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Risk Factors and Outcomes of Stem Cell Mobilization Failure in Multiple Myeloma Patients

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Keywords

Multiple myeloma · Poor mobilizers · Stem cell mobilization · Thrombocytopenia · Autologous hematopoietic stem cell transplantation

Abstract

Introduction: Autologous hematopoietic stem cell transplantation (ASCT) is a well-established treatment for patients with multiple myeloma (MM), and adequate stem cell collection must be assured before ASCT. However, prediction of poor mobilizers (PMs) is still difficult despite several risk factors for mobilization failure having been identified. ***Methods:*** We retrospectively analyzed MM patients at Taipei Veterans General Hospital in Taiwan who underwent stem cell collection between October 2006 and August 2020. A $CD34^+$ cell collection of $<1 \times 10^6$ cells/kg was defined as a mobilization failure. The primary endpoint was mobilization failure. The secondary endpoint was overall survival (OS). Odds ratios (ORs) and 95% confidence intervals (CIs) for mobilization failure were calculated using a logistic regression model. The cumulative incidence of mortality was estimated using the Kaplan-Meier method. ***Results:*** In the multivariate analysis, absolute monocyte count <500/μL (adjusted OR 10.75, 95% CI: 1.82–63.57, $p = 0.009$), platelet count <150,000/μL (adjusted OR 12.49, 95% CI: 2.65–58.89, $p = 0.001$) before mobilization, and time interval from diagnosis to stem cell harvest ≥180 days (adjusted OR 7.69, 95% CI: 1.61–36.87, $p = 0.011$) were risk factors for PMs. PM patients had poorer OS compared to patients with successful stem cell collection in the univariate analysis (log-rank test $p = 0.027$). The predicted probability of PMs was estimated by the multiple logistic regression model with a sensitivity of 84.6% and a specificity of 84.0%. ***Conclusion:*** Absolute monocyte count <500/μL, platelet count <150,000/μL, and treatment duration more than 180 days before stem cell mobilization are risk factors for unsuccessful stem cell collection. Our prediction models have high sensitivity and specificity for mobilization failure prediction and allow for early interventions for possible PMs.

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Introduction

Autologous hematopoietic stem cell transplantation (ASCT) is a well-established treatment for patients with multiple myeloma (MM), and patients with MM receiving ASCT have better progression-free survival compared to those without ASCT [1, 2]. Pretransplantation hematopoietic stem cell (HSC) mobilization is required for peripheral blood stem cell (PBSC) harvesting, and adequate stem cell collection must be assured before ASCT. However, several risk factors impact mobilization efficacy and lead to mobilization failure in poor mobilizers (PMs). Patients with mobilization failure have poorer outcomes compared to those with successful mobilization, partially owing to being incapable of receiving subsequent ASCT [3–5].

Failure of stem cell mobilization is roughly 6%–27% in MM patients, according to published literature [6–8]. Early interventions for possible PMs are likely to increase the total number of stem cells collected, avoid futile apheresis procedures, and reduce costs for patients who may need a second PBSC harvesting [9, 10]. Well-established risk factors include old age, previous radiotherapy, lenalidomide use, multiple chemotherapy cycles, and prior alkylating agent exposure [6, 8, 11–13]. However, it is still difficult to predict mobilization failure in MM patients despite several risk factors having been identified. To date, there is no predictive model for PMs before mobilization in patients with MM.

The definition of PMs in MM and lymphoma patients was proposed by the Gruppo Italiano per il Trapianto di Midollo Osseo (GITMO) working group in 2012, and the criteria for prediction of PMs were made [14]. The GITMO criteria were further validated by an Italian group but showed no significance between PMs and good mobilizers. Additionally, only 31.3% of the patients (71 of 227) had MM [15]. Wu et al. [16] reported a decision-tree algorithm for prediction of PMs in a cohort with positive and negative predictive values of 92.3% and 70.0%, respectively. Nonetheless, only 19% of those patients had MM.

In this work, we performed a single-center retrospective study to investigate the risk factors of PMs in MM patients. We then tried to create a scoring system that could predict PMs before stem cell mobilization.

Materials and Methods

Study Population

This is a retrospective cohort study to analyze the risk factors and the impact of poor stem cell mobilization on MM patients who underwent PBSC harvesting. All patients who were diagnosed with MM according to the International Myeloma Working Group (IMWG) criteria [17] at Taipei Veterans General Hospital between October 2006 and August 2020 were included in the study. Patients diagnosed with amyloidosis, solitary plasmacytomas, monoclonal gammopathy of undetermined significance, or smoldering myeloma were not included. Only MM patients who underwent PBSC harvesting were proceeded for further analysis. The study was approved by the Taipei Veterans General Hospital's Institutional Review Board (No. 2021-03-006CC).

HSC Mobilization

Mobilization is defined as the release of HSCs from bone marrow into peripheral blood following treatment with cytokine, targeted agents, and/or chemotherapy [18]. All of our patients received chemotherapy and granulocyte colony-stimulating factor (G-CSF) for stem cell mobilization, except one received G-SCF alone as mobilization regimen. All patients received G-CSF for at least 4 days in the PBSC harvesting course as a single (7 of 181 patients) or split (174 of 181 patients) dose until the last day of apheresis. The median dose of G-CSF was 9.46 μg/kg/day (range, 3.85–16.57 μg/kg/day). The chemomobilization regimen depended on the treating physician [13, 19]. The circulating stem cells were collected via leukapheresis for two consecutive apheresis days. Most patients who did not collect minimal stem cell dosage for an ASCT will proceed to the third apheresis session. Stem cell dosage collected between minimal and optimal number (5–6 $\times$ 10^6 $CD34^+$ cells/kg) proceeded to the third apheresis session depending on the treating physician [13, 20]. Patients with optimal $CD34^+$ cells collected for the first 2 days received the third apheresis if tandem transplantation was planned or decided by the treating physician. A collection of less than 1 $\times$ 10^6 $CD34^+$ cells/kg is defined as stem cell mobilization failure since the administration of stem cell doses <1 $\times$ 10^6 cells/kg has been associated with increased RBC transfusion requirement and engraftment failure in previous studies [21–24].

Leukapheresis, Stem Cell Freezing, and Thawing

Stem cells were collected by using the COBE Spectra apheresis system (version 6.1, COBE Laboratories) via 20 Fr intravenous catheters or central venous catheters according to the manufacturers' protocol. The total volume processed was 2–3 times of total blood volume. Acid-citrate-dextrose (ACD) was used as an anticoagulant with an ACD-to-whole blood ratio of 1:13 to 1:14 [25, 26]. The leukapheresis began when peripheral blood hematopoietic progenitor cells reached 20 $\times$ 10^6 cells/L [16, 27, 28].

Stem cells were transferred into the bags suitable for freezing (CryoMACS Freezing Bags). Pre-cooling plasma and cryoprotectant DMSO were mixed gently and transferred to the bags, with final DMSO concentration of 10%. A small amount of the mixed product was withdrawn for microorganism culture and preserved in the spike port of the bags as controls. The procedures were performed in the Biological Safety Cabinet. According to manufacturers' guidance, the bags and control samples were cooled in the controlled rate freezer (Planer Kryo 560-16) to implement cryopreservation protocols. At last, the bags and controls were transferred into liquid nitrogen freezers (MVE HEco 1500Series Freezer) for preservation [25, 26].

At the time of stem cell transplantation, the bags were transferred to the patient bedside and thawed in a sterilized thermostatic water bath (37°C). For quality control, the samples were sent for microorganism culture and cell viability analysis. The quality standard of thawed stem cells was microorganism culture-negative and cell viability >80% at our institution.

Data Collection

Data collection consisted of two parts, including recording baseline characteristics at MM diagnosis and before stem cell mobilization. At MM diagnosis, we collected patient characteristics,

including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage (International Staging System [ISS]), disease type, comorbidities (heart failure, chronic pulmonary disease, diabetes mellitus, and hypertension), and pathology reports on bone marrow aspiration and biopsy. In addition, we collected laboratory data such as hemoglobin, platelet count (PLT), levels of serum albumin, corrected serum ionized calcium, serum creatinine, serum lactate dehydrogenase, serum β2-microglobulin, and free light chain ratio both at MM diagnosis and before stem cell mobilization. Furthermore, we collected information about the number of prior lines of chemotherapy, time interval from diagnosis to stem cell harvest, mobilization regimens, radiotherapy before stem mobilization, and treatment modalities.

Statistical Analysis

The baseline characteristics of MM patients who underwent PBSC harvesting are shown as the total number (*n*) and proportion (%). The primary endpoint of this study was failure to collect total $CD34^+$ cells for $\geq 1 \times 10^6$ cells/kg after mobilization. We first investigated the risk of stem cell mobilization failure in relation to patient characteristics at diagnosis and before mobilization. Odds ratios (ORs) and 95% confidence intervals (CIs) for mobilization failure were calculated using a logistic regression model. Potential risk factors were selected using a univariate model, and those with $p < 0.1$ in the univariate model were included in a multivariate analysis. All independent risk factors identified in the multivariate analysis were then used to build a predictive model of poor mobilization. The β-coefficients of all significant risk factors in the multivariate logistic regression model were used to build a new risk-scoring system. We also built a simplified score by assigning one point to each significant variable. We presented the receiver operating characteristic (ROC) curve and defined an optimal cutoff value by Youden's index method and the closest-to-(0, 1) corner method to maximize the sensitivity and specificity for predicting the probability of poor mobilization. Model discrimination was estimated by sensitivity, specificity, and area under the curve (AUC).

The secondary outcome was overall survival (OS). The study cohort was followed from the date of PBSC harvesting until the date of death, dropout, or the end of March 2021. The cumulative incidence of mortality was estimated using the Kaplan-Meier method.

Sensitivity analysis was performed using different definitions of mobilization failure to identify risk factors of $CD34^+$ cell count yield $< 2 \times 10^6$ cells/kg [29–31], as well as $CD34^+$ cell count collected being less than 5×10^6 cells/kg [32–34]. All data management and statistical analysis were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and STATA statistical software, version 15.1 (StataCorp, College Station, TX, USA). All tests were two-sided with $p < 0.05$ indicating statistical significance.

Results

Clinical Characteristics of the Study Population

This study identified 628 patients diagnosed with MM at Taipei Veterans General Hospital between October 2006 and August 2020. Of them, 440 patients who did not receive stem cell harvest and 7 patients who were initially misclassified as MM were excluded. The final study cohort included 181 MM patients who underwent PBSC harvesting (shown in Fig. 1). The median age of the study patients was 59, ranging from 23 to 74, and 55.3% of the patients were men. ISS stages I, II, and III were 33.7%, 38.7%, and 26.5%, respectively. The median number of collected $CD34^+$ cells was 6.3 (interquartile range 3.3–10.2) $\times 10^6$ cells/kg. Fourteen patients (7.7%) failed to provide sufficient $CD34^+$ cells ($< 1 \times 10^6$ cells/kg). Total stem cells collected $\geq 1 \times 10^6$ $CD34^+$ cells/kg for the first day was reported in 138 patients (76.2%), $\geq 1 \times 10^6$ $CD34^+$ cells/kg for the first 2 days in 165 patients (91.2%). Total stem cells collected $\geq 2 \times 10^6$ $CD34^+$ cells/kg for the first day was reported in 92 patients (50.8%), $\geq 2 \times 10^6$ $CD34^+$ cells/kg for the first 2 days in 143 patients (79.0%). Total stem cells collected $\geq 5 \times 10^6$ $CD34^+$ cells/kg for the first day was reported in 29 patients (16.0%), $\geq 5 \times 10^6$ $CD34^+$ cells/kg for the first 2 days in 88 patients (48.6%) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525565). Demographics of the patients with and without sufficient $CD34^+$ cells collection are listed in Table 1.

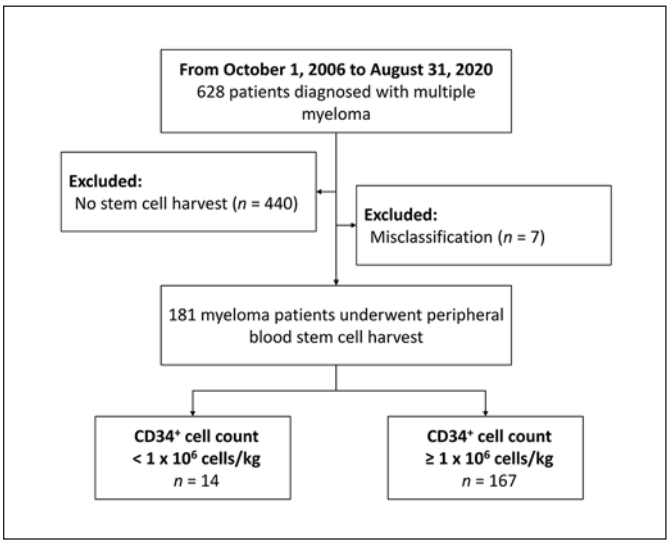

Fig. 1. Patient selection flowchart.

Risk Factors of Failure to Collect PBSCs after Mobilization

We used a logistic regression to identify potential risk factors of mobilization failure. In the univariate analysis, absolute monocyte count (AMC) <500/μL (OR 6.43), absolute neutrophil count (ANC) <3,000/μL (OR 3.99), >1 line of prior chemotherapy (OR 3.66), PLT <150,000/μL (OR 10.55), time interval from diagnosis to stem cell harvest ≥180 days (OR 9.69), and prior irradiation (OR 3.12) before mobilization were associated with failure to collect sufficient PBSCs (Table 2). In the multivariate analysis, AMC <500/μL (adjusted OR 10.75, 95% CI: 1.82–63.57, $p = 0.009$), PLT <150,000/μL (adjusted OR 12.49, 95% CI:

Table 1. Baseline characteristics of myeloma patients with and without sufficient $CD34^+$ cell dose

Characteristics	Total, $n = 181$	$CD34^+$ cell dose	
		$<1 \times 10^6$ cells/kg, $n = 14$	$\geq 1 \times 10^6$ cells/kg, $n = 167$
Median mobilization age, years (range)	59 (23–74)	62 (52–68)	58 (23–74)
Sex (male)	100 (55.3)	10 (71.4)	90 (53.9)
ECOG			
0–1	141 (77.9)	11 (78.6)	130 (77.8)
≥2	40 (22.1)	3 (21.4)	37 (22.2)
ISS stage			
I	61 (33.7)	3 (21.4)	58 (34.7)
II	70 (38.7)	5 (35.7)	65 (38.9)
III	48 (26.5)	6 (42.9)	42 (25.2)
Unknown	2 (1.1)	0 (0.0)	2 (1.2)
Heavy chain			
IgA	44 (24.3)	1 (7.1)	43 (25.8)
IgG	97 (53.6)	9 (64.3)	88 (52.7)
IgD	1 (0.6)	0 (0.0)	1 (0.6)
Light chain disease	38 (21.0)	4 (28.6)	34 (20.4)
Nonsecretory	1 (0.6)	0 (0.0)	1 (0.6)
Light chain			
Kappa	104 (57.5)	9 (64.3)	95 (56.9)
Lambda	76 (42.0)	5 (35.7)	71 (42.5)
Unknown	1 (0.6)	0 (0.0)	1 (0.6)
Comorbidities			
Heart failure	9 (5.0)	1 (7.1)	8 (4.8)
Chronic pulmonary disease	15 (8.3)	1 (7.1)	14 (8.4)
Diabetes mellitus	19 (10.5)	1 (7.1)	18 (10.8)
Hypertension	52 (28.7)	5 (35.7)	47 (28.1)
Laboratory data before mobilization			
AMC <500/μL	67/180 (37.2)	10/13 (76.9)	57/167 (34.1)
ANC <3,000/μL	86/180 (47.8)	10/13 (76.9)	76/167 (45.5)
>1 line of prior chemotherapy	27/181 (14.9)	5/14 (35.7)	22/167 (13.2)
Platelet <150,000/μL	30/180 (16.7)	8/13 (61.5)	22/167 (13.2)
Time interval from diagnosis to stem cell harvest ≥180 days	42/170 (24.7)	10/14 (71.4)	32/156 (20.5)
Laboratory data at MM diagnosis			
Plasma cells of bone marrow ≥60%	77/132 (58.3)	5/11 (45.5)	72/121 (59.5)
Hemoglobin <100 g/L	76/162 (46.9)	7/13 (53.9)	69/149 (46.3)
Platelet <150,000/μL	37/161 (23.0)	3/13 (23.1)	34/148 (23.0)
Serum albumin <35 g/L	73/159 (45.9)	7/13 (53.9)	66/146 (45.2)
Serum β2-microglobulin ≥466.5 nmol/L	41/150 (27.3)	5/11 (45.5)	36/139 (25.9)
Corrected serum calcium ≥3 mmol/L	14/154 (9.1)	0/13 (0.0)	14/141 (9.9)
Serum creatinine ≥176.8 μmol/L	24/161 (14.9)	3/13 (23.1)	21/148 (14.2)
Lactate dehydrogenase ≥250 U/L	28/159 (17.6)	2/13 (15.4)	26/146 (17.8)
Light chain ratio >100	54/141 (38.3)	2/10 (20.0)	52/131 (39.7)
First-line therapy			
VTD	88 (48.6)	6 (42.9)	82 (49.1)
VCD	21 (11.6)	0 (0.0)	21 (12.6)
VAD	13 (7.2)	1 (7.1)	12 (7.2)
Other	59 (32.6)	7 (50.0)	52 (31.1)
Prior radiation	23 (12.7)	4 (28.6)	19 (11.4)
Mobilization regimen			
G-CSF + chemotherapy	180 (99.4)	13 (92.9)	167 (100)
G-CSF alone	1 (0.6)	1 (7.1)	0 (0)
G-CSF dosage			
≥10 μg/kg/day	64 (35.4)	2 (14.3)	62 (37.1)
<10 μg/kg/day	117 (64.6)	12 (85.7)	105 (62.9)
Chemomobilization regimen			
HDCy	141 (77.9)	12 (85.7)	129 (77.2)
Cy plus other chemotherapy	30 (16.6)	1 (7.1)	29 (17.4)
Other regimens without Cy	9 (5.0)	0 (0)	9 (5.4)
No chemomobilization	1 (0.6)	1 (7.1)	0 (0)
Autologous transplant	138 (76.2)	2 (14.3)	136 (81.4)

ECOG, Eastern Cooperative Oncology Group performance; ISS, International Staging System; VTD, bortezomib, thalidomide, and dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; G-CSF, granulocyte colony-stimulating factor; HDCy, high-dose cyclophosphamide; Cy, cyclophosphamide.

Table 2. Risk factors for poor mobilization with $CD34^+$ cell yield $<1 \times 10^6$ cells/kg

Predictive variables	Univariate analysis		Multivariate analysis[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Mobilization age, years	1.06 (0.98–1.15)	0.150		
Sex (male)	2.14 (0.65–7.09)	0.214		
ECOG ≥2	0.96 (0.25–3.62)	0.950		
ISS stage				
I	reference			
II	1.49 (0.34–6.50)	0.598		
III	2.76 (0.65–11.68)	0.167		
Comorbidities				
Heart failure	1.53 (0.18–13.18)	0.699		
Chronic pulmonary disease	0.84 (0.10–6.91)	0.872		
Diabetes mellitus	0.64 (0.08–5.16)	0.672		
Hypertension	1.42 (0.45–4.45)	0.549		
Laboratory data before mobilization				
AMC <500/μL	6.43 (1.70–24.31)	0.006	10.75 (1.82–63.57)	0.009
ANC <3,000/μL	3.99 (1.06–15.02)	0.041	3.25 (0.60–17.81)	0.174
>1 line of prior chemotherapy	3.66 (1.12–11.94)	0.031	1.29 (0.25–6.57)	0.760
Platelet <150,000/μL	10.55 (3.16–35.15)	<0.001	12.49 (2.65–58.89)	0.001
Time interval from diagnosis to stem cell harvest ≥180 days	9.69 (2.85–32.91)	<0.001	7.69 (1.61–36.87)	0.011
Laboratory data at MM diagnosis				
Plasma cells of bone marrow ≥60%	0.57 (0.16–1.96)	0.370		
Hemoglobin <100 g/L	1.35 (0.43–4.22)	0.603		
Platelet <150,000/μL	1.01 (0.26–3.86)	0.993		
Serum albumin <35 g/L	1.41 (0.45–4.41)	0.551		
Serum β2-microglobulin ≥466.5 nmol/L	2.38 (0.69–8.29)	0.172		
Corrected serum calcium ≥3 mmol/L	–			
Serum creatinine ≥176.8 μmol/L	1.81 (0.46–7.14)	0.394		
Lactate dehydrogenase ≥250 U/L	0.84 (0.18–4.01)	0.826		
Light chain ratio >100	0.38 (0.08–1.86)	0.232		
First-line therapy	0.66 (0.22–1.98)	0.455		
VTD	0.88 (0.10–7.94)	0.908		
VCD	–			
VAD	reference			
Other	1.62 (0.18–14.40)	0.667		
G-CSF dosage ≥10 μg/kg/day	0.28 (0.06–1.28)	0.101		
Prior radiation	3.12 (0.89–10.92)	0.076	2.97 (0.49–17.83)	0.235

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance; ISS, International Staging System; VTD, bortezomib, thalidomide, and dexamethasone; VCD, bortezomib, cyclophosphamide, dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; G-CSF, granulocyte colony-stimulating factor. [a] All factors with $p < 0.1$ in the univariate analysis were included in the multivariate logistic regression models.

2.65–58.89, $p = 0.001$), and time interval from diagnosis to stem cell harvest ≥180 days (adjusted OR 7.69, 95% CI 1.61–36.87, $p = 0.011$) were the significant predictors of failure to collect PBSCs after mobilization.

Furthermore, a sensitivity analysis was performed to evaluate if the risk factors were still useful at different levels by using the threshold of 2×10^6 $CD34^+$ cells/kg and 5×10^6 $CD34^+$ cells/kg. PLT <150,000/μL (adjusted OR 5.97, 95% CI: 1.37–26.08, $p = 0.018$) and time interval from diagnosis to stem cell harvest ≥180 days (adjusted OR 6.56, 95% CI: 1.46–29.46, $p = 0.014$) were the risk factors for poor mobilization when the cutoff point for stem cell collection was defined as 2×10^6 $CD34^+$ cells/kg. When we used the threshold of 5×10^6 $CD34^+$ cells/kg, hypertension, PLT <150,000/μL, and time interval from diagnosis to stem cell harvest ≥180 days were the significant predictors of failure to collect PBSCs after mobilization (online suppl. Table 2). In summary, PLT <150,000/μL and time interval from diagnosis to stem cell harvest ≥180 days were independent risk factors of insufficient stem cell collection in all three thresholds of mobilization failure.

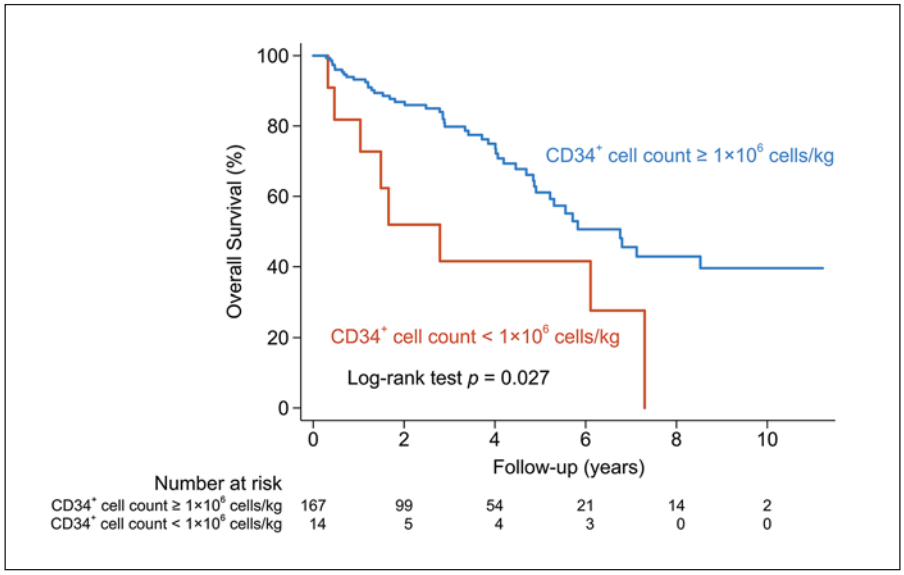

Fig. 2. Kaplan-Meier survival curves among patients with and without 1×10^6 $CD34^+$ cells/kg.

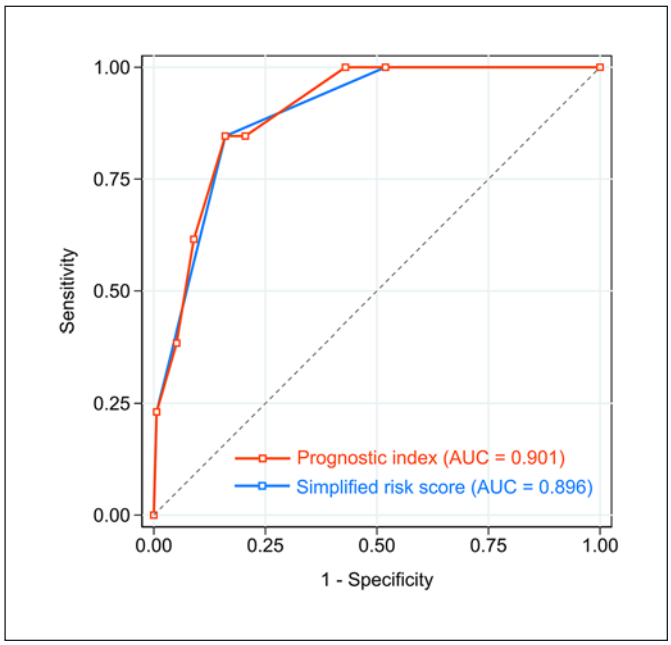

Fig. 3. ROC curves of prediction models for poor mobilization.

OS of MM Patients with and without Sufficient Stem Cell Collection

We further studied the impact of insufficient stem cell collection on patient survival. During the 11-year study period, 55 patients with MM (30.4%) died. The survival curves of patients with and without sufficient stem cell collection are shown in Figure 2. MM patients with insufficient stem cell collection had poorer OS compared with patients with successful stem cell collection (log-rank test $p = 0.027$, shown in Fig. 2).

We investigated the risk factors for mortality in the univariate analysis by the logistic regression model, and those with $p < 0.1$ in the univariate model were included in a multivariate analysis. Stem cells collected $<1 \times 10^6$ $CD34^+$ cells/kg, platelet <150,000/μL before mobilization, the time interval from diagnosis to stem cell harvest ≥180 days, and serum albumin <35 g/L at diagnosis were included in the multivariate analysis. However, no risk factors in the multivariate analysis were statistically significant despite the trend of the factors was equal to that in the univariate analysis (online suppl. Table 3).

Predicting Models and Validation of Risk Score

Multivariate logistic regression analysis was performed on the significant factors extracted from the multivariate analysis in Table 2 to determine the relationship between each variable on poor mobilization. The final model contains three variables, including AMC <500/μL (adjusted OR 11.28, 95% CI: 2.10–60.50, $p = 0.005$), PLT <150,000/μL (adjusted OR 11.85, 95% CI: 2.70–51.90, $p = 0.001$), and time interval from diagnosis to stem cell harvest ≥180 days (adjusted OR 9.79, 95% CI: 2.20–43.50, $p = 0.003$) (online suppl. Table 4). The predicted probability of poor mobilization was estimated by the following multiple logistic regression model:

$$\text{Index} = \frac{1}{1 + e^{5.88 - 2.42x_1 - 2.47x_2 - 2.28x_3}},$$

where x_1: AMC <500/μL, x_2: PLT <150,000/μL, and x_3: time interval from diagnosis to stem cell harvest ≥180 days. Using a ROC curve analysis based on the prognostic index, a cutoff point for prediction of poor mobilization is defined as a score at or above 0.20 (online suppl. Table 5A). The sensitivity of the equation is 84.6%, while the

Table 3. Models of predicting poor mobilization among patients with MM

Risk score	AIC	BIC	AUC	*p* value
Prognostic index[a]	68.9	75.2	0.901	0.631
Simplified risk score[b]	62.4	68.6	0.896	

OR, odds ratio; CI, confidence interval; AIC, Akaike information criterion; BIC, Bayesian information criterion; AUC, area under curve. The *p* value does not indicate a significant difference between the AUCs.

[a] $\text{Index} = \frac{1}{1+e^{5.88-2.42x_1-2.47x_2-2.28x_3}}$,

where x_1: AMC <500/μL, x_2: PLT <150,000/μL, and x_3: time interval from diagnosis to stem cell harvest ≥180 days. [b] Simplified risk score = [AMC <500/μL] + [PLT <150,000/μL] + [time interval from diagnosis to stem cell harvest ≥180 days].

specificity is 84.0% for predicting the possibility of mobilization failure.

A simpler risk model may be easier to use in clinical practice. We defined a simplified prognostic model by assigning one point for each of the three independent predictors (AMC <500/μL, PLT <150,000/μL, and time interval from diagnosis to stem cell harvest ≥180 days). The result shows that patients with a score at or above 2 would predict mobilization failure with a sensitivity of 84.6% and a specificity of 84.0% (online suppl. Table 5B). Figure 3 demonstrates the estimates of the ROC curves. The AUC is 0.901 for predicting poor mobilization using the prognostic index and 0.896 for those using a simplified risk model. There was no significant difference seen between the AUCs of the two prognostic indexes ($p = 0.631$) (Table 3). The calculator of the two models can be found on our Website. Please refer to https://wd.vghtpe.gov.tw/hemaonco/Fpage.action?muid=15117&fid=13842 or QR code in online supplementary Figure 1.

Discussion

This is the largest study on prediction of PMs in patients with MM in Asia so far. Our study has identified that low AMC, low PLT, and a treatment duration of more than 180 days before stem cell harvest is associated with mobilization failure. We created a risk model using three risk factors identified in this work that can predict PMs before stem cell mobilization.

For the minimum stem cell target for an ASCT, although some studies recommended 2×10^6 $CD34^+$ cells/kg as the minimal requirement cell dosage for an ASCT, there was still much evidence supporting using $1–2 \times 10^6$ $CD34^+$ cells/kg. The American Society for Blood and Bone Marrow Transplantation (ASBMT) recommended that using $1–2 \times 10^6$ $CD34^+$ cells/kg for an ASCT was acceptable in patients who benefited from ASCT and can be considered case by case [13]. Shpall et al. [35] reviewed clinical studies on the impact of $CD34^+$ cell doses infused and the outcomes for ASCT. They concluded that $1–2 \times 10^6$ $CD34^+$ cells/kg was adequate for ASCT, but $CD34^+$ cell doses of $\geq 5 \times 10^6$ cells/kg were considered an optimal target with reduced neutrophil and platelet engraftment period, the lower cost, and the reduced need for transfusion support. Pérez-Simón et al. [22] reported the relationship of long-term graft outcome and $CD34^+$ cells infused in 100 cancer patients who received ASCT. They found $CD34^+$ cell doses of more than 1.1×10^6 cells/kg were adequate for long-term graft function. Watts et al. [21] evaluated the predicting factors for blood cell engraftment in a cohort with 101 lymphoma patients and reported the minimal number of $CD34^+$ cells infused was 1.0×10^6 cells/kg. A single-center study with 28 myeloma patients investigated the OS and CD34+ cells infused. Their data showed the minimal $CD34^+$ cell doses were 1.0×10^6 cells/kg and patients who transplanted less than this threshold had a shorter survival period (80% patients survived at 80 months for $>1.0 \times 10^6$ $CD34^+$ cells/kg infused and 67% at 76 months for $<1.0 \times 10^6$ $CD34^+$ cells/kg infused) [24]. A large cohort with 810 patients who underwent ASCT aimed to re-evaluate the threshold for minimal $CD34^+$ cell doses for engraftment reported that $1–2 \times 10^6$ $CD34^+$ cells/kg was acceptable [36]. Recently, some investigators tried to redefine the minimal requirement $CD34^+$ cell doses for an ASCT. The reason is that despite the guidelines recommending a minimal $CD34^+$ cell dose of $\geq 2 \times 10^6$ cells/kg for ASCT, there was still much evidence supporting lower $CD34^+$ cell doses [37]. Furthermore, the defined "minimal cell doses" were based on cryopreserved stem cells; the actual $CD34^+$ cells infused may be lower than this threshold [38]. The improvement of the freezing and thawing technique can increase the infused stem cell dosage, lowering the minimum requirement target. Liu et al. [37] investigated the outcomes for 56 lymphoma patients who underwent ASCT with inadequate stem cell doses. They divided their patients into two groups. The first was the unfavorable HSC group,

with stem cells infused between 1 and 2×10^6 $CD34^+$ cells/kg. The second was poor HSC group, with $CD34^+$ cell doses $<1.0 \times 10^6$ cells/kg. The results showed that the median time to neutrophil engraftment (13 days vs. 11 days, $p = 0.007$) and platelet engraftment (17 days vs. 13 days, $p = 0.024$) was significantly longer in the poor HSC group. However, there was no engraftment failure reported in both groups. Furthermore, there was no significant difference in 3-year progression-free survival (hazard ratio 1.32, 95% CI 0.61–2.85, $p = 0.485$) and 3-year OS (hazard ratio 0.61, 95% CI 0.24–1.56, $p = 0.305$). Another study conducted by Jeyaraman et al. [38] with 84 MM and 24 lymphoma patients received ASCT using noncryopreserved stem cells. They found no significant difference in neutrophil and platelet engraftment time between $CD34^+$ cell doses infused $<2.0 \times 10^6$ cells/kg and $>2.0 \times 10^6$ cells/kg. In brief, $CD34^+$ cell doses of between 1 and 2×10^6 $CD34^+$ cells/kg are acceptable for ASCT. Patients who collected stem cells $>1.0 \times 10^6$ $CD34^+$ cells/kg can proceed to stem cell transplantation under thorough consideration.

Corso et al. [11] reported in a retrospective study that low white cell count, low PLT, previous melphalan treatment, and the interval between diagnosis and stem cell mobilization >6 months were associated with a lower number of $CD34^+$ cells collected, which is similar to our findings. Notably, the patients in their study were treated mainly with chemotherapy. Our patients were treated with both novel agent- and chemotherapy-based regimens, indicating that these risk factors could be applied to both chemotherapy- and novel agent-based treatment. A retrospective study by Musto et al. [39], which enrolled 1,348 newly diagnosed MM patients in five clinical trials, conducted by the GIMEMA – Multiple Myeloma Italian Network, identified four risk factors for poor stem cell mobilization. The risk factors were age >60 years, lenalidomide use, grade 3/4 hematological toxicity under induction therapy, and baseline cytopenia defined as ANC <1,000/μL, Hb < 10 g/dL, or PLT <100,000/μL. Two out of the four risk factors concerned blood cell count, revealing its importance in the prediction of unsuccessful PBSC collection. Furthermore, Baertsch et al. [40] investigated the relationship between low PLT and the need for plerixafor use in a retrospective study with 380 patients who underwent ASCT in Germany. They found that patients with low ANC (OR 0.843, 95% CI: 0.715–0.996, $p = 0.044$) and low PLT (OR 0.994, 95% CI: 0.989–0.998, $p = 0.003$) before mobilization were associated with a higher probability of plerixafor use, compared to patients with higher ANC and PLT. Yang et al. [28] reported low AMC before stem cell harvesting correlated with low $CD34^+$ cell yield. They performed a ROC curve analysis and showed high sensitivity (73.9%) and specificity (89.9%) when the cutoff value of AMC was 1.455×10^9/L. However, the study suggested that AMC could predict PMs only just before harvesting. Regarding the different thresholds, our study found that low PLT and treatment interval between diagnosis and stem cell mobilization more than 180 days before stem cell mobilization were independent risk factors of stem cell dose yield $<2 \times 10^6$ $CD34^+$ cells/kg and $<5 \times 10^6$ $CD34^+$ cells/kg. Abba C. Zubair et al. [41] evaluated predictive factors for PMs in 103 cases. The study enrolled plasma cell dyscrasias patients, lymphoma patients, and normal stem cell donors for allogeneic transplantation. They reported that a baseline PLT $\geq 151 \times 10^9$/μL could be predictive for a more than 5×10^6 $CD34^+$ cells/kg yield in treated plasma cell dyscrasia patients with a sensitivity of 95% and a specificity of 14%. Collectively, low blood cell counts, especially PLT, are associated with poor stem cell mobilization, low stem cell yield and PLT may be a surrogate for bone marrow reserve.

The platelet production is regulated by negative feedback according to the interaction between PLT, the number of megakaryocytes, and the concentration of thrombopoietin (TPO). Platelets and megakaryocytes internalize TPO via their receptor, Mpl, and resulted in a relatively low TPO level when there was an adequate PLT and megakaryocyte count, which decreased the production of platelet and megakaryocyte and vice versa [13]. The receptor of TPO is located not only on megakaryocytes and platelet but also on HSCs. TPO can increase the cycling and differentiation of HSCs when binding to its receptor, resulting in myelopoiesis, erythropoiesis, megakaryocytopoiesis, and the expansion of $CD34^+$ cells [42–44]. Bakeer et al. [45, 46] hypothesized that the predictive ability of low PLT for PMs was because low PLT reflected the decreased number or functional impairment of megakaryocytes, compromising the supportive role of megakaryocytes on $CD34^+$ cells expansion. However, low blood cell counts, PLT, and reduced megakaryocytes in MM patients may also be due to bone marrow pathology and treatment-related toxicity. Interestingly, several studies evaluated the influences of the addition of recombinant human TPO (rhTPO) on traditional mobilization regimens and showed an increased number of PBSC yields [47–49]. Nonetheless, the role of rhTPO on poor stem cell mobilization of MM patients has not been established. The dosage and timing for rhTPO administration are unclear, too. Further study for the application of rhTPO in MM patients with poor stem cell mobilization is needed.

Several previous studies have reported that the enumeration of peripheral blood $CD34^+$ cell count could predict PMs before PBSC harvesting. Moreover, in combination with the rising white blood cell count and PLT from nadir, the enumeration of peripheral blood $CD34^+$ cell count can also determine the timing of apheresis [50–53]. However, as there was no tool to accurately predict PMs before stem cell mobilization, the result was a delay in ear-

ly intervention. Baertsch et al. [40] created a ROC curve by using pre-mobilization PLT and ANC, but with a relatively low predictive value (sensitivity 38%, specificity 87% for low PLT; sensitivity 57%, specificity 77% for low ANC). Jantunen et al. [54] created a chemotherapy scoring system to predict PMs according to treatment regimens before stem cell mobilization. However, no threshold of mobilization failure was detected on the ROC curve (area under the curve 0.541, 95% CI: 0.375–0.706) [54]. Wu et al. [16] created a predictive model for poor stem cell mobilization with a sensitivity of 93.5% and a specificity of 65.7%. However, some of the factors in the model can be collected only before PBSC harvesting, making the model difficult to use. In comparison, our models are easy to use and have a high sensitivity and specificity for predicting PMs. Moreover, the models can predict mobilization failure before stem cell mobilization and make early intervention for mobilization failure possible.

According to our result, patients with high PM score pose a very high risk for mobilization failure and probably require remobilization or the use of a mobilization regimen different from good mobilizers. In addition, all except one of our patients received G-CSF plus chemotherapy (G + C) as mobilization regimen. The regimen may be, therefore, not suitable for patients with high PM scores. Plerixafor with G-CSF (P + G) for mobilization after mobilization failure with G-CSF alone was proven effective [55]. Furthermore, the combination was also effective for patients failing with G + C for mobilization and had better cost-effectiveness [56, 57]. Afifi et al. [58] compared front-line use of P + G to G-CSF plus cyclophosphamide as a mobilization regimen and reported stem cells to yield more than optimal dosage (5×10^6 $CD34^+$ cells/kg) were higher in the P + G group (94% vs. 83%, $p = 0.013$). Attolico et al. [59] evaluated plerixafor added to G-CSF plus chemotherapy (P + G + C) for mobilization in predicted PMs and reported the combination was safe and effective. The ASBMT also recommended P + G or P + G + C for remobilization regimen or mobilization failure prevention in high-risk groups [13]. As a result, we recommended P + G or P + G + C as the primary mobilization regimen for patients with high PM scores. However, National Health Insurance (NHI) only reimbursed plerixafor in patients proved as PMs in Taiwan. Furthermore, the application for reimbursement took roughly 2 weeks before use. Patients who collected suboptimal or inadequate cell doses and need plerixafor as salvage management should use at their own expense. Only 2 patients in our cohort used plerixafor. One patient was used for salvage management, resulting in good stem mobilization. The other patient used chemotherapy with G-CSF and pre-emptive plerixafor as a mobilization regimen. Unfortunately, the $CD34^+$ cells yield $<1.0 \times 10^6$ cells/kg for the patient.

Our data showed that the higher dosage of G-CSF had a trend of lower PM possibility. According to the ASBMT guideline [13], the first-line mobilization regimen in MM can be G-SCF alone with a dosage of ≥10 μg/kg/day for patients who did not receive more than one line of treatment or more than four cycles of lenalidomide-containing regimen. However, the optimal G-CSF dosage in G + C was not clear and differed between studies, with 5–10 μg/kg/day being most frequently used [60–63]. There was no head-to-head comparison of the mobilization effect between chemomobilization with a higher or lower dosage of G-CSF, either. We incorporated the G-CSF dosage of ≥10 μg/kg/day and <10 μg/kg/day into the analysis of risk factors of PMs and found it was not significant in the univariate analysis (OR 0.28, 95% CI: 0.06–1.28, $p = 0.101$) by the logistic regression model (Table 2). The result may be due to the small sample size and need a more extensive study population to evaluate the impact of higher dosage G-CSF on PMs in patients mobilized with G + C.

Zhu et al. [63] conducted a study with the addition of rhTPO to G + C for mobilization in patients with relapsed or refectory non-Hodgkin's lymphoma. The study group was rhTPO plus G + C ($n = 40$) and the control group was G + C ($n = 38$). The result showed that the total $CD34^+$ cells collected were significantly higher in the study group (6.35×10^6 cells/kg vs. 3.3×10^6 cells/kg, $p = 0.0054$). Moreover, stem cells harvested that reached minimal (100% vs. 86%, $p = 0.035$) and optimal target (72.9% vs. 41.3%, $p = 0.021$) were higher, also. rhTPO in combination with traditional mobilization may have a role in PMs, and more investigation was needed to evaluate the dosage and the timing of rhTPO.

Our study found that patients who underwent stem cell mobilization with a $CD34^+$ cell yield of less than 1×10^6 cells/kg are correlated with poorer OS compared to those with a $CD34^+$ cell yield of more than 1×10^6 cells/kg in the univariate analysis. A possible explanation is that patients with MM may be old, immunocompromised, fragile, or heavily treated. These factors can compromise PBSC harvesting and result in poor stem mobilization. However, PMs and low PLT were not statistically significant in the multivariate analysis despite a trend of significance was found. A more extensive study was needed to answer the questions and evaluated the impact of PMs and low PLT on mortality. Besides, we found ASCT was not a risk factor for mortality in the univariate logistic regression. Dhakal et al. [2] conducted a meta-analysis with 4 phase 3 randomized clinical trials for conventional meta-analysis and 5 for network meta-analysis in patients with MM and reported that ASCT did not affect OS in MM patients in the era of novel agents. The result may be due to the high come-out rate of new post-relapse medications.

This study has several limitations. First, because this is a retrospective study, our patients did not have a uniform treatment regimen or mobilization regimen. However, these factors make our risk score more reliable and applicable in the real world and clinical practice. Second, our study did not include risk stratification for every patient, to identify the influence of high-risk molecular patterns on stem cell yield. Nevertheless, it proves that our model can be applied to both high- and low-risk populations. Third, lenalidomide use has been established as a risk factor of PM. The British Society for Haematology guideline and the Medical Scientific Advisory Group to Myeloma Australia guideline recommended that patients treated with a lenalidomide-containing regimen should not exceed four cycles before stem cell harvesting to prevent mobilization failure [64, 65]. The induction therapy with a triple-combination regimen including a proteasome inhibitor, an immunomodulating agent, and a steroid was recommended across clinical guidelines. Lenalidomide with bortezomib and steroid (VRd) was the preferred option in transplant-eligible patients among guidelines and alternative lenalidomide to thalidomide (VTd) was recommended in areas where lenalidomide was not available [64–67]. In Taiwan, lenalidomide was not reimbursed by NHI as induction treatment in transplant-eligible patients. Most of our patients received VTd as the front-line treatment before undergoing ASCT. Only three cases of our cohort received lenalidomide-containing regimen as induction treatment. The effects of lenalidomide on PMs cannot be evaluated in our study. Finally, despite low PLT and PMs were found possible risk factors for mortality in the univariate analysis the multivariate analysis was not significant. This result may be due to inadequate statistical power, and larger sample size was needed to detect the effects of the risk factors on mortality.

Conclusion

In conclusion, we found that AMC <500/μL, PLT <150,000/μL, and a treatment duration of more than 180 days before stem cell mobilization are risk factors for unsuccessful stem cell collection. Furthermore, our prediction models have both high sensitivity and specificity for mobilization failure prediction. This is the largest study in an Asian population for prediction of PMs in MM patients, and our predicting models have the highest sensitivity and specificity in mobilization failure prediction among the published literature. Our model allows for pre-emptive plerixafor use or other early interventions for possible PMs and may reduce costs owing to mobilization failure.

Statement of Ethics

This study has been approved by the Institutional Review Board at Taipei Veterans General Hospital (no. 2021-03-006CC). For this type of study, formal consent is not required.

Conflict of Interest Statement

All authors declare no conflict of interest.

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Author Contributions

Chia-Jen Liu had full access to the study data and takes responsibility for data integrity and accuracy of data analysis and acts as guarantor and accepts responsibility for the integrity of the work as a whole. Te-Lin Hsu, Chun-Kuang Tsai, Chiu-Mei Yeh, and Chia-Jen Liu designed the study and provided the final interpretation of the results. Te-Lin Hsu, Chun-Kuang Tsai, Chiu-Mei Yeh, Fen-Lan Lin, and Chia-Jen Liu collected the data. Chiu-Mei Yeh and Chia-Jen Liu acquired the data and performed the statistical analysis and drafted the manuscript. Te-Lin Hsu, Chun-Yu Liu, Liang-Tsai Hsiao, Yao-Chung Liu, Hao-Yuan Wang, Po-Shen Ko, Ting-An Lin, and Wen-Chun Chen made critical revisions to the manuscript for important intellectual content. Po-Min Chen, Jin-Hwang Liu, and Jyh-Pyng Gau were the study supervisors. All authors have read and approved the final manuscript.

Data Availability Statement

The data of this study are not publicly available because the information can compromise the privacy of research participants, and the participants do not consent to public data release. Data requirements can direct to the corresponding author upon reasonable request.

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