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Engraftment Syndrome in Autologous Hematopoietic Stem Cell Transplant Patients: Incidence, Associated Risk Factors, Features, and Outcomes

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Background: Autologous stem cell transplantation (ASCT) is the standard treatment for multiple myeloma (MM) and refractory/relapsed (R/R) lymphoma patients. Engraftment syndrome (ES) is a non-infectious febrile syndrome during ASCT. This study focused on the incidence, risk factors, manifestations, and outcomes of patients with ES receiving ASCT.

Material/Methods: This retrospective cohort study included MM and R/R lymphoma patients who underwent ASCT at Chiang Mai University Hospital from January 2014 to September 2020. ES was diagnosed by the consensus of independent reviewers based on clinical manifestations, laboratory, and radiological findings.

Results: We included 124 patients, of whom 67 (54.1%) had lymphoma. The mean age was 48.0±12.3 years. The incidence of ES was 36.3%. The ES group had a significantly higher proportion of patients with fever, elevated liver enzymes, elevated bilirubin, hypoalbuminemia, and weight gain compared to the non-ES group. TNC more than 10×10^8 cells/kg was an independent risk factor for ES (odds ratio 2.94 with a 95% confidence interval of 1.15-7.50, P=0.024). ES was associated with longer length of stay (22.5±8.2 vs 16.9±6.4 days, P<0.001) but was not associated with overall survival (OS).

Conclusions: The incidence of ES in this cohort was 36.3%. Features observed in ES patients were fever, elevated liver enzymes, elevated bilirubin, and hypoalbuminemia. TNC of more than 10×10^8 cells/kg was an independent risk factor. ES was associated with longer length of stay but not survival outcomes.

Keywords: **Bone Marrow Transplantation • Incidence • Multiple Myeloma • Risk Factors**

Abbreviations: **ASCT** – autologous stem cell transplantation; **MM** – multiple myeloma; **R/R** – refractory/relapsed; **ES** – engraftment syndrome; **SC** – Spitzer criteria; **MC** – Maiolino criteria; **CC** – Cornell criteria; **TNC** – total nucleated cells; **OS** – overall survival; **RFS** – relapse-free survival; **NRM** – non-relapse mortality; **TRM** – transplant-related mortality; **HSCT** – hematopoietic stem cell transplantation; **AGVHD** – autologous graft-versus-host disease; **MDS** – myelodysplastic syndrome; **GGT** – Gamma-glutamyl transferase; **t-MDS** – transplantation-associated MDS; **IQR** – interquartile range; **PBSC** – peripheral blood stem cell; **ROC** – receiver operating characteristic

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Introduction

Autologous stem cell transplantation (ASCT) is the standard treatment for transplant-eligible multiple myeloma (MM) patients and for cases of refractory or relapsed (R/R) lymphoma [1,2]. Engraftment syndrome (ES), first defined by Lee et al in 1995 [3], is a febrile syndrome occurring around engraftment of neutrophils after hematopoietic stem cell transplantation (HSCT), usually presenting with fever, rash, pulmonary edema, and diarrhea, but rarely involves other organs. Diagnostic criteria of ES were proposed by Spitzer in 2001 and Maiolino in 2003 and have been used in many studies, as well as the modified version proposed by Cornell et al in 2013 [4-7]. Currently, none of the proposed criteria are unanimously accepted as a diagnostic criterion standard. Thus, ES [4] as a clinical syndrome is mainly diagnosed by clinical and laboratory features consistently reported in various studies, including the originally proposed criteria.

ES occurs more frequently after ASCT in various conditions, including MM and lymphoma, and is sometimes called autologous graft-versus-host disease (AGVHD). This syndrome was reported after ASCT with an incidence of 10-60%, depending on the criteria and study population [4-6,8,9]. Previous studies suggested that the development of ES was associated with multiple factors, including female sex [3,10-12], use of G-CSF [13], $CD34^+$ cell dose [6,11,12,14,15], use of bortezomib or lenalidomide [6], less aggressive chemotherapy [10,16], and peripheral blood stem cell use [5,12]. Evidence that ES affects treatment outcome is inconclusive, and Bryne et al reported possible graft-versus-myeloma effects [17], but more recent studies in lymphoma, MM, and breast cancer patients showed no improvement and indicated it might be related to longer length of stay or secondary myelodysplastic syndrome (MDS) [8,18,19].

This study focused on incidence, risk factors, features, treatment, and transplant-related outcomes in patients with ES receiving ASCT.

Material and Methods

Study Design and Participants

We conducted a single-center, retrospective study recruiting a cohort of patients with biopsy-proven MM or R/R lymphoma who underwent ASCT at the Bone Marrow Transplant Center, Chiang Mai University Hospital from January 2014 to September 2020. Post-transplantation data including relapse and death were collected. The study was conducted with approval from the Institutional Research Ethics Committee at the Faculty of Medicine, Chiang Mai University (Study code: MED-2563-07667).

Data Collection

We extracted data from electronic medical records, including demographic characteristics, family history of malignancies, chronic medical illness, diagnosis, previous treatment and transplantation, stem cell source, date of collection, mobilization, $CD34^+$ cell counts, total nucleated cell counts (TNC), transplantation (length of stay, conditioning regimen, clinical manifestation during hospitalization, antibiotics, antifungal, corticosteroid, and transfusion), and outcome after transplantation regarding relapse, graft failure, secondary malignancies, and deaths.

Diagnosis of Engraftment Syndrome

The diagnosis of engraftment syndrome (ES) in our study was initially done by 3 independent reviewers (SM, AT, and PP) who evaluated the medical records regarding clinical manifestation based on previously proposed criteria (**Supplementary Table 1**) in relation to time of engraftment to determine the diagnosis of ES and the consensus for the diagnosis was confirmed accordingly. ES was diagnosed with concordant evaluation of at least 2 out of the 3 reviewers. We thoroughly assessed clinical manifestations, including non-infectious fever, non-infectious diarrhea, unexplained weight gain, skin rash, respiratory symptoms (upper respiratory tract issues, dyspnea, hypoxemia, respiratory failure, and acute respiratory distress syndrome), new onset of jaundice, other clinical manifestations not previously mentioned in other publications (eg, neurological and cardiovascular manifestation) were reviewed to explore any association with engraftment syndrome. Laboratory results, including elevated liver enzymes, including gamma-glutamyl transferase (GGT), elevated bilirubin and creatinine, and abnormal thoracic imaging.

Outcomes

The primary outcome of this study was the effect of ES on overall survival (OS) after transplantation. The secondary outcomes were the effect on relapse-free survival (RFS), transplantation-related mortality (TRM), and non-relapse mortality (NRM). Features, including clinical manifestation, time to neutrophil and platelet recovery, and selected medications (amphotericin B, bortezomib, cyclophosphamide, G-CSF, and mobilization regimen) were analyzed for association with engraftment syndrome. Infection, secondary graft failure, transplantation-associated MDS (t-MDS) and transplantation-associated acute myeloid leukemia (t-AML), and secondary malignancies were our exploratory outcomes. Sensitivity and specificity of the 3 proposed criteria were performed and the committee's consensus compared, in addition to any correlation between each criterion.

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Statistical Analysis

Patient characteristics, stem cell harvesting, and transplantation-related data were reported as percentage for categorical values and as mean with standard deviation or as median with interquartile range (IQR) for continuous values. Comparisons between the data were made using Fisher's exact test or the chi-square test for categorical values and using a *t* test or Wilcoxon rank sum test for continuous values.

For detection of factors associated with ES, we assumed an ES incidence of 30%, with an adjustment based on possibility. The factors of interest must have been associated with at least a 3-fold higher risk of developing ES. With double-sided alpha of 0.05 and power of 0.80, the sample size would need to be at least 87 cases. Factors associated with ES were evaluated with a logistic regression model.

Survival outcomes (OS and RFS) were analyzed with the Cox regression model and presented using Kaplan-Meier curves. Regression models were performed in a stepwise manner, and only factors with a level of significance of a *P* value less than 0.1 from the univariable analysis were included in the backward-elimination multivariable analysis. All analyses were performed using STATA statistical software version 17.0 (StataCorp LLC, College Station, TX, USA).

Results

Participants

At our center, 124 patients who underwent ASCT were diagnosed with MM (46.0%) or R/R lymphoma (54.0%). Fifty-five patients (44.3%) were female. The mean age was 48 (SD 12.3) years, with an overall higher mean age of 54.3 (SD 7.2) years in the MM group in comparison to 42.6 (SD 13.2) years in the lymphoma group. The chronic medical illnesses of participants are all shown in **Table 1**. Chemo-mobilization was used in 56.3% of cases. Plerixafor was given in 14 (11.8%) participants, all in the lymphoma group. Median TNC was 10.2×10^8 cells/kg (IQR 6.8-16.4×10^8 cells/kg) and the median $CD34^+$ cell dose was 4.5×10^6 cells/kg (IQR 3.3-7.0×10^6 cells/kg). In all participants, peripheral blood stem cells were used as the source for transplantation.

Incidence of Engraftment Syndrome

ES was diagnosed in 45 (36.3%) participants based on the consensus of the independent reviewers. ES was diagnosed in 6 (4.8%), 69 (55.6%), and 74 (59.7%) using the Spitzer criteria (SC), Maiolino criteria (MC), and Cornell criteria (CC), respectively. The lymphoma group was diagnosed by our consensus with ES less frequently than the MM group (23.9% vs 50.9%). Regarding the sensitivity and specificity of each criterion, in comparison with our consensus, SC showed the highest specificity of 100% with a sensitivity of 13.3%, while CC showed the highest sensitivity of 84.4% with 54.4% specificity. All criteria including our consensus showed significant correlation with varying strength (**Table 2**).

Features of Engraftment Syndrome

The median times to neutrophil and platelet engraftments were 11 days (IQR 10-12 days) and 18 days (IQR 15-23 days), respectively. The median time to neutrophil engraftment in patients with ES did not differ from the non-ES group (11 (IQR 10-12) vs 10 (IQR 10-11) days, *P*=0.362), as well as the median time to platelet engraftment (19 (IQR 16-24) vs 18 (IQR 15-21) days, *P*=0.102).

Fever was significantly more frequent in the ES group (100% vs 84.8%, *P*=0.004). The median percentage of weight gain was significantly higher in the ES group (3.6% vs 2.6%, *P*=0.009). Elevation of bilirubin was more frequent in the ES group in comparison to the non-ES group (8.9% vs 0%, *P*=0.016), as well as elevation of the liver enzymes aspartate aminotransferase (AST) (22.2% vs 3.8%, *P*=0.002), alanine aminotransferase (ALT) (33.3% vs 15.2%, *P* = 0.024), alkaline phosphatase (ALP) (31.1% vs 8.9%, *P*=0.002), and gamma-glutamyl transferase (GGT) (66.7% vs 43.0%, *P*=0.011). Hypoalbuminemia was also more frequently observed in association with ES (77.8% vs 46.8%, *P*=0.001). There were no statistically significant differences in the other clinical manifestations, including diarrhea, skin rash, respiratory symptoms, and changes in thoracic imaging between the ES and non-ES group.

Risk Factors of Engraftment Syndrome

In the univariable analysis (**Table 3**), age 50 years and above was associated with ES (OR 2.65, 95%CI 1.23-5.68, *P*=0.012). Diagnosis of MM was significantly associated with ES (OR 3.3, 95%CI 1.54-7.09, *P*=0.002). Chemo-mobilization was associated with a lower risk of ES (OR 0.27, 95%CI 0.12-0.59, *P*=0.001). TNC dose of more than 10×10^8 cells/kg was associated with increased risk of ES (OR 3.09, 95%CI 1.40-6.78, *P*=0.005). Amphotericin B use was also associated with ES (OR 3.75, 95%CI 1.56-9.02, *P*=0.003). Late stem cell harvesting, defined as harvesting 6 months or more after diagnosis, was related to slower neutrophil engraftment compared to earlier harvesting (12±4.3 vs 10.8±1.7 days, *P*=0.036), and was also associated with increased risk of ES (OR 2.65, 95%CI 1.14-6.17, *P*=0.023). In the multivariable analysis after adjustment for diagnosis, the factors associated with increased risk of ES were only TNC of more than 10×10^8 cells/kg (OR 2.94, 95%CI 1.15-7.50, *P*=0.024) and amphotericin B use (OR 4.33, 95%CI 1.57-11.94, *P*=0.005).

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Table 1. Patient characteristics.

Parameter	Overall (N=124)	Lymphoma (N=67)	Myeloma (N=57)
Female (%)	55 (44.3)	27 (40.3)	28 (49.1)
Age, Mean (SD)	48.0 (±12.3)	42.6 (±13.2)	54.3 (±7.2)
History			
Hypertension (%)	24 (19.4)	8 (11.9)	16 (28.1)
Diabetes mellitus (%)	6 (4.8)	2 (3.0)	4 (7.0)
Dyslipidemia (%)	18 (14.5)	4 (6.0)	14 (24.6)
Chronic kidney disease (%)	1 (0.8)	0 (0)	1 (1.8)
Coronary artery disease (%)	2 (1.6)	1 (1.5)	1 (1.8)
Heart failure (%)	2 (1.6)	1 (1.5)	1 (1.8)
Thyroid disorder (%)	3 (2.4)	1 (1.5)	2 (3.5)
Cirrhosis (%)	1 (0.8)	0 (0)	1 (1.8)
Solid malignancy (%)	2 (1.6)	1 (1.5)	1 (1.8)
Number of previous regimens			
1 regimen (%)	86 (69.4)	34 (50.8)	52 (81.2)
>1 regimen (%)	38 (30.6)	33 (49.2)	5 (8.8)
Previous transplantation (%)	7 (5.6)	0 (0)	7 (12.3)
Stem cell source (PBSC) (%)	124 (100)	67 (100)	57 (100)
Mobilization			
GCSF alone (%)	52 (43.7)	4 (6.0)	48 (92.3)
Chemo-mobilization (%)	67 (56.3)	63 (94.0)	4 (7.7)
Plerixafor use (%)	14 (11.8)	14 (20.9)	0 (0)
Time to harvest			
Early (within 6 months) (%)	44 (37.6)	40 (59.7)	4 (8.0)
Late (beyond 6 months) (%)	73 (62.4)	27 (40.3)	46 (92.0)
Stem cell dosage			
TNC $\times 10^8$ cells/kg, median (IQR)	10.2 (6.8-16.4)	9.1 (6.1-13.3)	12.9 (8.4-21.82)
$CD34^+$ $\times 10^6$ cells/kg, median (IQR)	4.5 (3.3-7.0)	4.4 (3.3-7.5)	4.5 (3.2-6.5)
Time to transplantation, mean, months (SD)	9.6 (±5.0)	8.4 (±3.8)	11.0 (±5.8)

PBSC – peripheral blood stem cell, TNC – total nucleated cell.

Table 2. Correlation, sensitivity, and specificity of criteria from the Committee Consensus.

Criteria	Sensitivity (%)	Specificity (%)	Correlation (R)	*P* value	ROC
Spitzer criteria	13.3	100	0.299	<0.001	0.567
Maiolino criteria	82.2	59.5	0.404	<0.001	0.709
Cornell criteria	84.4	54.4	0.694	<0.001	0.694

ROC – receiver operating characteristic.

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Table 3. Risk factors of engraftment syndrome.

Risk factors	ES (N=45)	Non-ES (N=79)	Univariable analysis			Multivariable analysis		
			OR	95% CI	*P* value	OR	95% CI	*P* value
Female, N (%)	21 (46.7)	34 (43.0)	1.16	0.55-2.42	0.696	–	–	–
Age >50 (%)	30 (66.7)	34 (43.0)	2.65	1.23-5.68	0.012	2.17	0.79-5.96	0.134
Diagnosis								
Lymphoma (%)	16 (35.6)	51 (64.6)	Ref			–	–	–
MM (%)	29 (64.4)	28 (35.4)	3.30	1.54-7.09	0.002	2.12	0.83-5.41	0.114
No. of regimens >1 (%)	13 (28.9)	25 (31.6)	0.88	0.39-1.95	0.749	–	–	–
Cyclophosphamide use (%)	42 (93.3)	71 (89.9)	1.58	0.40-6.27	0.518	–	–	–
Previous BMT (%)	3 (6.7)	4 (5.1)	1.34	0.29-6.27	0.711	–	–	–
Late stem cell harvest (%)	32 (76.2)	41 (54.7)	2.65	1.14-6.17	0.023	1.42	0.46-4.39	0.548
Mobilization								
Chemo-mobilization (%)	16 (36.4)	51 (68.0)	0.27	0.12-0.59	0.001	0.41	0.07-2.42	0.322
GCSF alone (%)	28 (63.6)	24 (32.0)	Ref			–	–	–
Plerixafor use (%)	2 (4.5)	12 (16.0)	0.25	0.05-1.17	0.079	0.21	0.35-1.24	0.085
Time to transplantation, months in median (IQR)	8.9 (7.3-10.4)	8.2 (6.2-11.2)	1.02	0.95-1.10	0.554	–	–	–
TNC dose ≥10×10^8 cells/kg, N (%)	31 (47.7)	13 (23.8)	3.09	1.40-6.78	0.005	2.94*	1.15-7.50	**0.024**
CD34 ($\times10^6$ cells/kg), median (IQR)	4.2 (2.9-6.0)	4.6 (3.4-8.0)	0.99	0.95-1.03	0.612	–	–	–
Neutrophil engraftment, days in median (IQR)	11 (10-12)	10 (10-11)	1.05	0.95-1.16	0.378	–	–	–
Platelet engraftment, days in median (IQR)	19 (16-24)	18 (15-21)	1.00	0.98-1.03	0.690	–	–	–
Engraftment ALC, cells in median (IQR)	160 (81-269)	180 (80-325)	1.00	1	0.126	–	–	–
Amphotericin B use (%)	17 (37.8)	11 (13.9)	3.75	1.56-9.02	0.003	4.33*	1.57-11.94	**0.005**

* Adjusted for diagnosis. MM – multiple myeloma, TNC – total nucleated cell, ALC – absolute lymphocyte count.

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Table 4. Outcome of transplantation.

	Overall	ES	Non-ES	*P* value
Length of stay (day) (SD)	18.9 (±7.6)	22.5 (±8.2)	16.9 (±6.4)	<0.001
NRM (%)	4 (3.2)	1 (2.2)	3 (3.8)	1.000
TRM (%)	2 (1.6)	0 (0)	2 (2.5)	0.534
Graft failure (%)	3 (2.4)	2 (4.4)	1 (1.3)	0.298
t-MDS (%)	1 (0.81)	0 (0)	1 (1.27)	1.000
Secondary malignancy (%)	1 (0.81)	0 (0)	1 (1.27)	1.000
Antibiotic duration (day) (IQR)	12 (9-16)	16 (11-20)	11 (8-14)	<0.001
Antifungal duration (day) (IQR)	7 (4.5-14)	5 (4-12)	9 (7-14.5)	0.233
Amphotericin B use (%)	28 (22.6)	17 (37.8)	11 (13.9)	0.003
Packed red cell, U (IQR)	0.5 (0-1)	1 (0-2)	0 (0-1)	0.123
Platelet, U (IQR)	15 (10-24)	15 (10-30)	15 (10-23)	0.156
Corticosteroid use (%)	12 (9.7)	12 (26.7)	0 (0)	<0.001

NRM – non-relapse mortality; TRM – transplantation-related mortality; t-MDS – transplantation-related myelodysplastic syndrome.

Transplantation Outcomes

As shown in **Table 4**, the ES was associated with longer hospital stay (22.5±8.2 days vs 16.9±6.4 days, *P*<0.001). Durations of antibiotics and amphotericin B use were significantly longer in the ES compared to the non-ES group. Corticosteroid use was significantly higher in the ES group (26.67% vs 0%, *P*<0.001). Steroid was used in 12 patients (26.7%). The difference between ES with steroid use versus no steroid use were elevated aspartate aminotransferase (AST) (*P*=0.007) and elevated creatinine (*P*=0.028) in the steroid group. Steroid-resistant ES was not observed. There were no statistically significant differences regarding NRM, TRM, graft failure, secondary malignancy, or number of blood component transfusions between the ES and non-ES groups.

With the median follow-up time of 35 months (IQR 24.3-63.3 months) in the overall cohort, median OS were not reached in either the ES or non-ES groups. There was no significant difference found in OS and RFS between the groups (**Figure 1**). Subgroup analysis for OS and RFS of lymphoma or MM patients also showed no significant differences.

Discussion

ES is a clinical syndrome that may be affected by various confounding factors such as patient characteristics, treatment received, and complications during transplantation. Diagnosis made based solely on the criteria used might account for the differences in prevalence among studies. Our study used an independent review process and comparisons were made in accordance with criteria-based diagnoses. In our study, the incidence of ES was 36.29%, and previous studies have reported incidences ranging from 3% to 60%, depending on the criteria used and the study population [3,20]. All diagnostic criteria showed varying degrees of correlation with the committee's consensus. SC had the highest specificity (100%) and CC showed the highest sensitivity (84.4%). ES is the clinical syndrome, but the lack of specific markers for diagnosis means that physicians can only suspect but not definitely confirm ES. CC and MC offer sensitivity advantages, reducing the likelihood of missing a diagnosis of ES. Both criteria can be used as screening tools for ES. SC has high specificity and can more accurately guide appropriate treatment. ES cases requiring treatment are rare [21]. Corticosteroids or immunosuppressive agents are the only preferred treatment choice for severe ES [8]. It is crucial to rule out other causes before considering corticosteroid use, especially infectious cause of fever.

Our study found that fever, hepatobiliary involvement, hypoalbuminemia, and weight gain were significant clinical features in ES patients, consistent with previous studies [2,5,6,10-12,18,22-29]. In agreement with previous studies, we found that febrile episodes were significantly associated with ES, and the condition itself should always be looked for in patients receiving ASCT. However, fever as a consequence of infections, whether from bacteria, viruses, or fungi, should be first excluded. As for other features reported to be associated with ES in previous studies, neither respiratory system issues, rash, diarrhea, nor renal involvement were found to be significant. This might be related to the differences in characteristics

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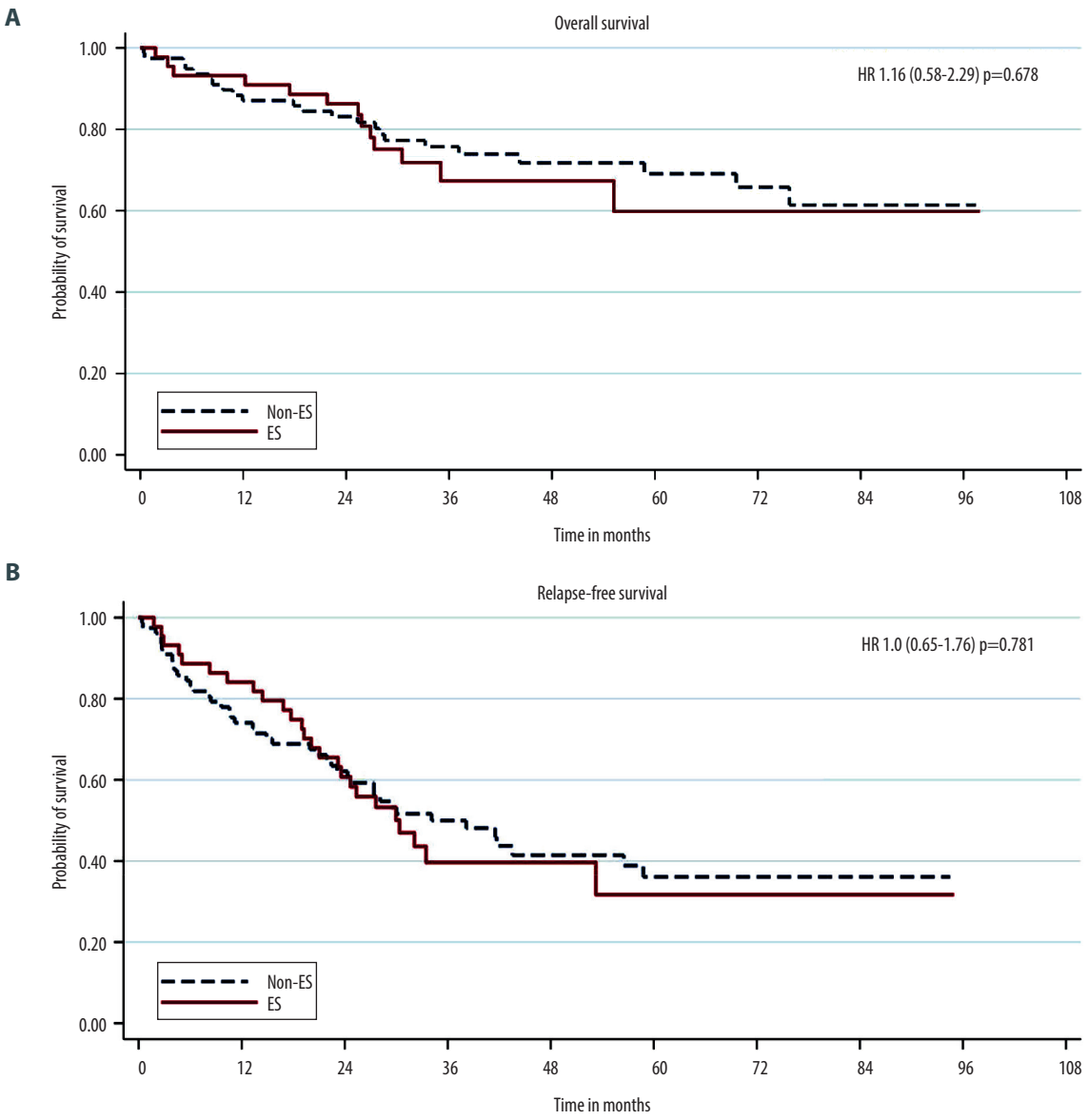

Figure 1. (**A**) Overall survival in engraftment syndrome and non-engraftment syndrome groups. (**B**) Relapse-free survival in engraftment syndrome and non-engraftment syndrome groups *(Stata 17.0, StataCorp LLC, College Station, TX, USA)*.

and diagnosis from other cohorts, or due to difficulties in distinguishing ES from chemotherapy complications. In addition, ES patients in our study had milder symptoms compared to previous studies, as indicated by a lower rate of corticosteroid use deemed necessary by the treating physician, as well as the lack of mortality from ES. We did not observe a difference of time to neutrophil engraftment between groups, which was inconclusively reported in previous studies and warrants further investigation [5,6,12,14,25-27,29,30].

Among other various previously reported risk factors, the present study found that advanced age, hypertension, MM, late stem cell harvesting, amphotericin B use, and high-dose TNC were associated with increased risk of ES in univariable analysis. Our findings regarding advanced age, MM, amphotericin B, and high-dose TNC were concordant with the findings in previous studies [6,12,14,22,24,31,32]. While chemo-mobilization was associated with significantly lower risk of ES, Plerixafor use was associated with a non-significant trend of protection, in contrast to a study in which Plerixafor was associated with increased risk of ES [32]. In the multivariable analysis after adjustment for diagnosis, only high TNC dose and amphotericin B use were associated with increased risk of ES. A possible explanation is that in the case of the higher

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transplantation cell dose, a higher concentration of cytokine would be released at the time of engraftment, increasing the risk of ES. Previous studies also showed a significant correlation between the incidence of ES and the stem cell dose [12,14,22,24], The increase risk of ES with amphotericin B was consistent with previous reports [5,12]. From our perspective, the relationship between the amphotericin B use and the increased risk of ES might be attributed to the treatment of febrile episodes unresponsive to antibiotics, which may reflect ES rather than the effect of the drug itself.

As previously reported, we also observed significantly increased hospital stay in the ES group [5,23-25], which might be due to the time to complete the course of antibiotics, which was significantly longer in this group, or due to monitoring the complications during corticosteroid therapy. Survival analyses, as also reported by many other studies [5,12,26,33,34] showed no significant differences in ES status between OS and RFS. A possible explanation might be that ES is due to a brief episode of cytokine surge during engraftment; thus, the effects or changes made by ES would last for a certain period and the syndrome has little effect on prognosis [5,12].

The strength of our study is that it determined the prevalence of ES in ASCT for both MM and lymphoma patients. We used consensus diagnosis based on diagnostic criteria and compared all the criteria for the diagnosis of ES. We also identified the risk factors of ES that can identify high-risk patients and inform early treatment to prevent overt ES with its associated high morbidity and mortality. Our study has some limitations. First, its retrospective nature necessarily entails some missing data, which might have affected some of the results. Second, the diagnosis of ES was made based on clinical and laboratory manifestations, which can affect the prevalence. Larger studies are needed on engraftment syndrome. Identification of biological markers might offer the opportunity for early diagnosis and preemptive early treatment.

Conclusions

ES was associated with longer length of hospital stay, while overall survival, relapse-free survival, and other transplant-related outcomes were not affected. Higher TNC cell dose was significantly associated with increased risk of ES.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Table

Supplementary Table 1. Proposed criteria for engraftment syndrome.

Manifestation	Spitzer criteria 2001	Maiolino criteria 2003	Cornell criteria 2013
Non-infectious febrile episodes	• Fever >38.3°C • Without positive cultures or response to ATB	• Fever >38°C • Without positive cultures or response to ATB	• Fever >38°C • Without positive culture and no response to ATB
Non-infectious diarrhea		• 2 or more episodes of liquid defecation per day	• 2 or more episodes of liquid defecation per day
Rash	• Rash >25% of BSA • Not caused by medication	• Diffuse MP rash • Not caused by infection	• MP rash >25% of BSA • Not due to drug or infection
Weight gain	• 2.5% weight gain	• 3.0% weight gain	
Hepatobiliary manifestation	• TB >2 mg/dL • Transaminase 2× UNL	• None	• TB >2 mg/dL • Transaminase 2× UNL
Renal manifestation	• Creatinine at least 2× baseline	• None	- None

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Supplementary Table 1 continued. Proposed criteria for engraftment syndrome.

Manifestation	Spitzer criteria 2001	Maiolino criteria 2003	Cornell criteria 2013
Respiratory manifestation			
Pulmonary imaging	• Non-cardiogenic pulmonary edema	• Pulmonary edema by CXR or CT not by infection, cardiac causes, or PE	• Pulmonary edema by CXR or CT not by infection, or cardiac causes
Other manifestation	• Unexplained transient encephalopathy	• None	• Transient encephalopathy
Onset of interested events	• 4 days within engraftment period	• 1 day prior to engraftment and anytime period post-engraftment	• 3 days prior and within 10 days post-engraftment

ATB – antibiotic; BSA – body surface area; MP – maculo-papular; TB – total bilirubin; UNL – upper normal limit; CXR – chest roentgenograph; CT – computed tomography; PE – pulmonary embolism.

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