Risk factors of primary poor graft function after allogeneic hematopoietic stem cell transplantation in patients with myeloid tumors

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Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative therapy but can result in significant complications including poor graft function (PGF). Little is known about the risk factors of primary PGF occurring after allo-HSCT. We retrospectively analyze the clinical data of 146 patients with myeloid tumors who underwent allo-HSCT at our hospital from January 2015 to December 2021. The relevant clinical parameters affecting the occurance of primary PGF after allo-HSCT were selected for univariate and multivariate analysis. Then, the difference in overall survival (OS) between groups were analyzed. The results of univariate and multivariate analysis showed that $CD34^+$ cell dose 5×10^6 /kg (P = 0.010) and the pre-transplant CRP 10 mg/L (P = 0.020) were independent risk factors for primary PGF after allo-HSCT. The primary PGF was an independent factor related to poor OS for patients with myeloid tumors (P = 0.046). In conclusion, monitoring the pre-transplant CRP and ensuring $CD34^+$ cell dose $\geq5\times10^6$ /kg in graft are effective measures to prevent the occurance of primary PGF after allo-HSCT. The occurance of primary PGF affects the overall survival of patients with myeloid tumors who underwent allo-HSCT and we should do a good job in prevention and treatment of primary PGF at an early stage.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can be a curative procedure for malignant and non-malignant hematologic conditions. However, allo-HSCT is complicated by significant transplant-related mortality of which poor graft function is one of the main contributors. Poor graft function (PGF) is a serious and intractable complication after allo-HSCT, which is often accompanied by severe neutropenia and thrombocytopenia. It is associated with the complications of infection and bleeding, which has a high mortaliy rate. Compared with patients with secondary PGF, patients with primary PGF have a much lower hematologic recovery rate[1], which seriously affects the quality of life and prognosis[2].Previous studies have suggested that cell dose, donor type, blood mismatch, GVHD, serum ferritin level, splenomegaly, and cytomegalovirus infection are closely related to PGF. The specific pathological mechanism of primary PGF remains to be further studied[3].

We retrospectively analysis the clinical data of patients with myeloid tumors who underwent the first allo-HSCT in our hospital from 2015 to 2021, in order to find the risk factors of primary PGF after allo-HSCT, leading to the development of better prediction and prevention.

Patients And Methods

Patients

Patients diagnosed with myeloid tumors according to WHO 2016 AML diagnostic criteria and MDS diagnostic criteria followed by the first allo-HSCT at The First Affiliated Hospital of Chongqing Medical University between January 2015 and December 2021 were retrospectively reviewed. It will be excluded if the patients has one of the conditions as follows (1) the occurance of graft rejection or secondary PGF. (2) Died during the process of conditioning regimen, cell reinfusion, or within 28 days after transplantation. A total of 146 patients were enrolled according to the above criteria. patients were divided into primary group (n=9), and good graft function (GGF) group (n=137) (Figure 1) .

Definitions

Diagnostic criteria for PGF: the two- or three-lineage cell count did not reach the engraftment standard after transplantation. (1. Absolute neutrophil count (ANC)>0.5×10^9/L in consecutive 3 days and no granulocyte colony-stimulating factor (G-CSF) was be applied. 2. Platelet (PLT) > 20×10^9/L in consecutive 7 days without platelet transfusion. 3. Hemoglobin (HGB) > 70 g/L in consecutive 3 days and no red blood cell transfusion.) Then, the bone marrow smear

prompted myeloproliferative hypoplasia, and the primary disease was in remission (no recurrence). Furthermore, The chimerism testing of patient showed complete donor chimerism, without severe graft-versus-host disease (GVHD)[4, 5]. The graft rejection, which is defined as mixed chimerism or complete recipient chimerism, was excluded in patients with PGF. Other potential causes of pancytopenia after transplantation were excluded as well, including active infectious diseases or drug-induced myelosuppression[6]. PGF can be divided into primary PGF and secondary PGF. The primary PGF was difined that initial engraftment did not occur[3]. The good graft function (GGF) was defined as engraftment of both neutrophils and platelets and hemoglobin concentration > 70 g/L without transfusion support beyond day 28 post-transplantation[5].

Disease states at allo-HSCT relies on bone marrow aspiration/biopsy and minimal residual disease[3]. The patients were classified into a high-risk group,a intermediate-risk group and a low-risk group according to the International Prognostic Scoring System (IPSS) model of MDS and NCCN Guidelines Version 2.2022 of AML. Then, patients with myelodysplastic syndrome (MDS) at intermediate risk-1 or intermediate risk-2 were all included in the intermeddiate-risk group.

The splenomegaly was defined as splenic thickness > 4 cm or craniocaudal length > 12 cm^3.The diagnosis and grading of acute graft-versus-host disease (aGVHD) refer to the the criteria of Glucksberg. The degree of infection refers to the CTCAE5.0 standard. CMV or EBV positive was defined as the quantification of CMV-DNA or EBV-DNA >1×10^3 copies/mL.

Overall survival (OS) was defined as the time after transplantation to the date of death or last follow-up due to any cause.

Transplantation Conditioning Regimen

Among the conditioning regimens, Busulfan+Cyclophosphamide (BUCY) was the fundamental conditioning regimen. Among them, 42 patiens were combined with Fludarabine+Cytarabine (FA), 22 patients were combined with decitabine (DEC), 15 patients were combined with idarubicin (IDA), 11 patients were combined with DEC + FA, 8 patients were combined with DEC + Cytarabine, and 5 patients were combined with Cladribine + Cytarabine(CA). there were 17 patients combined other conditioning regimens. Among them, some patients were treated with post transplantation cyclophosphamide (PTCy).

GVHD Prophylaxis

The prevention of GVHD mainly adopts tacrolimus (FK506) / cyclosporin A (CsA) + mycophenolate mofetil (MMF) + short-term methotrexate (MTX) .Patients with HLA-mismatched or matched unrelated donor additionally received anti-human thymocyte globulin (ATG) / ATG-Fresenius (ATG-F) and/or PTCy; patients with HLA-matched didn't receive or received a lower dose of ATG/ATG-F.

Virus Prophylaxis

Ganciclovir and foscarnet sodium were given to prevent viral infection. It would be replaced with acyclovir after hematopoietic reconstitution. gammaglobulin were transfused weekly within the 30 days after allo-HSCT. Beyond the day 30, when to transfuse the gammaglobulin was up to the patient's condition. Monitoring the copynumber of EBV-DNA and CMV-DNA by fluorescence quantitative PCR before allo-HSCT. Monitor the copynumber of EBV-DNA and CMV-DNA once a week within the 30 days after allo-HSCT. IF positive, monitor 2-3 times a week. For the persistently negative patients, monitor every 0.5-1 month in the later period.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 26.0 software and GraphPad Prism 5 Software. For the analysis of risk factors for primary PGF, The t test or nonparametric test was used to compare the measurement data between groups, and the chi-square test or Fisher's exact test was used to compare the enumeration data between groups. The test methods above were all used for univariate analysis. Logistic stepwise regression was used for multivariate

analysis.In addition, the endpoint event was OS. The Kaplan-Meier method and Cox regression were used to estimate survival curves. In the Kaplan-Meier method, the Log-Rank test was used for comparison between groups, but the Tarone-Ware test replaced it when two survival curves crossed. All statistical tests were 2-sided, and a *P* value < 0.05 was considered statistically significant.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and all methods were performed in accordance with the relevant guidelines and regulations.

Results

Incidence and Characteristics

A total of 146 patients were enrolled, including 76 males and 70 females, with a median age of 36 years (13-65 years) at the time of transplantation. The diseases included 121 cases of acute myeloid leukemia and 25 cases of myelodysplastic syndrome. Of the 146 patients, 97 underwent HLA-haploidentical related donor(HRD) HSCT, 39 underwent matched sibling donor(MSD) HSCT, and 10 underwent matched unrelated donor(MUD) HSCT(4 cases of HLA full match, 6 cases of 9/10 match).

The median $CD34^+$ cell dose which were transfused into the 146 patients was 6.70 (1.01-23.91) × 10^6 /kg. Of the 146 patients analyzed, 145 cases (99.32 %) had the neutrophil engraftment within the 28 days after the allo-HSCT, and the median time of neutrophil engraftment was 13 (8-21) days. 137 cases (93.84 %) had the platelet engraftment within the 28 days after the allo-HSCT, and the median time of platelet engraftment was 13 (8-28) days.

Until the follow-up deadline of July 1, 2022, 9 patients (6.16 %) were diagnosed with primary PGF. The characteristics of the patients with primary PGF are presented in Table 1. The primary PGF group comprised 6 males (66.67 %) and 3 females (33.33 %) , of whom 5 were diagnosed with AML(55.56 %), 4 with MDS(44.44 %). The medium age of patients was 37 years (28-53 years). Of the 9 patients with primary PGF, 7(77.78 %) underwent HLA-haploidentical related donor HSCT, 1(11.11 %) underwent matched unrelated donor HSCT, and 1(11.11 %) underwent matched sibling donor HSCT. Moreover, 5(55.56 %) were diagnosed CMV infection and 3(33.33 %) were diagnosed EBV infection.

Table 1

Characteristics of Patients with Primary PGF

ID	Age ,yr	Sex	Disease	significantly enlarged spleen	CR/PR	Risk Stratification	Donor Type	$CD34^+$ ($\times 10^6$ /kg)	CMV Infection	Pre-transplant CRP 10 mg/L
1	35	M	AML	No	Yes	MR	HRD	3.98	No	Yes
2	29	M	MDS	Yes	No	MR	HRD	11.00	Yes	No
3	48	F	MDS	No	No	MR	HRD	2.42	Yes	Yes
4	37	M	AML	No	Yes	MR	MUD	5.24	No	Yes
5	28	M	AML	No	Yes	HR	HRD	3.86	No	No
6	53	F	MDS	Yes	No	MR	MSD	4.88	Yes	Yes
7	34	F	AML	No	Yes	MR	HRD	1.77	No	Yes
8	39	M	MDS	No	No	MR	HRD	4.42	Yes	Yes
9	46	M	AML	No	Yes	MR	HRD	6.71	Yes	Yes

Abbreviations: M, male; F, female; CR, complete remission; PR, partial remission; HR, high risk; MR, medium risk; HRD, HLA-haploidentical related donor; MUD, matched unrelated donor; MSD, matched sibling donor; CMV, cytomegalovirus.)

Compared with the GGF group, the primary PGF group had a much lower median of CD34+ cell dose (4.42×106 /kg versus 7.09×106 /kg; *P* = 0.027) (Figure 2a). The median of pre-transplant CRP was much higher in the primary PGF group compared with the GGF group (47.20 mg/L versus 6.97 mg/L; *P* = 0.013) (Figure 2b).

Risk Factors for Primary PGF

In univariate analysis, patients with MDS(*p*=0.047), the length or thickness of spleen increased at least twice (*P*=0.003), disease states at allo-HSCT not reach at CR/PR (*P*=0.025), cytomegalovirus infection(*P*=0.025), and $CD34^+$ cell dose 5×10^6 /kg(*P*=0.020) were identified as risk factors of primary poor graft function after allo-HSCT in patients with myeloid tumors (Table 2). On multivariate logistic analysis, 2 independent risk factors were identified: $CD34^+$ cell dose 5×10^6 /kg (*P*=0.010; OR, 13.842; 95% CI, 1.890 to 101.384) and the pre-transplant CRP 10 mg/L(*P* =0.020; OR, 23.754; 95% CI, 1.650 to 342.006) (Table 3).

Table 2

Univariate analysis of risk factors for primary PGF

Risk Factor	Primary PGF group n=9 n %	GGF group n=137 n %	*P*	Risk Factor	Primary PGF group n=9 n %	GGF group n=137 n %	*P*
Sex			0.497	PTCy			0.139
Male	6 7.9%	70 92.1%		Yes	2 18.2%	9 81.8%	
Female	3 4.3%	67 95.7%		No	7 5.2%	128 94.8%	
Age,yr			1.000	$CD34^+$ cell dose,$x10^6$/kg			**0.020**
≤45	6 6.7%	84 93.3%		5	6 14.0%	37 86.0%	
45	3 5.4%	53 94.6%		≥5	3 2.9%	100 97.1%	
Disease			**0.047**	aGVHD			0.662
AML	5 4.1%	116 95.9%		Yes	2 7.7%	24 92.3%	
MDS	4 16.0%	21 84.0%		No	7 5.8%	113 94.2%	
Disease states at HSCT			**0.025**	ATG/ATG-F,mg/kg			1.000
CR/PR	5 4.0%	120 96.0%		ATG≤6.5 or ATG-F≤13	3 5.4%	53 94.6%	
NR/Relapse	4 19.0%	17 81.0%		ATG 6.5 or ATG-F 13	6 6.7%	84 93.3%	
Risk stratification			0.438	CMV infection			**0.025**
Low risk	0 0.0%	17 100.0%		Yes	5 15.6%	27 84.4%	
Medium risk	8 8.5%	86 91.5%		No	4 3.5%	110 96.5%	
High risk	1 2.9%	34 97.1%		EBV infection			0.733
Blood mismatch			1.000	Yes	3 4.8%	59 95.2%	
Identical	5 6.2%	76 93.8%		No	6 7.1%	78 92.9%	
Mismatch	4 6.2%	61 93.8%		Splenomegaly			**0.003**
Sex mismatch			0.078	Not splenomegaly	7 4.9%	137 95.1%	
Identical	8 9.8%	74 90.2%		Significantly enlarged spleen	2 100.0%	0 0.0%	

Mismatch	1 1.6%	63 98.4%		Fungal infection before allo-HSCT			1.000
HLA			1.000	Yes	1 5.6%	17 94.4%	
Identical	2 4.7%	41 95.3%		No	8 6.3%	120 93.7%	
Mismatch	7 6.8%	96 93.2%		Bloodstream Infection after allo- -HSCT within 30 days			0.136
Chemotherapy co- -urses before HSCT			0.355	Yes	3 13.6%	19 86.4%	
≤3	9 7.3%	114 92.7%		No	6 4.8%	118 95.2%	
3	0 0.0%	23 100.0%		Pre-transplant CRP,mg/L			0.088
Donor type			0.339	≤10	2 2.6%	74 97.4%	
HRD	7 7.2%	90 92.8%		10	7 10.0%	63 90.0%	
MSD	1 2.6%	38 97.4%		degree of Infection before allo-HSCT			0.161
MUD	1 10.0%	9 90.0%		Grade 0-2	7 5.2%	127 94.8%	
				Grade 3	2 16.7%	10 83.3%	

Abbreviations: CR, complete remission; PR, partial remission; NR, non-remission; Not splenomegaly, splenic thickness 8 cm and craniocaudal length 24 cm; Significantly enlarged spleen, splenic thickness ≥8 cm or craniocaudal length ≥24 cm.

Significant values are in bold type.

Table 3

Multivariate analysis of risk Factors for primary PGF

Clinical characteristics	*B*	*S.E.*	*Wald*	*OR*	*95%CI*	*P*
$CD34^+$ cell dose $5x10^6$ /kg	2.628	1.016	6.690	13.842	1.890~101.384	0.010
Pre-transplant CRP 10 mg/L	3.168	1.361	5.419	23.754	1.650~342.006	0.020

Survival analysis

The median time of follow-up was 16.38 months (1.10-80.37 months). Disease relapse occurred in 17 patients(11.64 %), and 22 patients(15.07 %) died (9 patients died of severe infection, 5 patients died of disease deterioration or relapse, 3 patient died of hemorrhage, 4 patient died of organ failure, and 1 patients died of GVHD). The 5-year OS rate of all patients was 75.6 % (95%CI: 62.9 %-88.3 %). Then, we choosed some clinical parameters in the Table 2 which may affect the OS of

patients with myeloid tumors who underwent allo-HSCT to do the univariate and multivariate analysis. the 3-year OS rate of the primary PGF group was 52.5 % (95%CI: 12.5 %-92.5 %), and the 3-year OS rate of the GGF group was 82.8 % 95%CI 74.6 %~91.0 % . The OS rate of the primary PGF group was significantly lower than that of the GGF group (P=0.046, Figure 3). Furthermore, using a Cox regression model, we identified primary PGF (P =0.046; HR, 3.669; 95% CI, 1.024 to 13.151) as an independent factor related to poor OS for patients with myeloid tumors (Figure 4).

Discussion

At present, there are few reports refer to the risk factors of PGF after allo-HSCT at home and abroad. According to the reports, the incidence of PGF after allo-HSCT in patients with hematologic malignancies ranged from 5 % to 27 %[1] . In our study, the incidence of primary PGF in patients with myeloid tumors was 6.16 %, Similar to the previous reports.

It is affirmed that the lower $CD34^+$ cell dose in the graft has an effect on the occurance of PGF[7]. Some studies suggest that the $CD34^+$ cell dose $<5\times10^6$/kg is an independent risk factor for the occurrence of primary PGF[3]. The results of this study are the same. The higher $CD34^+$ cell dose in the graft can overcome the HLA Barriers by inducing immune tolerance, promoting the engraftment of neutrophil and platelet[8]. It suggests that in order to improve the success rate of engraftment, $CD34^+$ cell should be transfused as many as possible during the allo-HSCT, ensuring that the $CD34^+$ cell dose $\geq5\times10^6$ /kg.

It has been reported that splenomegaly is associated with PGF[9] because the infused $CD34^+$ cells could be sequestered by the spleen, resulting in a delayed homing and hypocellular bone marrow[10]. Furthermore, the newly generated blood cells could easily get trapped and destroyed by the enlarged spleen[11]. The results of univariate analysis in our study suggest that significantly enlarged spleen (the length or thickness of spleen increased at least twice) was a risk factor for the occurance of primary PGF. Spleen removal before transplantation can promote hematopoietic reconstitution after transplantation. However, The results of multivariate analysis in our study showed that significantly enlarged spleen wasn't an independent risk factor for the development of primary PGF in patients with myeloid tumors after allo-HSCT. Maybe the engraftment delay which contributed by hypersplenism can be counterbalanced when the $CD34^+$ cell dose 5.7 $X10^6$ /kg in the graft[12].

Many studies have shown that CMV infection after transplantation is a risk factor for the occurance of PGF[7,13].CMV not only inhibit the bone marrow hematopoiesis by infecting myeloid cells, but also by infecting bone marrow stromal cells[14]. In addition, CMV can inhibits the engraftment of donor bone marrow cells by downregulation of hemopoietin gene expression in recipient stroma[15]. The results of univariate analysis in our study showed that patients with CMV infection after transplantation were more likely to develop primary PGF, suggesting that the prevention and treatment of viral infection should be attached importance to.

The effect of pre-transplant CRP on the development of primary PGF is unclear. The results of our study showed that pre-transplant CRP>10 mg/L was an independent risk factor (P=0.020) for the development of primary PGF in patients with myeloid tumors after allo-HSCT. Patients with pre-transplant CRP>10 mg/L are often indicated that combined with systemic inflammation or infection. some of inflammatory mediators contribute to remodel the bone marrow niche which favors the preferential expansion of clonal leukemic cells, hence promoting the emergence and progression of malignant myeloid disease, and resulting in the decrease of normal HSCs[16-18]. It may be related to the development of primary PGF[19]. However, it's needed to expand the sample size to prove the conclusion.

The incidence of PGF after allo-HSCT in different hematological diseases is different[1,20]. The results of univariate analysis in our study showed that patients with MDS were more likely to develop primary PGF among the patients with myeloid tumors. But the conclusion needs be further verified and explored. In addition, It is still controversial that whether the disease states at allo-HSCT is a risk factor of primary PGF. Some reports have shown that the incomplete remission of the

hematological diseases at allo-HSCT is closely related to the occurrence of PGF [3], and there are also reports indicate that the the disease states at allo-HSCT has nothing to do with the occurrence of PGF[21]. The results of univariate analysis in our study showed that the patients with complete remission or partial remission at allo-HSCT were less likely to develop primary PGF. The relationship between the disease states at allo-HSCT and the primary PGF remains to be further studied.

Previous studies suggest that patients with PGF have significantly lower OS rates than patients with good graft funciton[3,7]. The results of our study are consistent with the above results, suggesting that in order to improve the OS rate of patients, the occurrence of PGF after allo-HSCT should be prevented and treated as much as possible.

Conclusions

To sum up, $CD34^+$ cell dose 5×10^6 /kg and the pre-transplant CRP 10 mg/L were independent risk factors of primary PGF after allo-HSCT for patients with myeloid tumors. The occurance of primary PGF after Allo-HSCT in patients with myeloid tumors will reduce the OS rate. Hence, monitoring the pre-transplant CRP and $CD34^+\geq5\times10^6$ /kg in the graft have an effect on preventing the occurance of primary PGF after allo-HSCT. The occurrence of primary PGF will affect the overall survival rate of transplant patients, and early prevention and treatment of primary PGF is required.

Declarations

Author contributions

Zhang, L.Y. and Xiong, Y.Y. performed statistical analyses and drafted the manuscript. Liao, M.Y., Xiao, Q., Tang, X.Q., Luo, X.H., Zhang, H.B., Wang, L. and Liu, L. supervised the study process. All authors contributed to the collection of data, and critically reviewed and revised the manuscript.

Data availability statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Figures

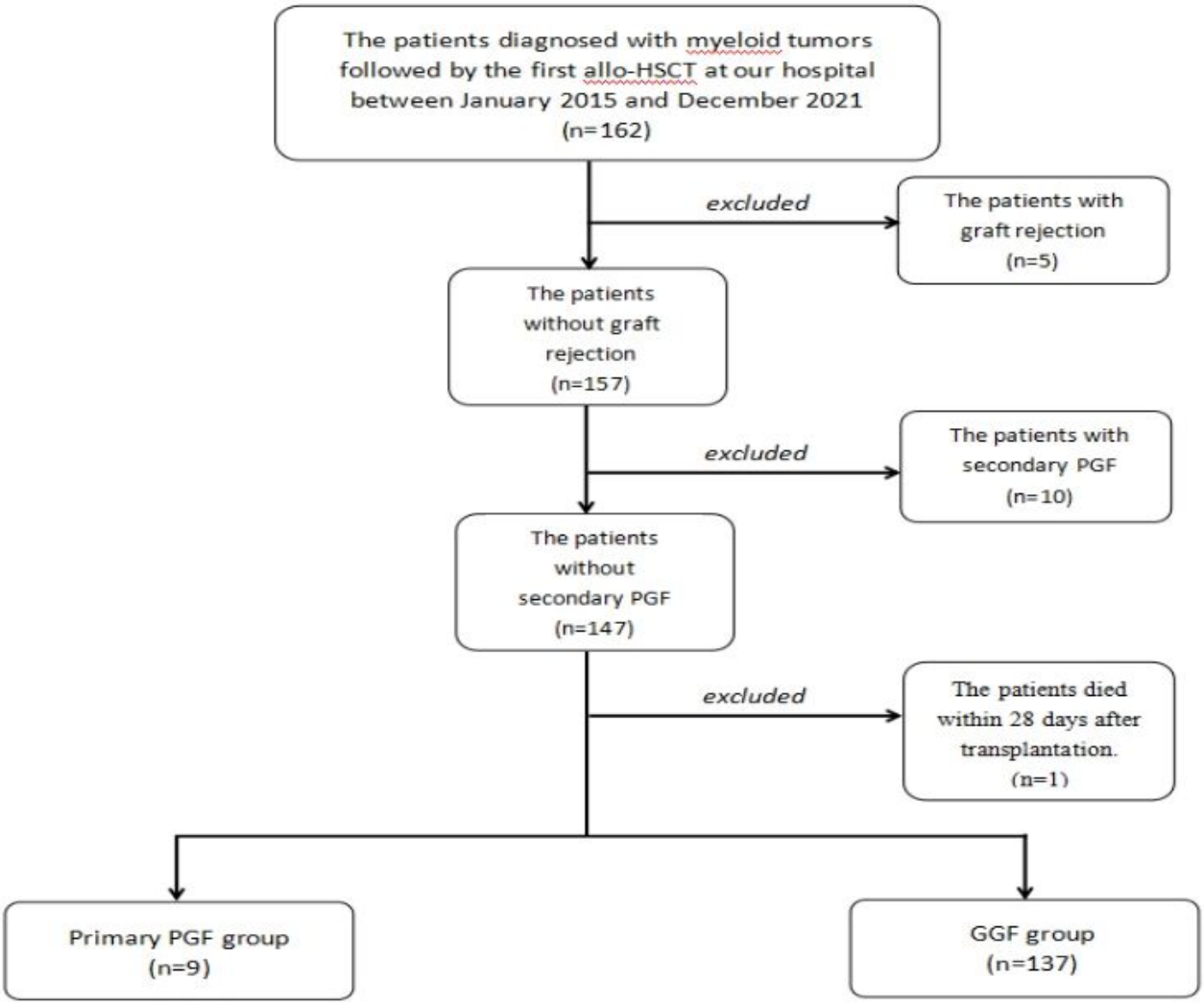

Figure 1

The flowchart for screening out patients who measure up to the criteria.

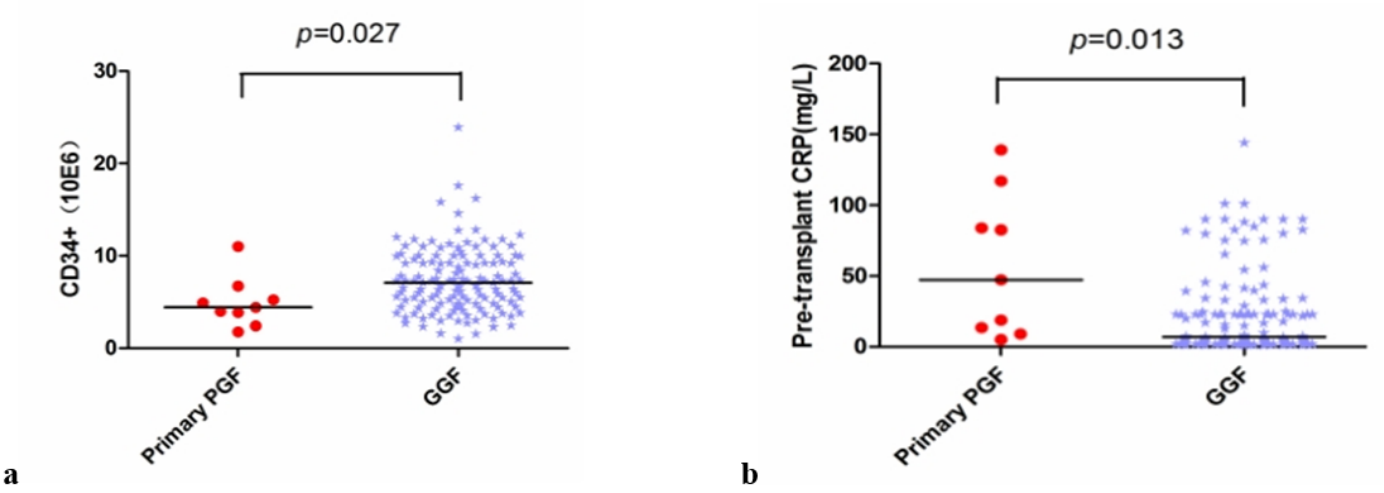

Figure 2

The comparison between primary PGF group and GGF group. (a. Median of $CD34^+$ cell dose infused in the primary PGF group and GGF group. **b.** Median of pre-transplant CRP in the primary PGF group and GGF group.)

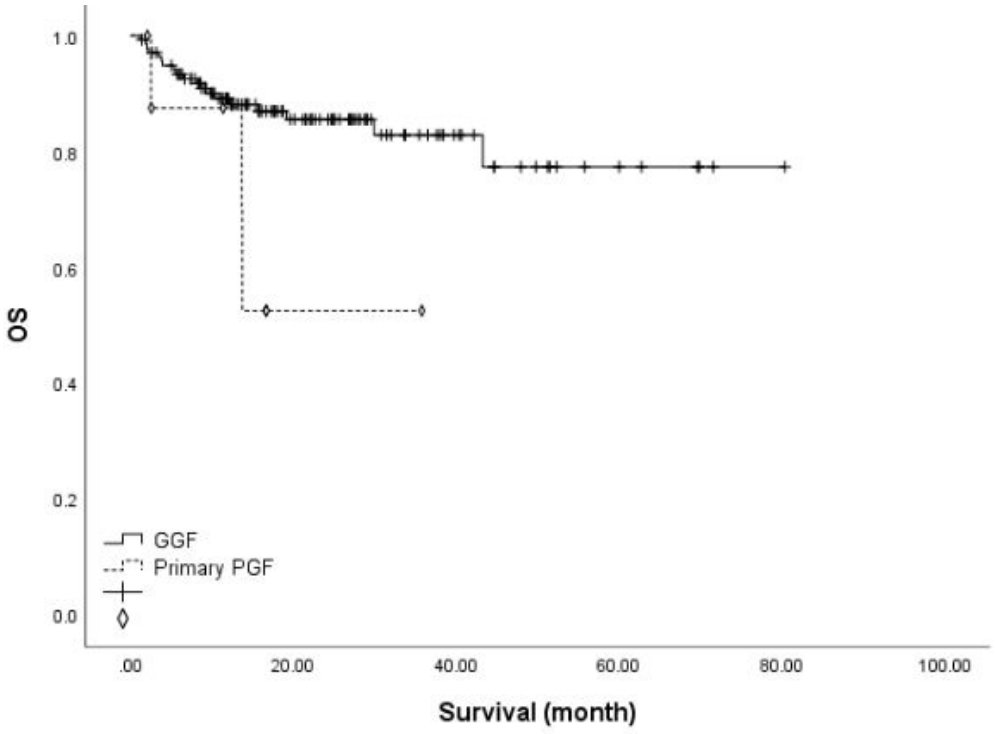

Figure 3

Survival curves of OS for different groups. GGF OS vs primary PGF OS: *P*=0.046

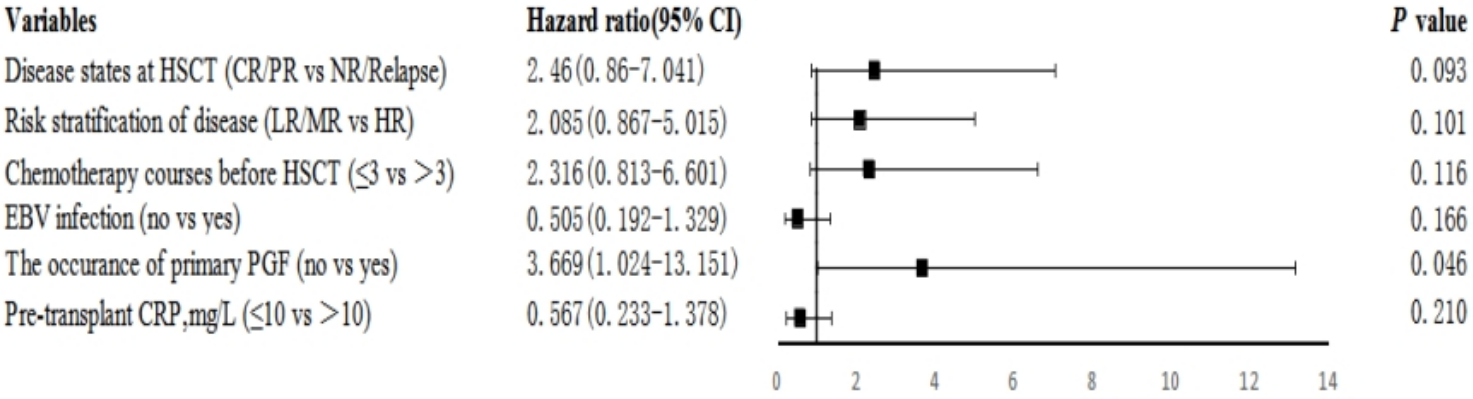

Figure 4

The forest plot of multivariate Analysis for OS (CR, complete remission; PR, partial remission; NR, non-remission; LR, low risk; MR, medium risk; HR, high risk.)