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Plerixafor-based mobilization and mononuclear cell counts in graft increased the risk of engraftment syndrome after autologous hematopoietic stem cell transplantation

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Abstract

Engraftment syndrome (ES) is one of the most common complications in the early phase after autologous hematopoietic stem cell transplantation (ASCT), and we aimed to evaluate the incidence and risk factors for ES patients receiving ASCT in the era of plerixafor-based mobilization. A total of 294 were enrolled, and 16.0% (n = 47) experienced ES after ASCT. The main clinical manifestations were fever (100%), diarrhea (78.7%), skin rash (23.4%), and hypoxemia/pulmonary edema (12.8%). Plerixafor-based mobilization was associated with higher counts of $CD3^+$ cells, $CD4^+$ cells, and $CD8^+$ cells in grafts. In univariate analysis of the total cohort, age ≥60 years, receiving ASCT at complete remission (CR), higher number of mononuclear cell (MNC), $CD3^+$ cell counts, $CD4^+$ cells as well as $CD8^+$ cells transfused and plerixafor-based mobilization were associated with ES after ASCT. Multivariate analysis showed that age ≥60 years (P = .0014), receiving ASCT at CR (P = .002), and higher number of MNC transfused (P = .026) were associated with ES in total cohort. In plasma cell disease subgroup, age ≥60 years (P = .013), plerixafor-based mobilization (P = .036), and receiving ASCT at CR (P = .002) were associated with ES. Patients with more risk factors had a higher risk of ES. The 1-year probabilities of relapse, non-relapse mortality, and survival were comparable between patients with and without ES. Thus, plerixafor-based mobilization may influence the composition of T lymphocytes in grafts and increase the risk of ES, particularly in patients with plasma cell disease.

Key Words: Autologous stem cell transplantation; Engraftment syndrome; Plerixafor; Risk factors

1. INTRODUCTION

Autologous hematopoietic stem cell transplantation (ASCT) is one of the most important therapies for hematologic malignancies, particularly for patients with lymphoma or plasma cell disease.[1,2] Although many new drugs have been widely used for these patients, ASCT is still the irreplaceable therapy for long-term disease-free survival.[3,4]

Engraftment syndrome (ES) is one of the most common complications in the early phase after ASCT, which is characterized by non-infectious fever and various clinical findings, such as skin rash, diarrhea, pulmonary infiltrates, weight gain, and neurological manifestations.[5] Although the ES is commonly described in allogeneic HSCT recipients, it actually firstly reported in ASCT recipients. The incidence of ES is 7% to 59% across previous studies because of different diagnostic criteria.[6–9] In addition, some studies observed that ES might increase the risk of non-relapse mortality (NRM) after ASCT particularly for the pediatric patients.[10,11] Thus, how to predict and prevent ES is important to prevent early mortality after ASCT.

Several risk factors had been reported to be associated with ES after ASCT, such as female gender,[12,13] children below 8 years of age,[14] older age group recipients,[15] the type of malignancy (solid tumor, eg, breast cancer),[8,16] patients transplanted in early phase,[8] and exposition to bortezomib or lenalidomide prior to ASCT.[17,18] Particularly, graft is the most important variable for ES after ASCT. For example, some studies observed that

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mobilization with high-dose granulocyte-colony stimulating factor (G-CSF),[14] higher number of mononuclear cell (MNC) transfused,[12] and a high number of $CD34^+$ cells/kg infused[8] could increase the risk of ES. However, most of these studies were conducted before the era that plerixafor was widely used for stem cell mobilization, and whether plerixafor-based mobilization would increase the risk of ES is still unclear.

Thus, in the present study, we aimed to evaluated the incidence and risk factors for ES patients receiving ASCT, particularly that whether plerixafor-based mobilization would increase the risk of ES after ASCT.

2. MATERIALS AND METHODS

2.1. Patients

We performed a retrospective study in Peking University, Institute of Hematology (PUIH). Including criteria were as followed: (1) patients received ASCT from January 1, 2015, to December 30, 2022, and (2) had complete medical information. The study was approved by the Ethics Committee of Peking University People's Hospital (approval number: 2022PHB033-001), and written informed consent was obtained from all subjects before study entry, in accordance with the Declaration of Helsinki.

2.2. Transplantation protocols

Stem cell mobilization was performed by G-CSF with or without plerixafor (0.24 mg/kg body weight). Plerixafor was used when patients had the following high-risk factors for poor mobilization or mobilization failure: (1) treatment-related factors, including the number of previous chemotherapy cycles; previous exposure to melphalan, fludarabine, platinum-based regimens, alkylating agents, or lenalidomide; previous multiline chemotherapy; or previous bone marrow (BM) radiotherapy; (2) patient-related factors, including advanced age, female, advanced disease; and diabetes mellitus; and (3) BM-related factors, including BM involvement and thrombocytopenia.[19] Plasma cell disease patients received conditioning regimen with melphalan.[3] Lymphoma patients mainly received conditioning regimen with BEAM (bendamustine, etoposide, cytarabine, and melphalan).[4] ASCT was performed on day 0 with at least 2.0×10^6 $CD34^+$ cells/kg patients' body weight. All patients received weight-adapted G-CSF (filgrastim at 5 μg/kg body weight per day) starting at day +6 after ASCT and lasting until neutrophil engraftment.

2.3. Clinical definitions and assessments

According to the criteria of Grant et al,[20] ES was diagnosed as the presence of either both major criteria or one of the major criteria and two minor criteria. The major criteria included (1) non-infectious fever (body temperature >38.0°C), (2) erythematous rash covering ≥25% of the patient's body surface area. The minor criteria included (1) weight gain ≥2.5% of baseline, (2) non-cardiogenic, non-infectious pulmonary symptoms including pulmonary edema and pulmonary infiltrates identified on X-ray, and (3) non-infectious diarrhea ≥2 episodes of liquid stools in a 24-hour period. These symptoms must appear within 24-hour after neutrophil engraftment (defined as the first day of absolute neutrophil counts exceeding 0.5×10^9/L on 2 consecutive days) to be considered as part of ES.

2.4. Statistical analysis

Characteristics of patients were summarized by descriptive statistics, that is, using counts (percentages) for categorical variables and using median (range) or cut-off value determined by an receiver operating characteristic (ROC) curve for continuous variables. Subject variables were compared using the χ^2 test for categorical variables and the Mann–Whitney *U* test for continuous variables. Multivariate analysis was performed using logistic regression with a forward selection procedure to determine independent influence factors involving dichotomous variables selected from the univariate analysis. The parameters with $P < .10$ according to the univariate analysis were entered into a multivariate model. The probability of survival was estimated with the Kaplan-Meier method and were compared using the log-rank test. Statistical analyses were performed using 1-way analysis of variance (ANOVA) for comparisons among the groups. Analyses were performed using SPSS 24 (SPSS Inc./IBM, Armonk, New York). Unless otherwise specified, all *P* values were 2-sided and $P < .05$ was considered significant.

3. RESULTS

3.1. Patients' characteristics

The characteristics of 294 patients are summarized in Table 1. Most of the patients were diagnosed as lymphoma (16.0%) and plasma cell disease (78.9%), and 32.7% of them received both G-CSF and plerixafor for stem cell mobilization. All patients achieved neutrophil and platelet engraftments, with a median time of 10 days (range 7–21) days and 12 days (range 6–91) days, respectively. Meanwhile, the median counts of MNC, $CD34^+$ cell, $CD3^+$ lymphocyte, $CD3^+CD4^+$ lymphocyte, and $CD3^+CD8^+$ lymphocyte transfused in total cohort were 8.96 (2.88–58.44) versus 7.21 (1.87–37.73) × 10^8/kg ($P < .001$), 3.53 (1.14–13.88) versus 3.49 (0.38–33.0) × 10^6/kg ($P = .767$), 3.76 (0.68–133.48) versus 1.52 (0.03–34.60) × 10^8/kg ($P < .001$), 2.09 (0.45–66.37) versus 0.87 (0.01–26.79) × 10^8/kg ($P < .001$), and 1.62 (0.18–57.66) versus 0.50 (0.01–16.33) × 10^8/kg ($P < .001$), respectively, for those with and without plerixafor-based mobilization. The median follow-up was 1572 days (range, 96–3227) days.

3.2. Characteristics of ES

A total of 47 (16.0%) patients experienced ES after ASCT, and the median time from ASCT to the onset of ES was 9 (range 6–13) days. The clinical manifestations of ES are shown in Figure 1. Fever was the most common symptom, with the median maximum temperature of 38.1°C (range 37.4°C–39.8°C) when ES was diagnosed. Eleven (23.4%), 6 (12.8%), and 37 (78.7%) patients had skin rash, hypoxemia or pulmonary edema, and diarrhea. Four (8.5%) patients showed new onset bilateral diffuse infiltration in chest computed tomography (CT)/X-ray. The clinical manifestations of ES between patients with lymphoma or plasma cell disease are shown in Table 2.

3.3. Risk factors for ES

Multivariate analysis showed that age ≥60 years (odds ratio [OR], 3.26; 95% confidence interval [CI], 1.62–6.58; $P = .001$), receiving ASCT at complete remission (CR; OR, 2.89; 95% CI, 1.47–5.68; $P = .002$), and higher number of MNC transfused (OR, 2.12; 95% CI, 1.10–4.12; $P = .026$) were associated with a higher risk of ES after ASCT in total cohort (Table 3). Thus, patients were categorized into low-risk group (0–1 risk factor, n = 215), intermediate-risk group (2 risk factors, n = 70), and high-risk group (3 risk factors, n = 9). The ratio of ES in the intermediate-risk group (28.6% vs 10.2%, $P < .001$) and the high-risk group (55.6% vs 10.2%, $P < .001$) were significantly higher than that of the low-risk group, while the ratio of ES in the high-risk group was also significantly higher than that of the intermediate-risk group (55.6% vs 28.6%, $P = .032$, **Fig. 2A**).

Table 1

Patient characteristics.

Characteristics	Engraftment syndrome		*P* value
	Yes (n = 47)	No (n = 247)	
Median age at auto-HSCT, y (range)	57 (21–69)	53 (12–70)	.009
Gender, n (%)			.177
Male	22 (46.8)	142 (57.5)	
Female	25 (53.2)	105 (42.5)	
Disease types, n (%)			.863
Multiple myeloma	37 (78.7)	185 (74.9)	
DLBCL	5 (10.6)	27 (10.9)	
Amyloidosis	2 (4.3)	8 (3.2)	
ALK-positive large B cell lymphoma	0	9 (3.6)	
Hodgkin lymphoma	1 (2.1)	5 (2.0)	
Others	2 (4.2)	13 (5.2)	
Chemotherapy courses before auto-HSCT, median (range)	4 (2–12)	5 (2–24)	.468
Use of chemotherapeutic drugs, n (%)			
Bortezomib	38 (80.9)	191 (77.3)	.594
Lenalidomide	16 (34.0)	105 (42.5)	.280
Rituximab	6 (12.8)	29 (11.7)	.893
Daratumumab	1 (2.1)	14 (5.7)	.312
Cyclophosphamide	26 (55.3)	148 (59.9)	.556
Disease status before allo-HSCT, n (%)			.020
CR	27 (57.4)	90 (36.4)	
VGPR/PR	18 (38.3)	149 (60.3)	
SD	2 (4.3)	8 (3.2)	
Time from disease diagnosis to transplantation, median (mo, range)	7 (4–24)	8 (3–96)	.365
MNC counts in graft, median (range, $\times 10^8$/kg)	8.90 (3.87–58.44)	7.60 (1.87–37.73)	.094
$CD34^+$ cell counts in graft, median (range, $\times 10^6$/kg)	3.72 (1.90–15.58)	3.49 (0.38–33.0)	.845
$CD3^+$ lymphocyte counts in graft, median (range, $\times 10^6$/kg)	290.09 (16.62–5756.10)	201.49 (3.44–13348.12)	.051
$CD3^+CD4^+$ lymphocyte counts in graft, median (range, $\times 10^6$/kg)	179.18 (10.33–3700.20)	105.75 (1.41–6636.74)	.021
$CD3^+CD8^+$ lymphocyte counts in graft, median (range, $\times 10^6$/kg)	116.58 (5.28–2819.71)	74.01 (1.21–5765.94)	.036

ALK = anaplastic lymphoma kinase, Auto-HSCT = autologous hematopoietic stem cell transplantation, CR = complete response, DLBCL = diffuse large B-cell lymphoma, MNC = mononuclear cell, PR = partial response, SD = stable disease, VGPR = very good partial response.

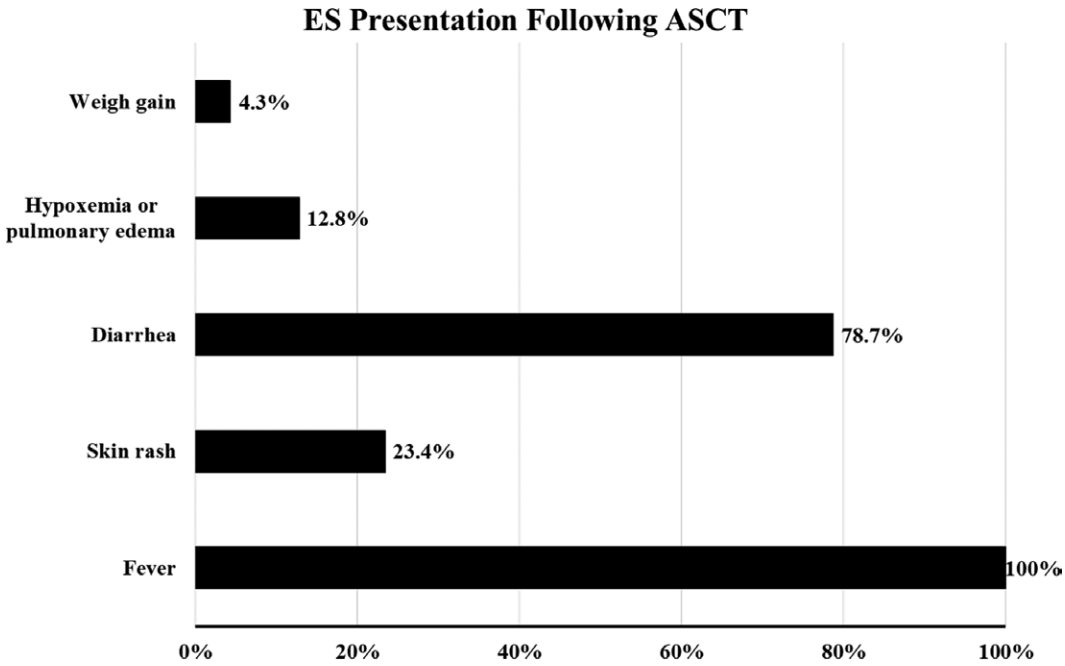

Figure 1. Engraftment syndrome presentation following autologous hematopoietic stem cell transplantation.

In the subgroup analysis of plasma cell disease patients, age ≥60 years (OR, 2.63; 95% CI, 1.22–5.65; *P* = .013), plerixafor-based mobilization (OR, 2.20; 95% CI, 1.05–4.58; *P* = .036), and receiving ASCT at CR (OR, 3.19; 95% CI, 1.50–6.77; *P* = .002) were associated with a higher risk of ES after ASCT (Table 4). The same as the total population, patients were categorized into low-risk group (0 risk factor, n = 85), intermediate-risk group (1 risk factor, n = 89), and high-risk group (2–3 risk factors, n = 60). The ratio of ES in the intermediate-risk group (19.1% vs 3.5%, *P* = .005) and the high-risk group (31.7% vs

Table 2

The clinical manifestations of ES between patients with lymphoma or plasma cell disease.

Characteristics	Engraftment syndrome		*P* value
	Plasma cell disease (n = 39)	Lymphoma (n = 8)	
Time from ASCT to the onset of ES, median (range)	9 (6–13)	8 (7–10)	.112
Maximum temperature, median (range)	38.1 (37.4–39.8)	38.2 (37.8–39.0)	1.000
Skin rash, n (%)	8 (20.5)	3 (37.5)	.301
Hypoxemia or pulmonary edema, n (%)	6 (15.4)	0	.235
Diarrhea, n (%)	32 (82.1)	5 (62.5)	.218
Wight gain, n (%)	2 (5.1)	0	.513

ASCT = autologous hematopoietic stem cell transplantation, ES = engraftment syndrome.

Table 3

Univariate and multivariate analysis of variables related to engraftment syndrome in total patients underwent autologous hematopoietic stem cell transplantation.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age						
<60 y		1			1	
≥60 y	2.83	1.48–5.41	.002	3.26	1.62–6.58	.001
Mobilization protocol						
No plerixafor		1				
Plerixafor	2.42	1.29–4.53	.006			
Disease status before allo-HSCT						
Beyond CR (VGPR + PR + SD)		1			1	
CR	2.36	1.25–4.44	.008	2.91	1.47–5.78	.002
MNC counts						
$<8.70 \times 10^8$/kg		1			1	
$\geq 8.70 \times 10^8$/kg	1.95	1.05–3.64	.036	2.12	1.10–4.12	.026
CD3+ lymphocyte counts						
$<2.42 \times 10^8$/kg		1				
$\geq 2.42 \times 10^8$/kg	2.41	1.24–4.68	.009			
CD3+CD4+ lymphocyte counts						
$<1.23 \times 10^8$/kg		1				
$\geq 1.23 \times 10^8$/kg	2.05	1.10–3.96	.032			
CD3+CD8+ lymphocyte counts						
$<0.80 \times 10^8$/kg		1				
$\geq 0.80 \times 10^8$/kg	2.37	1.22–4.60	.011			

CI = confidence interval, CR = complete response, HSCT = hematopoietic stem cell transplantation, MNC = mononuclear cell, OR = odds ratio, PR = partial response, SD = stable disease, VGPR = very good partial response.

3.5%, $P < .001$) were significantly higher than that of the low-risk group, while the ratio of ES in the high-risk group was also significantly higher than that of the intermediate-risk group (31.7% vs 19.1%, $P = .037$; **Fig. 2B**). In the subgroup analysis of lymphoma patients, no risk factors were associated with ES.

3.4. Treatment and clinical outcomes of ES patients

All of the patients received corticosteroid treatment for ES, and all of them achieved CR after treatment. The 1-year probabilities of relapse, NRM, progression-free survival (PFS), and overall survival (OS) were 4.3% (95% CI, 0%–9.9%) versus 4.5% (95% CI, 2.0%–7.0%) with $P = .416$, 0 versus 0.8% (0%–2.0%) with $P = .270$, 95.7% (95% CI, 90.1%–100%) versus 94.7% (95% CI, 92.0%–97.4%) with $P = .227$, and 100% versus 97.6% (95% CI, 95.6%–99.6%) with $P = .433$, respectively, for patients with and without ES (Table 5).

4. DISCUSSION

In the present study, we observed that the incidence of ES was 16.0% after ASCT. Age ≥60 years and receiving ASCT at CR were associated with ES in total cohort and plasma cell disease subgroup. In addition, a higher number of MNC transfused was the risk factor of ES in total cohort and plerixafor-based mobilization was the risk factor of ES in plasma cell disease subgroup. Patients with more risk factors had a higher risk of ES. Thus, this is the study firstly identified the risk factor of ES in the era that plerixafor was widely used in stem cell mobilization.

Plerixafor selectively and reversibly antagonizes the chemokine receptor 4 (CXCR4) chemokine receptor and blocks binding of stromal cell-derived factor-1α provides a mechanism for mobilization of $CD34^+$ stem cells from the BM to the peripheral blood (PB) where they can be collected for ASCT. In addition, plerixafor mobilization could also influence the number of other immune cells. The numbers of B and T lymphocytes in patients receiving G-CSF plus plerixafor mobilization were higher than those receiving G-CSF mobilization alone.[21–23] Particularly, Righi et al[24] demonstrated that the CXCR4 antagonism selectively induced the reduction of intratumoral T regulatory cells (Tregs), and suppression of Tregs after high-dose chemotherapy in combination with activation and expansion of effector T cells by ex vivo costimulation may be one of the mechanisms of ES. Plerixafor can also improve lymphocyte recovery after ASCT through mobilization of more mature lymphocytes,[25,26] and T cell rapid recovery after transplantation can induce ES.[27] Thus, T lymphocyte subgroup was important in the occurrence

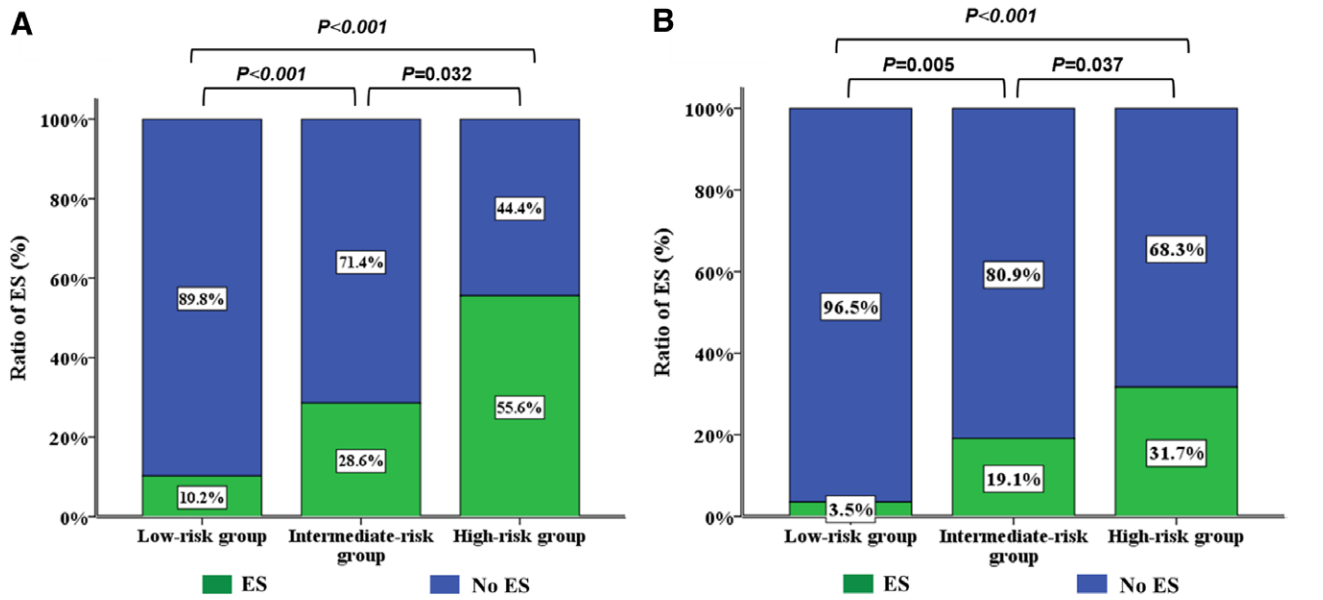

Figure 2. Probability of engraftment syndrome according to risk stratification in total patients underwent ASCT (A). Probability of engraftment syndrome according to risk stratification in patients with plasma cell diseases underwent ASCT (B).

Table 4

Univariate and multivariate analysis of variables related to engraftment syndrome in patients with plasma cell diseases underwent autologous hematopoietic stem cell transplantation.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age						
<60 y		1			1	
≥60 y	2.55	1.26–5.18	.009	2.63	1.22–5.65	.013
Mobilization protocol						
No plerixafor		1			1	
Plerixafor	2.78	1.38–5.60	.004	2.20	1.05–4.58	.036
Disease status before allo-HSCT						
Beyond CR (VGPR + PR + SD)		1			1	
CR	2.91	1.43–5.90	.003	3.19	1.50–6.77	.002
$CD34^+$ cell counts						
$\leq 3.50 \times 10^6$/kg		1				
$>3.50 \times 10^6$/kg	2.03	1.00–4.10	.049			
CD3+ lymphocyte counts						
$<2.42 \times 10^8$/kg		1				
$\geq 2.42 \times 10^8$/kg	2.23	1.07–4.65	.033			
CD3+CD8+ lymphocyte counts						
$<0.80 \times 10^8$/kg		1				
$\geq 0.80 \times 10^8$/kg	2.37	1.14–4.94	.022			

CI = confidence interval, CR = complete response, HSCT = hematopoietic stem cell transplantation, MNC = mononuclear cell, OR = odds ratio, PR = partial response, SD = stable disease, VGPR = very good partial response.

of ES after ASCT. In the present study, we observed that the numbers of MNC, $CD3^+$ lymphocyte, $CD3^+CD4^+$ lymphocyte, and $CD3^+CD8^+$ lymphocyte transfused were higher in patients with plerixafor-based mobilization. This suggested that plerixafor-based mobilization influenced the composition of T lymphocytes and contributed to the occurrence of ES after ASCT. On the other hand, plerixafor is mainly used for stem cell mobilization in patients with plasma cell diseases, which may explain that the influence of plerixafor-based mobilization on ES was most significantly in patients with plasma cell disease.

We observed that age older than 60 years was associated with ES after ASCT in total cohort and patients with plasma cell disease, which was supported by other studies.[15,18] An explanation for the older age in the ES group might be immunosenescence/inflammaging. Recent research work revealed a basal, subclinical, and non-infectious, age-related inflammation triggered by

Table 5

Transplant outcomes for patients who underwent ASCT in different subgroup cases.

		Engraftment syndrome		
	Total patients (n = 300)	**Yes (n = 47)**	**No (n = 247)**	***P* value**
Engraftment time (d, range)				
Neutrophil	11 (7–17)	10 (7–13)	11 (7–17)	.038
Platelet	11 (6–23)	11 (6–17)	11 (6–23)	.120
1-y relapse	13 (4.4%)	2 (4.3%)	11 (4.5%)	.416
1-y NRM	2 (0.7%)	0	2 (0.8%)	.270
1-y PFS	275 (94.9%)	45 (95.7%)	230 (94.7%)	.227
1-y OS	284 (98.0%)	47 (100%)	237 (97.6%)	.433

ASCT = autologous hematopoietic stem cell transplantation, NRM = non-relapse mortality, OS = overall survival, PFS = progression-free survival.

higher activation and expression of the NLRP3 inflammasome with consecutive higher basal interleukin-1 (IL-1) production during senescence.[28,29] IL-1 is one of the cytokines suspected to play a crucial role in the pathogenesis of ES so that age-related disposition to IL-1 production might promote ES development.[30,31] Additionally, elderly people had higher counts of neutrophils and pro-inflammatory monocytes.[32] Since ES occurs during recovery of cells of the innate immune system and due to their suspected role in ES pathogenesis, age-related alterations of these cells might also contribute to ES.

We also observed that the disease status was associated with ES after ASCT. However, previous studies found no association between disease status before ASCT and ES.[33,34] In our study, patients receiving ASCT at CR had a tendency of receiving a higher number of $CD34^+$ cell than those without CR (3.85 vs 3.42, $P = .057$), which might the reason that disease status was associated with ES. However, the relationship between disease status before allo-HSCT and ES should be further identified in future.

Whether ES would influence the mortality and survival after ASCT was controversial.[31] There may be considerably more NRM in children compared with adults.[31] Foncillas et al[10] observed that ES could increase the risk of NRM in children. Madero et al[11] reported 8% NRM in persons with ES compared with 5% in controls. However, we observed that 1-year relapse, NRM, PFS, and OS were comparable between patients with and without ES. This may be because that patients were older in the present study. The median age of our patients were 54 years, and in the previous studies which observed that ES increased the risk of NRM, the median age of patients was 4 to 8 years.[10,11]

This study was limited by the retrospective designed and the relatively small sample of patients, particularly for the lymphoma subgroup. Thus, the influence of plerixafor-based mobilization on ES should be further confirmed.

In conclusion, we firstly observed that plerixafor-based mobilization may influence the composition of T lymphocytes in grafts and increase the risk of ES, particularly in patients with plasma cell disease. Our results should be further confirmed by prospective, large-scale studies.

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AUTHOR CONTRIBUTIONS

X.-D.M. designed the study and supervised the manuscript preparation. L.-Q.C., Q.W., B.-N.L., and Z.-Y.Z. analyzed and verified the data and wrote the manuscript. All of the other authors participated in the collection of patient data. All of the authors read and approved the final version of this manuscript.

REFERENCES

[1] Zinzani PL. Autologous hematopoietic stem cell transplantation in non-Hodgkin's lymphomas. *Acta Haematol* 2005;114(4):255–259.
[2] Morè S, Corvatta L, Manieri VM, et al. Autologous stem cell transplantation in multiple myeloma: where are we and where do we want to go? *Cells* 2022;11(4):606.
[3] Plasma Cell Disease Group, Chinese Society of Hematology, Chinese Medical Association; Chinese Myeloma Committee-Chinese Hematology Association. [Chinese guidelines of autologous stem cell transplantation for multiple myeloma (2021)]. *Zhonghua Xue Ye Xue Za Zhi* 2021;42(5):353–357.
[4] Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 1995;13(3):588–595.
[5] Lee CK, Gingrich RD, Hohl RJ, Ajram KA. Engraftment syndrome in autologous bone marrow and peripheral stem cell transplantation. *Bone Marrow Transplant* 1995;16(1):175–182.
[6] Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, Nucci M. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant* 2003;31(5):393–397.
[7] Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001;27(9):893–898.
[8] González-Vicent M, Ramírez M, Sevilla J, et al. Engraftment syndrome after autologous peripheral blood progenitor cell transplantation in pediatric patients: a prospective evaluation of risk factors and outcome. *Bone Marrow Transplant* 2004;34(12):1051–1055.
[9] Schmid I, Stachel D, Pagel P, Albert MH. Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant* 2008;14(4):438–444.
[10] Foncillas MA, Diaz MA, Sevilla J, et al. Engraftment syndrome emerges as the main cause of transplant-related mortality in pediatric patients receiving autologous peripheral blood progenitor cell transplantation. *J Pediatr Hematol Oncol* 2004;26(8):492–496.
[11] Madero L, Vicent MG, Sevilla J, Prudencio M, Rodríguez F, Díaz MA. Engraftment syndrome in children undergoing autologous peripheral blood progenitor cell transplantation. *Bone Marrow Transplant* 2002;30(6):355–358.
[12] Edenfield WJ, Moores LK, Goodwin G, Lee N. An engraftment syndrome in autologous stem cell transplantation related to mononuclear cell dose. *Bone Marrow Transplant* 2000;25(4):405–409.
[13] Carreras E, Fernández-Avilés F, Silva L, et al. Engraftment syndrome after auto-SCT: analysis of diagnostic criteria and risk factors in a large series from a single center. *Bone Marrow Transplant* 2010;45(9):1417–1422.
[14] Nishio N, Yagasaki H, Takahashi Y, et al. Engraftment syndrome following allogeneic hematopoietic stem cell transplantation in children. *Pediatr Transplant* 2009;13(7):831–837.
[15] Gorak E, Geller N, Srinivasan R, et al. Engraftment syndrome after nonmyeloablative allogeneic hematopoietic stem cell transplantation: incidence and effects on survival. *Biol Blood Marrow Transplant* 2005;11(7):542–550.
[16] Moreb JS, Kubilis PS, Mullins DL, Myers L, Youngblood M, Hutcheson C. Increased frequency of autoaggression syndrome associated with autologous stem cell transplantation in breast cancer patients. *Bone Marrow Transplant* 1997;19(2):101–106.
[17] Mori Y, Yoshimoto G, Yuda JI, et al. Previous exposure to bortezomib is linked to a lower risk of engraftment syndrome after autologous hematopoietic stem cell transplantation. *Leuk Lymphoma* 2019;60(1):271–273.
[18] Cornell RF, Hari P, Zhang MJ, et al. Divergent effects of novel immunomodulatory agents and cyclophosphamide on the risk of engraftment syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant* 2013;19(9):1368–1373.
[19] Chinese Society of Hematology, Chinese Medical Association;, & Chinese Society of Clinical Oncology (CSCO). Lymphoma-treatment alliance. *Zhonghua Xue Ye Xue Za Zhi* 2020;41(12):979–983.
[20] Grant A, Chapman LRM, Mitchell R, O'Brien TA. Engraftment syndrome following hematopoietic stem cell transplant: a review of the literature. *Clin Transplant* 2020;34(6):e13875.
[21] Teipel R, Oelschlagel U, Wetzko K, et al. Differences in cellular composition of peripheral blood stem cell grafts from healthy stem cell donors mobilized with either granulocyte colony-stimulating factor (G-CSF) alone or G-CSF and plerixafor. *Biol Blood Marrow Transplant* 2018;24(11):2171–2177.
[22] Fruehauf S, Veldwijk MR, Seeger T, et al. A combination of granulocyte-colony-stimulating factor (G-CSF) and plerixafor mobilizes more primitive peripheral blood progenitor cells than G-CSF alone: results of a European phase II study. *Cytotherapy* 2009;11(8):992–1001.

[23] Gaugler B, Arbez J, Legouill S, et al. Characterization of peripheral blood stem cell grafts mobilized by granulocyte colony-stimulating factor and plerixafor compared with granulocyte colony-stimulating factor alone. *Cytotherapy* 2013;15(7):861–868.
[24] Righi E, Kashiwagi S, Yuan J, et al. CXCL12/CXCR4 blockade induces multimodal antitumor effects that prolong survival in an immunocompetent mouse model of ovarian cancer. *Cancer Res* 2011;71(16):5522–5534.
[25] Tanhehco YC, Vogl DT, Stadtmauer EA, O'Doherty U. The evolving role of plerixafor in hematopoietic progenitor cell mobilization. *Transfusion* 2013;53(10):2314–2326.
[26] Porrata LF, Gertz MA, Inwards DJ, et al. Early lymphocyte recovery predicts superior survival after autologous hematopoietic stem cell transplantation in multiple myeloma or non-Hodgkin lymphoma. *Blood* 2001;98(3):579–585.
[27] Rapoport AP, Stadtmauer EA, Aqui N, et al. Rapid immune recovery and graft-versus-host disease-like engraftment syndrome following adoptive transfer of costimulated autologous T cells. *Clin Cancer Res* 2009;15(13):4499–4507.
[28] Youm YH, Grant RW, McCabe LR, et al. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. *Cell Metab* 2013;18(4):519–532.
[29] Latz E, Duewell P. NLRP3 inflammasome activation in inflammaging. *Semin Immunol* 2018;40:61–73.
[30] Cornell RF, Hari P, Drobyski WR. Engraftment syndrome after autologous stem cell transplantation: an update unifying the definition and management approach. *Biol Blood Marrow Transplant* 2015;21(12):2061–2068.
[31] Spitzer TR. Engraftment syndrome: double-edged sword of hematopoietic cell transplants. *Bone Marrow Transplant* 2015;50(4):469–475.
[32] Ray D, Yung R. Immune senescence, epigenetics and autoimmunity. *Clin Immunol* 2018;196:59–63.
[33] Sheth V, Jain R, Gore A, Ghanekar A, Saikia T. Engraftment syndrome: clinical features and predictive factors in autologous stem cell transplant. *Indian J Hematol Blood Transfus* 2018;34(3):448–453.
[34] Pramanik R, Kancharla H, Bakhshi S, et al. Engraftment syndrome: a retrospective analysis of the experience at a tertiary care institute. *Clin Hematol Int* 2019;1(2):114–119.