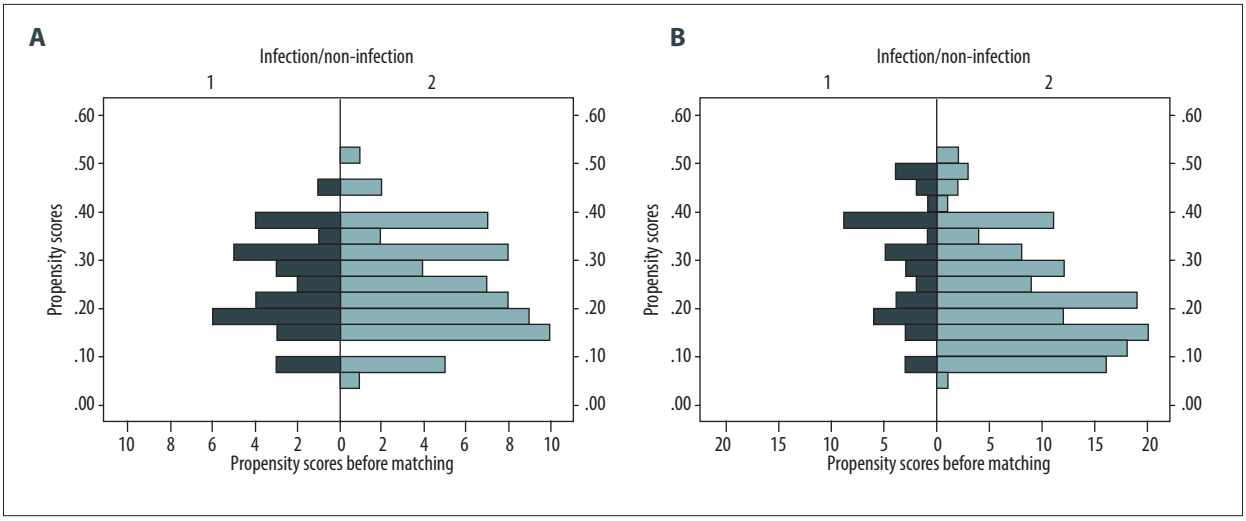

Figure 1. Propensity scores before matching (**A**) and after matching (**B**). For each pulmonary infection case, a set of 2 patients was selected as controls from those without pulmonary infection, matched for age (<20 y, 20–40 y, 41–60 y, or >60 y), disease and stage, days from diagnosis to transplantation, median $CD34^+$, and mononuclear cells infused.

Diagnosis of pulmonary infections and treatment

Samples were collected from the sputum, blood, and bronchoalveolar lavage (BAL) fluid if possible. Chest HRCT was performed when patients were highly suspected to have a pulmonary infection. PCT and CRP, as well as G and GM assays, were measured. Cultivation or next-generation sequencing of BAL fluid or lung biopsy were performed to confirm pathogenic organisms.

Once pneumonia was diagnosed, empirical broad-spectrum antibiotics were instituted if there was suspected bacterial pneumonia until a specific pathogen was identified, and targeted therapy was initiated accordingly. Active IFD was defined as possible, probable, or proven according to the EORTC criteria [21]. The specific antifungal treatment was administrated at the discretion of the managing physician. In addition, we used PSI (Pneumonia Severity Index) scores to weigh the prognosis of pulmonary infection [22].

Definitions of clinical outcome

Platelet count ≥20×10^9/L for 7 consecutive days without transfusion was defined as platelet engraftment (primary platelet recovery). Secondary failure of platelet recovery (SFPR) was diagnosed in patients who had previously fulfilled the criteria for trilineage recovery after alloHSCT, with platelet count <20×10^9/L or ≥20×10^9/L with transfusion for more than 7 consecutive days [23,24]. Good graft function (GGF) was defined as persistent successful engraftment (ANC > 0.5×10^9/L for 3 consecutive days, PLT counts >20×10^9/L for 7 consecutive days and hemoglobin levels > 70 g/L without transfusion support) beyond 28 days after HSCT [25]. Prolonged thrombocytopenia (PT) was defined as the engraftment of all peripheral blood cell lines other than a platelet count ≤80×10^9/L for more than 90 days after alloHSCT [9,23]. Impaired platelet recovery was included in PT and SFPR. CMV and EBV viremia were defined as >1000 viral copies/ml plasma by PCR. Diffuse pulmonary infection was defined as diffuse lesions in ≥2 pulmonary lobes. Scattered pulmonary infection was defined as lung consolidation of 1 lung segmental lobe, or single and multiple lung nodules based on CT scan.

Chimerism analyses were performed by DNA fingerprinting for single-nucleotide polymorphism in bone marrow samples as introduced in our previous publication [26] (sensitivity >0.01% recipient signals).

Statistical analysis

Greedy-type 1: 2 matching technology without replacement was performed to match patients with pulmonary infection and patients without (Figure 1). Matching of the logit of the propensity-score began with high accuracy (0.00001), and then gradually decreased to minimum precision accuracy (0.1). Univariate and multivariate logistic regression were used to examine the risk factors associated with platelet recovery. The considered fixed risk factors included the following: age at transplantation (age <40 y *vs.* age ≥40 y), gender, disease type, HLA disparity (matched *vs.* mismatched), donor–recipient gender matching (others *vs.* female–male), ABO compatibility (matched *vs.* mismatched), donor–recipient relationship (related or unrelated), conditioning regimen (without ATG *vs.* with ATG, without CTX *vs.* with CTX, without Flu *vs.* with Flu), aGvHD, CMV/EBV viremia, pulmonary infection, upper respiratory infection, gastrointestinal infection, and blood stream infection. Survival data

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were analyzed with Kaplan-Meier method and compared with log-rank test. Overall survival (OS) was defined as the date from alloHSCT to death. Treatment-related mortality (TRM) curves were constructed in the competing risks framework, considering death without relapse after alloHSCT as a competing event. Variables are presented as frequency and percentage and compared using the chi-square test or Wilcoxon rank sum test. A P value less than 0.05 was defined as statistically significant. SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and R3.4.2 were used in statistics analysis.

Results

Patient characteristics

Among the 253 evaluable patients, 54% (136/253) were male. The median age was 36 years (range, 11–72 years) and the median follow-up was 36 months. Within 100 days after alloHSCT, 25% (62/253) of patients had a pulmonary infection, and 34% (87/253) of patients received unrelated donor alloHSCT. The mean time for neutrophil and platelet engraftment were 13.34±2.66 days and 15.19±8.32 days, respectively. The incidence of aGvHD for the whole cohort was 23% (59/253). The probabilities of OS and TRM at 3 years after alloHSCT were 79.5±2.7% and 20.53±0.07%, respectively. After propensity-score-matched analysis, 50 patients with pulmonary infection and 100 patients without included in further analysis. The clinical characteristics of the 50 patients with pulmonary infection are shown in Table 1.

Propensity-score-matched analysis

Propensity-score-matched analysis included 150 patients (50 patients with pulmonary infection and 100 patients without). The median follow-up was 28 months in cohorts with pulmonary infection and 38 months in those without. There was higher incidence of pulmonary infection in patients who received grafts from HLA-mismatched donors compared with HLA-matched donors [53.8% (21/39) *vs.* 26.1% (29/111), *P*=0.002. CMV and EBV viremia were more frequent in pulmonary infection patients. The difference in the incidences of grade II–IV aGvHD between the groups was not significant (28% *vs.* 22%, *P*=0.417; Table 2).

Pulmonary infection occurred at a median time of +32 days [range: –10 to +97 days]. The incidences of pulmonary infection were 10% (5/50) during conditioning, 36% (18/50) in the first 30 days after alloHSCT, 40% (20/50) at 60 days, and 12% (6/50) at 90 days after alloHSCT. Fungal pneumonia (30/50, 60%) was more common than bacterial pneumonia (14/50, 28%) and viral pneumonia (1/50, 2%). Polymicrobial pneumonia was diagnosed in 4 patients. In 30 cases of fungal pneumonia, 5 were proven and 12 were probable (Table 1). There were 12 patients diagnosed pneumonia with specific pathogenic organisms through sputum cultivation (5/12, 42%) or invasive diagnostic procedure, including microbial culture and next-generation sequencing of BAL fluid (5/12, 42%), and lung biopsy (2/12, 16%).

The mean times for neutrophil engraftment were 14.55±4.18 days and 12.93±1.93 days (*P*=0.012), and 19.29±13.96 days and 13.94±4.12 days (*P*=0.012) for platelet engraftment for patients with and without pulmonary infection, respectively. Among patients with pulmonary infection, 2 patients failed to engraft, and the other 48 patients achieved full donor engraftment as measured by SNP-PCR, in which 33% (16/48) patients achieved GGF, 21% (10/48) patients with SFPR, and 46% (22/48) patients with PT.

The incidence of PT in patients with pulmonary infection was 44% (22/50), and 9% (9/100) in the corresponding matched group (*P*<0.001). Megakaryocyte counts in patients with pulmonary infection were lower than that in patients without pulmonary infection [median number: 36 (range, 0 to 450) *vs.* 44 (range, 0 to 1000)/slice (1.5×3 cm^2), *P*=0.010]. Seventeen patients (17/50, 34%) developed pulmonary infection before platelet engraftment. The platelet engraftment was delayed in these patients than in patients without pulmonary infection [mean time: 28.33±21.91 days *vs.* 13.94±4.12 days, *P*=0.024]. Of them, 10 patients (10/17, 59%) developed PT, and the percentage was markedly higher than in patients without pulmonary infection (9/100, 9.00%; *P*<0.001). The difference in time for platelet engraftment between patients with diffuse (n=9) and scattered pulmonary infection (n=39) was not significant. (20.11±12.35 days *vs.* 19.10±14.45 days, *P*=0.848)

Thirty-three patients developed pulmonary infection after primary platelet recovery, of whom 24% (8/33) patients developed SFPR. The platelet counts at 90 days after alloHSCT in patients with pulmonary infection were lower than in patients without pulmonary infection. [median: 55×10^9/L (range, 2–188×10^9/L) *vs.* 128×10^9/L (range, 8–308×10^9/L), *P*<0.001]

To determine the specificity of the impact of pulmonary infection on platelet recovery, we enrolled patients with upper respiratory tract infection, gastrointestinal infection, and blood stream infection during alloHSCT as non-pulmonary infection controls. There was a weak relationship between infections in other sites and impaired platelet recovery (infection *vs.* non-infection: upper respiratory tract infection: 13.61±2.59 days *vs.* 13.83±4.45, *P*=0.731; gastrointestinal infection: 13.71±4.04 days *vs.* 13.83±4.45, *P*=0.919; blood stream infection: 17.21±15.02 days *vs.* 13.83±4.45, *P*=0.343).

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Table 1. Clinical characteristics of the patients with pulmonary infection.

Case No.	Diagnosis	Sex	Age (yrs)	Donor	HLA	Days of pulmonary infection	Pathogen/ microorganisms	Platelet engraftment	Platelet recovery	Outcome	Causes of death
1	B-ALL	M	25	MSD	8/10	41	Fungi/*Aspergillus* sp. (proven)	12	GGF	Survival	
2	B-ALL	F	38	MUD	9/10	–10	Fungi	16	PT	Death	GvHD
3	MDS-EB1	M	22	MUD	10/10	25	Fungi	16	PT	Survival	
4	AML	M	23	MUD	9/10	37	Fungi	14	SFPR	Survival	
5	B-ALL	F	29	MUD	10/10	88	Bacteria	11	PT	Death	Respiratory failure
6	AML	F	53	MSD	10/10	–6	Bacteria, Fungi	14	PT	Death	GvHD
7	B-ALL	F	25	MSD	5/10	71	*Pneumocystis carinii* (proven)	12	GGF	Death	Pulmonary infection
8	T-ALL	M	48	MUD	10/10	63	Fungi	20	PT	Survival	
9	AML	M	47	MUD	10/10	32	Fungi	14	PT	Survival	
10	B-ALL	M	30	MSD	7/10	36	Fungi	95	PT	Survival	
11	AML	M	51	MUD	10/10	47	Fungi	12	PT	Survival	
12	AML	F	24	MUD	8/10	32	Fungi	20	SFPR	Survival	
13	AML	F	45	MSD	10/10	–5	Bacteria	10	GGF	Survival	
14	AML	M	35	MUD	10/10	35	Fungi	26	GGF	Survival	
15	AML	M	49	MUD	10/10	–5	Fungi	13	PT	Survival	
16	AML	M	26	MSD	7/10	21	Fungi	25	PT	Survival	
17	MDS-EB1	M	30	MSD	10/10	97	Fungi	17	PT	Survival	
18	AML	M	43	MSD	10/10	53	Fungi/*Aspergillus fumigatus* (proven)	12	GGF	Survival	
19	T-ALL	M	30	MSD	10/10	76	Fungi/*Aspergillus flavus* (proven)	15	GGF	Survival	
20	AML	F	28	MUD	8/10	38	Bacteria, Fungi	11	SFPR	Death	Respiratory failure
21	CML	F	46	MSD	5/10	52	Fungi	12	GGF	Survival	
22	T-ALL	M	25	MSD	10/10	32	Fungi	15	PT	Survival	
23	AML	M	35	MSD	10/10	19	Bacteria/ *Streptococcus pneumoniae*	13	GGF	Survival	
24	AML	M	27	MUD	9/10	12	Fungi	22	GGF	Survival	
25	AML	F	39	MUD	9/10	12	Bacteria	14	PT	Survival	
26	B-ALL	F	19	MSD	9/10	40	Bacteria/ *Stenotrophomonas maltophilia*	12	PT	Survival	
27	MDS	M	52	MSD	6/10	6	Fungi	30	SFPR	Death	GvHD
28	AML	M	45	MUD	10/10	62	Bacteria	16	PT	Survival	

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Table 1 continued. Clinical characteristics of the patients with pulmonary infection.

Case No.	Diagnosis	Sex	Age (yrs)	Donor	HLA	Days of pulmonary infection	Pathogen/ microorganisms	Platelet engraftment	Platelet recovery	Outcome	Causes of death
29	AML	M	30	MSD	6/10	36	Bacteria	21	PT	Death	Respiratory failure
30	B-ALL	F	35	MSD	10/10	8	Bacteria	16	PT	Survival	
31	MDS-EB2	M	29	MUD	10/10	–2	Fungi	13	GGF	Survival	
32	T-ALL	M	32	MUD	10/10	35	Fungi	12	GGF	Survival	
33	AML	M	57	MUD	10/10	16	Bacteria/ *Enterococcus faecali*	49	SFPR	Death	Respiratory failure
34	AML	F	25	MSD	5/10	10	Bacteria	36	PT	Death	Pulmonary infection
35	AML	M	19	MSD	5/10	1	Bacteria	Graft failure	/	Death	Heart failure
36	AML	F	40	MSD	10/10	61	Fungi/*Aspergillus* sp. (proven)	13	GGF	Survival	
37	MDS-EB1	F	28	MUD	10/10	26	Bacteria/ *Streptococcus pneumoniae*	29	PT	Survival	
38	MDS-EB1	F	54	MSD	10/10	4	Bacteria, Fungi	Graft failure	/	Survival	
39	AML	M	52	MSD	9/10	35	Bacteria/*Escherichia coli*	19	GGF	Survival	
40	B-ALL	F	22	MSD	10/10	51	virus	15	GGF	Survival	
41	AML	F	54	MUD	9/10	29	Fungi	28	PT	Survival	
42	T-ALL	M	37	MUD	9/10	40	Bacteria	13	SFPR	death	Cerebral hemorrhage
43	AML	F	59	MSD	10/10	43	Fungi/*Aspergillus fumigatus* (proven)	12	GGF	Survival	
44	B-ALL	F	30	MUD	8/10	15	Fungi	11	SFPR	Death	GvHD
45	AML	M	55	MUD	10/10	17	Fungi	12	GGF	Survival	
46	AML	M	27	MUD	9/10	48	Fungi	13	SFPR	Survival	
47	CML	F	47	MSD	10/10	56	Bacteria, Fungi	25	SFPR	Death	GvHD
48	AML	M	47	MSD	10/10	18	Fungi	12	SFPR	Death	Respiratory failure
49	B-ALL	F	30	MSD	10/10	25	Fungi	43	PT	Survival	
50	AML	F	50	MSD	10/10	17	Fungi	15	PT	Survival	

AML – acute myelocytic leukemia; B-ALL – B-cell acute lymphocytic leukemia; CML – chronic myelogenous leukemia; MDS – myelodysplasia syndrome; EB – excess blast; F – female; M – male; GVHD – graft versus host disease; MUD – HLA-matched unrelated donor; MSD – HLA-matched sibling donor; HLA – human leukocyte antigen; V – Voriconazole; C – Caspofungin; P – Posaconazole; M – Micafungin; GGF – good graft function; SFPR – secondary poor graft function; PT – prolonged or isolated thrombocytopenia.

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Table 2. Factors associated with pulmonary infection and platelet recovery.

Factors	With infection (n=50)	Without infection (n=100)	Statistics	*P*
Donor-recipient gender match, n (%)			0.932	0.334
Female–Male	9 (18)	25 (25)		
Others	41 (82)	75 (75)		
Donor types, n (%)			8.503	0.014
Sibling	22 (44)	68 (68)		
Haploid	5 (10)	8 (8)		
Unrelated	23 (46)	24 (24)		
ABO match, n (%)			1.970	0.160
Matched	17 (34)	46 (46)		
Mismatched	33 (66)	54 (54)		
HLA match, n (%)			9.979	0.002
10/10	29 (58)	82 (82)		
Others	21 (42)	18 (18)		
Conditioning regimen, n (%)			0.054	0.816
With ATG	23 (46)	44 (44)		
Without ATG	27 (54)	56 (56)		
WBC before HSCT, M±SD ($\times 10^{12}$/L)	3.97±2.24	4.65±2.92	–1.574	0.118
HB before HSCT (g/L)	94.32±20.35	97.90±21.00	–0.993	0.323
PLT before HSCT ($\times 10^{9}$/L)	141.04±71.99	164.94±103.33	–1.643	0.103
CMV viremia, n (%)			11.189	0.001
Yes	19 (38)	14 (14)		
No	31 (62)	86 (86)		
EBV viremia, n (%)			6.122	0.013
Yes	3 (6)	0 (0)		
No	47 (94)	100 (100)		
aGvHD (II–IV), n(%)			0.658	0.417
Yes	14 (28)	22 (22)		
No	36 (72)	78 (78)		
Other infections, n (%)			2.037	0.153
Yes	27 (54)	66 (66)		
No	23 (46)	34 (34)		
Neutrophils engraftment, M±SD days	14.55±4.18	12.93±1.93	2.583	0.012
Platelet engraftment, M±SD days	19.29±13.96	13.94±4.12	3.508	0.012
Megakaryocytes, n (%)			9.296	0.010
<7	9 (19)	29 (31)		
7–35	17 (35)	13 (14)		
>35	22 (46)	52 (55)		

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Table 2 continued. Factors associated with pulmonary infection and platelet recovery.

Factors	With infection (n=50)	Without infection (n=100)	Statistics	*P*
Bone marrow platelets, n (%)			4.835	0.028
Clusters	17 (34)	53 (53)		
Scattered	33 (66)	47 (47)		
3 year OS, %	71.5±6.4	80.2±4.2	2.271	0.132

ATG – antithymocyte globulin; HSCT – hematopoietic stem cell transplantation; HLA – human leukocyte antigen; WBC – leukocyte; HB – hemoglobin; PLT – platelet; CMV – cytomegalovirus; EBV – EB virus; GvHD – graft-versus-host disease; OS – overall survival; M – mean; SD– standard deviation.

Table 3. Univariate analysis associated with impaired platelet recovery.

	OR	95% CI	Statistics	P
Age/years				
<40 *vs.* ≥40	0.715	0.399–1.284	1.262	0.261
Gender				
Male *vs.* Female	0.678	0.383–1.201	1.776	0.183
Conditioning regimen				
ATG, without *vs.* with	1.303	0.739–2.296	0.838	0.360
CTX, without *vs.* with	0.991	0.477–2.061	0.001	0.981
Flu, without *vs.* with	0.771	0.421–1.413	0.706	0.401
Donor-recipient gender match				
Others *vs.* Female–Male	1.038	0.517–2.086	0.011	0.916
Donor type				
Related *vs.* unrelated	1.750	0.985–3.109	3.637	0.056
ABO match				
Matched *vs.* mismatched	1.098	0.618–1.952	0.101	0.751
HLA match				
Matched *vs.* mismatched	2.638	1.450–4.798	10.103	**0.001**
CMV viremia				
No *vs.* yes	3.306	1.726–6.331	13.012	**<0.001**
EBV viremia				
No *vs.* yes	4.544E9	0–	0	0.999
aGvHD (II–IV)				
No *vs.* yes	2.025	1.079–3.801	4.829	**0.028**
Pulmonary infection				
No *vs.* yes	6.103	3.237–11.505	31.255	**<0.001**
Upper respiratory tract infection				
No *vs.* yes	0.620	0.334–1.151	2.298	0.130

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Table 3 continued. Univariate analysis associated with impaired platelet recovery.

	OR	95% CI	Statistics	P
Gastrointestinal infection				
No *vs.* yes	0.974	0.411–2.307	0.004	0.952
Blood stream infection				
No *vs.* yes	2.167	0.996–4.712	3.804	0.051
CD34⁺ cells, ×10⁶/kg				
≤2 *vs.* >2	2.143	0.903–5.083	2.990	0.084
MNC, ×10⁸/kg				
≤3 *vs.* >3	2.671	0.322–22.124	0.829	0.363

CTX – cyclophosphamide; Flu – fludarabine; ATG – anti-thymocyte globulin; HLA – human leukocyte antigen; CMV – cytomegalovirus; EBV – EB virus; aGvHD – acute graft-versus-host disease; MNC – mononucleated cells.

Table 4. Multivariable analysis associated with impaired platelet recovery.

	OR	95% CI	Statistics	*P*
HLA match				
Matched *vs.* mismatched	2.009	1.025–3.935	4.132	**0.042**
CMV viremia				
No *vs.* Yes	2.003	0.951–4.217	3.343	0.068
aGvHD (II–IV)				
No *vs.* Yes	1.803	0.875–3.715	2.555	0.110
Pulmonary infection				
No *vs.* Yes	5.335	2.735–10.407	24.120	**<0.001**

HLA – human leukocyte antigen; CMV – cytomegalovirus; aGvHD – acute graft-versus-host disease.

Univariate and multivariate analysis

Univariable logistic regression analysis contained patient characteristics such as age (<40 years *vs.* ≥40 years), sex (female *vs.* male), conditioning regimen, donor characteristics, transfused cells, and infections. Univariable logistic regression showed that impaired platelet recovery was strongly associated with HLA mismatch (OR 2.638, 95% CI: 1.450–4.798, *P*=0.001), CMV viremia (OR: 3.306, 95% CI: 1.726–6.331, *P*< 0.001), grade II–IV aGvHD (OR: 2.025, 95% CI: 1.079–3.801, *P*=0.028), and pulmonary infection (OR 6.103, 95% CI: 3.237–11.505, *P*<0.001, Table 3). These 4 factors were then enrolled in the multivariable analysis. Multivariable logistic regression showed that pulmonary infection was a significant independent risk factor for impaired platelet recovery (OR: 5.335, 95% CI: 2.735–10.407, *P*<0.001, Table 4).

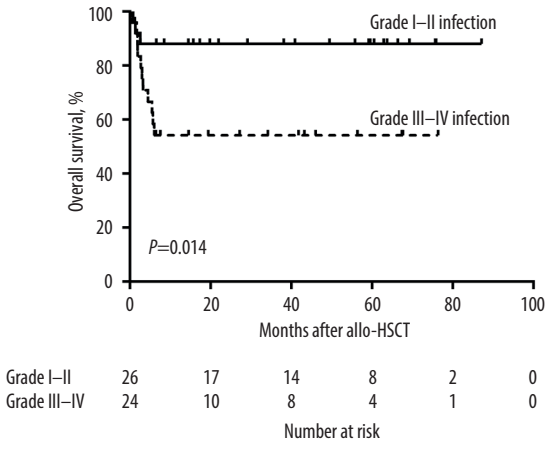

Figure 2. Patients with grade III–IV pulmonary infection were associated with worse OS (54.2±10.2%) when compared to patients who had grade I–II infection (88.1±6.4%, *P*=0.014).

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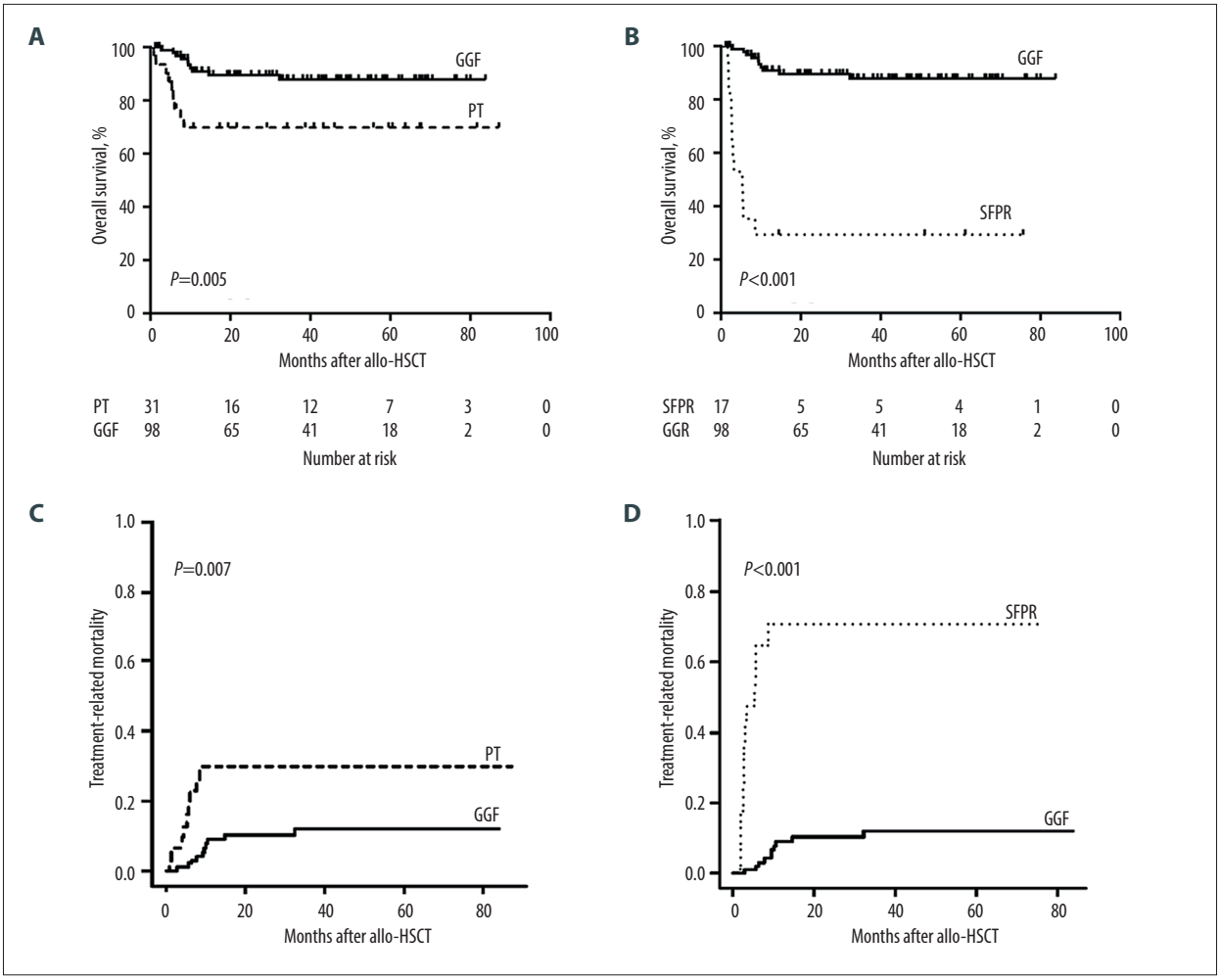

Figure 3. The probability of OS at 3 years after alloHSCT was 69.9±8.4% in the patients with PT (**A**), 29.4±11.1% in patients with SFPR (**B**), and 87.9±3.6% in patients with GGF (PT *vs.* GGF: *P*=0.005; SFPR *vs.* GGF: *P*<0.001). The probability of TRM at 3 years was 30.13±0.74% in patients with PT (**C**), 70.59±1.39% in patients with SFPR (**D**), and 12.12±0.13% in patients with GGF (PT *vs.* GGF: *P*=0.007; SFPR *vs.* GGF: *P*<0.001).

Survival outcomes

The probability of OS at 3 years after alloHSCT was 71.5±6.4% for patients with pulmonary infection and 80.2±4.2% for patients without pulmonary infection (*P*=0.132). The patients were further grouped into 2 subgroups depending on infection severity. Grade III–IV infection conferred a worse OS at 3 years (54.2±10.2% *vs.* 88.1±6.4%, *P*=0.014) compared to patients with grade I–II infection (Figure 2). The probability of OS in patients with pulmonary infection in the first month (n=18) was 66.7±11.1%, and 76.9±8.3% for patients (n=26) who developed pulmonary infection during the second and third months. (*P*=0.410).

The probability of OS at 3 years after alloHSCT was 55.2±7.3% in the group with impaired platelet recovery and 87.9±3.6% in patients with GGF (*P*<0.001). Patients with PT or SFPR had inferior survival compared with patients with GGF (3-year OS: PT: 69.9±8.4%, *P*=0.005, Figure 3A; SFPR: 29.4±11.1%, *P*<0.001, Figure 3B). TRM was increased in patients with impaired platelet recovery (impaired platelet recovery: 44.78±0.55% *vs.* GGF: 12.12±0.13%, *P*<0.001). The probabilities of TRM at 3 years were 30.13±0.74% in patients with PT and 70.59±1.39% in patients with SFPR (Figure 3C, 3D).

Discussion

To the best of our knowledge, this study is the first on platelet recovery and pulmonary infection within 100 days after alloHSCT. We performed propensity score matching to balance baseline patient characteristics. The incidence of PT in patients with pulmonary infection were 44% (22/50) and 9% (9/100) in the corresponding matched group (P<0.001).

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Despite the advances in prophylaxis and therapy of infections, pulmonary infections remain a major cause of death in more than 40% of alloHSCT recipients [27–29]. In the present retrospective study, we identified 62 cases of pulmonary infection (62/253, 25%) during the transplant procedure, in which pneumonia was diagnosed based on clinical symptoms, microbial culture, biochemical assay, invasive diagnostic procedures, and imaging results. Fungal infection was the leading etiology for pneumonia within 100 days after transplantation. Patients received levofloxacin prophylaxis in our study, which was reported in previous studies to lower the proportion of early bacterial infection after transplantation [14,30]. Although CMV viremia was documented in 33 out of 150 patients, only 1 patient developed CMV-related pneumonia. Dynamic monitoring of the CMV viral load in plasma and improved preemptive antiviral therapy contribute to the lower incidence of CMV pneumonia. As expected, the incidences of CMV and EBV viremia were still higher in patients with pulmonary infection than in patients without (Table 2). Pulmonary infection delayed the immune reconstitution, which facilitated the reactivation of viruses. Myelosuppression caused by CMV infection itself, and ganciclovir-induced cytopenia, were more difficult to manipulate, both of which contributed to impaired platelet recovery, and then shorter survival. Of the 10 patients who developed SFPR, 3 died of aGvHD and 3 died of respiratory failure. Four patients who had CMV viremia received ganciclovir preemptive therapy and recovered from SFPR. PT and SFPR were associated with shorter OS and higher TRM, consistent with a previous study [24]. The underlying association between aGvHD and impaired platelet recovery has been extensively studied by others and by our group [10,23,31,32]. We have suggested that bone marrow may be a potential aGvHD target through immune-mediated cytopenias. In the present study, although the distribution of aGvHD was balanced in the 2 groups, aGvHD still had an impact on platelet recovery in the whole cohort in univariate analysis.

In 36 surviving patients with pulmonary infection, only 15 (42%) achieved GGF, which shows that pulmonary infection may have a close relationship with platelet recovery. Pulmonary infection was a risk factor for impaired platelet recovery [OR 5.335, 95% CI (2.735–10.407), $P<0.001$]. Of note, infections in other sites did not have any overt impacts on platelet recovery, which suggests that platelet recovery is related to a direct impact on pulmonary disruption rather than a systemic inflammatory state.

Infection, iron overload, aGvHD, CMV infection, the use of ganciclovir or valganciclovir, and *in vivo* T cell depletion are significantly associated with increased risk of SFPR [10,23,24,31,33]. Thrombopoiesis, which occurs within a specialized bone marrow microenvironment, is a complex biological process that is initiated with the differentiation of hematopoietic stem cells (HSCs) to megakaryocytic progenitors and eventually results in the maturation of megakaryocytes to produce functional platelets [18,34]. A recent study showed that the lungs in mice dynamically released platelets, representing almost 50% of total platelets production [35]. In a state of thrombocytopenia and relative stem cell shortage in the bone marrow, those progenitors can repopulate the bone marrow, and contribute to multiple hematopoietic lineages [36]. Therefore, lung injury is associated with reduced number of megakaryocytes from the lungs, and this may result in thrombocytopenia.

Our study had several limitations. First, the analysis was retrospective. Second, small size is a major limitation in our study, which made it difficult to comprehensively analyze the potential variables affecting platelet recovery. However, our propensity score-matched model showed that pulmonary infection has a powerful and specific effect on platelet recovery. Multicenter clinical trials on this topic are needed.

Conclusions

The incidence of impaired platelet recovery in patients with pulmonary infection following alloHSCT was relatively high. Pulmonary infection during alloHSCT is related to an increased risk of impaired platelet recovery (SFPR and PT) and is related to worse OS and higher TRM. Further research should concentrate on the underlying mechanism of pulmonary infection and impaired platelet recovery, which could help improve the prognosis of alloHSCT recipients.

Conflict of interest

None.

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References:

1. Moneib H, Hafez H, Abdalla A et al: Day +100 platelet count predicts survival after allogeneic hematopoietic stem cell transplantation in children with hematologic malignancies. Clin Lymphoma Myeloma Leuk, 2019; 19(5): e221–27
2. Yamazaki R, Kuwana M, Mori T et al: Prolonged thrombocytopenia after allogeneic hematopoietic stem cell transplantation: Associations with impaired platelet production and increased platelet turnover. Bone Marrow Transplant, 2006; 38(5): 377–84
3. First LR, Smith BR, Lipton J et al: Isolated thrombocytopenia after allogeneic bone marrow transplantation: Existence of transient and chronic thrombocytopenic syndromes. Blood, 1985; 65(2): 368–74
4. Bernstein SH, Nademanee AP, Vose JM et al: A multicenter study of platelet recovery and utilization in patients after myeloablative therapy and hematopoietic stem cell transplantation. Blood, 1998; 91(9): 3509–17
5. Dominietto A, Raiola AM, van Lint MT et al: Factors influencing haematological recovery after allogeneic haemopoietic stem cell transplants: Graft-versus-host disease, donor type, cytomegalovirus infections and cell dose. Br J Haematol, 2001; 112(1): 219–27
6. Anasetti C, Rybka W, Sullivan KM et al: Graft-v-host disease is associated with autoimmune-like thrombocytopenia. Blood, 1989; 73(4): 1054–58
7. Verdonck LF, de Gast GC, van Heugten HG et al: Cytomegalovirus infection causes delayed platelet recovery after bone marrow transplantation. Blood, 1991; 78(3): 844–48
8. Chang YJ, Xu LP, Liu DH et al: Platelet engraftment in patients with hematologic malignancies following unmanipulated haploidentical blood and marrow transplantation: Effects of CD34+ cell dose and disease status. Biol Blood Marrow Transplant, 2009; 15(5): 632–38
9. Zhang X, Fu H, Xu L et al: Prolonged thrombocytopenia following allogeneic hematopoietic stem cell transplantation and its association with a reduction in ploidy and an immaturation of megakaryocytes. Biol Blood Marrow Transplant, 2011; 17(2): 274–80
10. Lin Y, Hu X, Cheng H et al: Graft-versus-host disease causes broad suppression of hematopoietic primitive cells and blocks megakaryocyte differentiation in a murine model. Biol Blood Marrow Transplant, 2014; 20(9): 1290–300
11. Schneider RC, Zapol WM, Carvalho AC: Platelet consumption and sequestration in severe acute respiratory failure. Am Rev Respir Dis, 1980; 122(3): 445–51
12. Carvalho AC, Quinn DA, DeMarinis SM et al: Platelet function in acute respiratory failure. Am J Hematol, 1987; 25(4): 377–88
13. Yang M, Li CK, Li K et al: Hematological findings in SARS patients and possible mechanisms (review). Int J Mol Med, 2004; 14(2): 311–15
14. Aguilar-Guisado M, Jimenez-Jambrina M, Espigado I et al: Pneumonia in allogeneic stem cell transplantation recipients: A multicenter prospective study. Clin Transplant, 2011; 25(6): E629–38
15. Martin-Pena A, Aguilar-Guisado M, Espigado I et al: Prospective study of infectious complications in allogeneic hematopoietic stem cell transplant recipients. Clin Transplant, 2011; 25(3): 468–74
16. Weiner RS, Bortin MM, Gale RP et al: Interstitial pneumonitis after bone marrow transplantation. Assessment of risk factors. Ann Intern Med, 1986; 104(2): 168–75
17. Forslow U, Mattsson J, Ringden O et al: Decreasing mortality rate in early pneumonia following hematopoietic stem cell transplantation. Scand J Infect Dis, 2006; 38(11–12): 970–76
18 De Botton S, Sabri S, Daugas E et al: Platelet formation is the consequence of caspase activation within megakaryocytes. Blood, 2002; 100(4): 1310–17
19. Zhang Y, Zhang Y, Chen Q et al: Allogeneic hematopoietic stem cells transplantation improves the survival of intermediate-risk acute myeloid leukemia patients aged less than 60 years. Ann Hematol, 2019; 98(4): 997–1007
20. Zhang WP, Wang ZW, Hu XX et al: Preconditioning with fludarabine, busulfan and cytarabine versus standard BuCy2 for patients with acute myeloid leukemia: A prospective, randomized phase II study. Bone Marrow Transplant, 2019; 54(6): 894–902
21. De Pauw B, Walsh TJ, Donnelly JP et al: Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis, 2008; 46(12): 1813–21
22. Aronsky D, Haug PJ: Assessing the quality of clinical data in a computer-based record for calculating the pneumonia severity index. J Am Med Inform Assoc, 2000; 7(1): 55–65
23. Akahoshi Y, Kanda J, Gomyo A et al: Risk factors and impact of secondary failure of platelet recovery after allogeneic stem cell transplantation. Biol Blood Marrow Transplant, 2016; 22(9): 1678–83
24. Bruno B, Gooley T, Sullivan KM et al: Secondary failure of platelet recovery after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2001; 7(3): 154–62
25. Kong Y, Chang YJ, Wang YZ et al: Association of an impaired bone marrow microenvironment with secondary poor graft function after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2013; 19(10): 1465–73
26. Shao Y, Wang JM, Gong SL et al: [A novel single nucleotide polymorphism-based method for quantitative assessment of chimerism after allogeneic stem cell transplantation.] Zhonghua Xue Ye Xue Za Zhi, 2010; 31(2): 92–96 [in Chinese]
27. Chi AK, Soubani AO, White AC, Miller KB: An update on pulmonary complications of hematopoietic stem cell transplantation. Chest, 2013; 144(6): 1913–22
28. Sirithanakul K, Salloum A, Klein JL, Soubani AO: Pulmonary complications following hematopoietic stem cell transplantation: Diagnostic approaches. Am J Hematol, 2005; 80(2): 137–46
29. He GL, Chang YJ, Xu LP et al: Impact of pre-transplant pulmonary infection developed in horizontal laminar flow unit on the outcome of subsequent allogeneic hematopoietic stem cell transplantation. J Thorac Dis, 2016; 8(8): 2219–25
30. Guthrie KA, Yong M, Frieze D et al: The impact of a change in antibacterial prophylaxis from ceftazidime to levofloxacin in allogeneic hematopoietic cell transplantation. Bone Marrow Transplant, 2010; 45(4): 675–81
31. Kim DH, Sohn SK, Jeon SB et al: Prognostic significance of platelet recovery pattern after allogeneic HLA-identical sibling transplantation and its association with severe acute GVHD. Bone Marrow Transplant, 2006; 37(1): 101–8
32. Akahoshi Y, Kimura SI, Gomyo A et al: Delayed platelet recovery after allogeneic hematopoietic stem cell transplantation: Association with chronic graft-versus-host disease and survival outcome. Hematol Oncol, 2018; 36(1): 276–84
33. Sakamoto S, Kawabata H, Kanda J et al: High pretransplant hepcidin levels are associated with poor overall survival and delayed platelet engraftment after allogeneic hematopoietic stem cell transplantation. Cancer Med, 2017; 6(1): 120–28
34. Kong Y, Cao XN, Zhang XH et al: Atorvastatin enhances bone marrow endothelial cell function in corticosteroid-resistant immune thrombocytopenia patients. Blood, 2018; 131(11): 1219–33
35. Lefrancais E, Ortiz-Munoz G, Caudrillier A et al: The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature, 2017; 544(7648): 105–9
36. Alexander WS, Roberts AW, Nicola NA, Li R, Metcalf D: Deficiencies in progenitor cells of multiple hematopoietic lineages and defective megakaryocytopoiesis in mice lacking the thrombopoietic receptor c-Mpl. Blood, 1996; 87(6): 2162–70

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