Bone-Related Extramedullary Disease in Newly Diagnosed Myeloma Patients is an Independent Poor Prognostic Predictor

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ABSTRACT

BACKGROUND: Bone-related extramedullary disease (EMD-B) is mass of clonal plasma cells derived from adjacent bone lesions and has obvious heterogeneities in clinical outcomes. This retrospective study aims to evaluate the treatment outcomes and long-term prognosis of newly diagnosed myeloma patients with EMD-B.

METHODS: This was a retrospective study conducted in Beijing Chaoyang Hospital from January 1, 2010 to December 31, 2019. Seventy-seven newly diagnosed multiple myeloma patients with EMD-B were selected. Propensity score matching (1:2) was used to match patients with and without EMD-B. After matching, 132 patients without extramedullary disease (non-EMD) were included in the study. All patients received bortezomib-based regimens as induction therapy.

RESULTS: After matching, baseline data of the 2 groups were comparable. The Cox regression analysis of patients with EMD-B showed that age, paravertebral lesions, and immunoglobulin D (IgD) type may have adverse effects on survival. Bone-related extramedullary disease at new diagnosis was a risk predictor of survival (hazard ration [HR] = 1.80, 95% confidence interval [CI]: 1.09-2.98, $P = .022$). The median survival time of the EMD-B group was significantly shorter than that of the non-EMD group (52 months vs 96 months, $P = .043$). Induction therapy did not show any significant differences in effectiveness between the 2 groups. Autologous stem cell transplantation (ASCT) significantly increased complete remission rate of patients with EMD-B (EMD-B vs non-EMD: no ASCT 15.7% vs 31.9%, $P = .035$; ASCT 42.3% vs 48.8%, $P = .626$) and improved their median overall survival rate (EMD-B vs non-EMD: no ASCT 49 months vs 75 months, $P = .003$; ASCT not reached vs 96 months, $P = .505$).

CONCLUSIONS: This study demonstrated that newly diagnosed myeloma patients with EMD-B had poor outcomes, which could be improved by ASCT.

KEYWORDS: Extramedullary disease, multiple myeloma, proteasome inhibitor, autologous stem cell transplantation, propensity score

Introduction

Multiple myeloma (MM) is defined by the malignant proliferation of clonal plasma cells generally restricted to the bone marrow. Some patients develop extramedullary disease (EMD) at the time of diagnosis or when relapse/progression occurs. Generally, EMD is divided into 2 groups: bone-related extramedullary disease (EMD-B) and soft tissue–related extramedullary disease (EMD-S). The latter group has been verified to have a poor prognosis in many studies.[1-3]

EMD-B is derived from adjacent bone lesions. For newly diagnosed multiple myeloma (NDMM), the reported incidence of EMD varies from 2.1% to 32%, of which EMD-S is no more than 7%.[4,5] The incidences of EMD-B are quite different, ranging from 6% to 34%.[6,7] Generally, they are thought to have the same nature as intramedullary lesions.[8] However,

obvious heterogeneities have been observed. In the era of novel agents, few studies have focused on EMD-B. Deng et al[5] demonstrated that when treated with bortezomib-based regimens, the overall survival (OS) rate for NDMM patients with EMD was superior to that for NDMM patients without EMD (EMD vs non-EMD: 16.5 months vs 40 months, $P < .001$). Another study reported that multiple sites of EMD predicted poor OS and progression-free survival (PFS) rates compared with non-EMD (median OS: 8.3~11.2 months vs 38.1 months; median PFS: 17.6~30.8 months vs 61.4 months).[9] However, the above studies did not distinguish between EMD-B and EMD-S. Gagelmann et al[3] reported a similar 3-year OS between EMD-B and non-EMD, under the condition of autologous stem cell transplantation (ASCT), but there were no data for patients not eligible for transplantation. In that case, the character of EMD-B was debatable, and more detailed research is necessary. This retrospective study aims to evaluate the treatment outcome and long-term prognosis of

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newly diagnosed myeloma patients with EMD-B and provide a clear profile of their clinical characteristics.

Methods

Study populations

From January 1, 2010 to December 31, 2019 in Beijing Chaoyang Hospital, a total of 100 NDMM patients with EMD-B who had detailed and available clinical data were included in this study. Two hundred non-EMD patients were selected as the control group based on admission time and induction regimens consistent with each patient in the EMD-B group. Propensity score matching (PSM) was used to ensure that baseline data between the 2 groups were comparable. The diagnosis of MM was made according to the International Myeloma Working Group (IMWG) Guidelines. Bone-related extramedullary disease was identified according to (1) MM diagnosis; (2) radiologic findings (including computed tomography, positron emission tomography combined with computed tomography and magnetic resonance imaging); and (3) pathologic evidence of plasmacytoma adjacent to the bone.

Study variables

Baseline clinical data including age, sex, MM stage, percentage and immune phenotype of plasma cells in bone marrow, cytogenetic abnormalities, biochemical tests, induction regimens, transplantation, and treatment response were obtained. Fluorescence in situ hybridization (FISH) reports were collected. All bone marrow samples were sent to the central laboratory for FISH testing. During the detection process, CD138-positive cells were first sorted by the immunomagnetic bead method, and then a total of 200 myeloma cells in the interphase were counted. Five probes were used: p53/CSP17, 1q21/1p36, IgH/CCND1, IgH/FGFR3, and IgH/MAF. If the test result was greater than the threshold, it was positive. The MM stage included the International Staging System (ISS), the Revised International Staging System (R-ISS), and the Durie-Salmon System (DS). All patients received bortezomib-based therapy.

Study outcomes

Treatment responses were evaluated according to IMWG criteria. Mean endpoints were PFS and OS. The second endpoint was treatment response, categorized as complete remission (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD). Very good partial response was defined as "serum and urine M-protein detectable by immunofixation but not on electrophoresis or ⩾90% reduction in serum M-protein plus urine M-protein level less than 100 mg per 24 h." MR was defined as "⩾25% but ⩽49% reduction of serum M-protein and reduction in 24 h urine M-protein by 50%~89%.

In addition to the above-listed criteria, if present at baseline, a 25%~49% reduction in SPD of soft tissue plasmacytomas was also required." Those without effectiveness assessment were recorded as not evaluated (NE). Progression-free survival was calculated from the date of diagnosis to the disease's first progression. Overall survival was calculated from the date of diagnosis to the date of death or last follow-up.

Propensity score matching

Propensity score matching was used to ensure a comparable sample between patients with EMD-B and non-EMD. The propensity score of each included patient was calculated. Covariates were selected based on prognostic indicators of OS and baseline differences between the 2 groups. We matched 2 non-EMD patients to 1 patient with EMD-B using the nearest neighbor method with a caliper width of 0.2. Comparability of the groups after matching was assessed by inspection of the balance of baseline variables. After being matched, 77 patients in the EMD-B group and 132 patients in the non-EMD group were selected.

Statistical analysis

Continuous variables were compared using the Student *t* test or the Mann-Whitney test. Categorical variables were compared using χ^2 or the Fisher exact test. Survival analyses were estimated using the Kaplan-Meier method and log-rank test. The Cox proportional hazard models were used to estimate univariate and multivariate factors for the endpoint with hazard ratios (HR) and 95% confidence intervals (CIs). The Cox model was built using stepwise forward likelihood-ratio testing. $P < .05$ was defined statistically significant. Statistical descriptions were achieved with IBM SPSS 26.0 (Armonk, NY, USA).

All cutoff values of continuous variables below were calculated through receiver-operating characteristic curves. Subgroup analyses were performed for sex (men and women), age (<60 years; ⩾60 years), bone marrow plasma cell (BMPC) (<47.5%; ⩾47.5%), lactate dehydrogenase (LDH) (<185 U/L; ⩾185 U/L), calcium (Ca) (<2.50 mmol/L; ⩾2.50 mmol/L), ASCT (yes; no), DS stage (I, II, and III), ISS stage (I, II, and III), R-ISS stage (I, II, and III), and first-line regimens (proteasome inhibitor [PI] + immunomodulatory drugs [IMiDs]; PI + chemotherapy). The outcome for all subgroup analyses was OS. Analyses were performed with R (V.4.1.1) and RStudio (2021.09.0-351).

Ethics approval and consent

This study was approved by the ethics committee of Beijing Chaoyang Hospital, Capital Medical University (approval ID: 2021-722 and approval date: January 10, 2022). Our institution's ethics committee supported our retrospective study without the need for informed consent.

Table 1. Baseline characteristics before and after propensity score matching.

		BEFORE PS MATCHING		*P*	AFTER PS MATCHING		*P*
		EMD-B (N = 100)	NON-EMD (N = 200)		EMD-B (N = 77)	NON-EMD (N = 132)	
Gender	Men	59 (59.0%)	118 (59.0%)	1.000	45 (58.4%)	73 (55.3%)	.659
	Women	41 (41.0%)	82 (41.0%)		32 (41.6%)	59 (44.7%)	
Induction regimens	PI + IMiDs	42 (42.0%)	85 (42.5%)	.934	31 (40.3%)	56 (42.4%)	.759
	PI + chemotherapy	58 (58.0%)	115 (57.5%)		46 (59.7%)	76 (57.6%)	
ASCT	No ASCT	63 (63.0%)	130 (65.0%)	.733	51 (66.2%)	91 (68.9%)	.686
	ASCT	37 (37.0%)	70 (35.0%)		26 (33.8%)	41 (31.1%)	
DS	I	7 (7.0%)	5 (2.5%)	.012	4 (5.2%)	5 (3.8%)	.726
	II	14 (14.0%)	16 (8.0%)		9 (11.7%)	12 (9.1%)	
	III	79 (79.0%)	179 (89.5%)		64 (83.1%)	115 (87.1%)	
ISS	I	37 (37.0%)	38 (19.0%)	<.001	24 (31.2%)	31 (23.5%)	.067
	II	34 (34.0%)	68 (34.0%)		30 (39.0%)	40 (30.3%)	
	III	29 (29.0%)	94 (47.0%)		23 (29.9%)	61 (46.2%)	
R-ISS	I	28 (28.0%)	25 (12.5%)	.001	16 (20.8%)	22 (16.7%)	.742
	II	58 (58.0%)	124 (62.0%)		48 (62.3%)	85 (64.4%)	
	III	14 (14.0%)	47 (23.5%)		13 (16.9%)	25 (18.9%)	
Age	years	57 (50~66)	58 (52~66)	.620	57 (51~66)	58 (52~66)	.911
BMPC	%	18.0 (7.0~40.0)	34.8 (21.0~49.5)	<.001	25 (12.5~51.0)	33 (18.8~48.8)	.145
WBC	×10⁹/L	5.23 (4.13~6.21)	5.15 (3.87~6.70)	.939	5.22 (4.10~6.17)	5.13 (3.85~6.65)	.925
HGB	g/L	112.68 (±30.660)	99.96 (±27.098)	<.001	104.68 (±25.342)	106.14 (± 26.263)	.692
PLT	×10⁹/L	177 (142~228)	181 (126~228)	.774	175 (132~228)	190 (131~229)	.647
ALB	g/L	38.1 (33.3~41.7)	34.9 (28.9~40.0)	<.001	37.3 (31.9~39.9)	36.3 (31.6~40.5)	.909
LDH	U/L	170 (142~210)	162 (136~201)	.459	170 (142~215)	165 (138~197)	.531
ALP	U/L	73 (58~94)	82 (63~109)	.039	80 (60~100)	81 (64~106)	.337
sCr	mmol/L	69.3 (58.6~78.95)	77.7 (63.65~131.85)	.001	69.6 (58.70~79.2)	76.45 (61.95~120.35)	.047
Ca	mmol/L	2.30 (2.21~2.40)	2.21 (2.12~2.33)	<.001	2.29 (2.18~2.41)	2.22 (2.14~2.35)	.183

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ASCT, autologous stem cell transplantation; BMPC, bone marrow plasma cell; Ca, calcium; DS, Durie-Salmon System; EMD-B, bone-related extramedullary disease; HGB, hemoglobin; IMiDs, immunomodulator drugs; ISS, International Staging System; LDH, lactate dehydrogenase; non-EMD, no extramedullary disease; PI, proteasome inhibitor; PLT, platelet; PS: propensity score; R-ISS, Revised International Staging System; sCr, serum creatinine; WBC, white blood cell.

Results

Clinical baseline characteristics

A total of 300 (100/200) NDMM (with or without EMD-B) patients were enrolled in this study. Specific baseline characteristics are summarized in Table 1. Before PSM, patients with EMD-B showed lower creatinine levels (median Cr level: 69.3 mmol/L vs 77.7 mmol/L, *P* = .001) and lower ISS/R-ISS stage III (29% vs 47%, *P* < .001/14% vs 23.5%, *P* = .001), a lower percentage of baseline BMPCs (18.0% vs 34.8%, *P* < .001), and higher hemoglobin (112.68 g/L vs 99.96 g/L, *P* < .00) and albumin (38.1 g/L vs 34.9 g/L, *P* < .001) levels than non-EMD patients. These data may suggest that patients with EMD-B have a lower disease burden and better performance status at initial diagnosis. After PSM, the baseline data of the 2 groups were comparable (Table 1).

Table 2. EMD-B characteristics.

		EMD-B (N = 100)	NON-EMD (N = 200)	*P*
Location	Paravertebral	43 (43.0%)		
	Others	57 (57.0%)		
EMD number	1	60 (60.0%)		
	2	14 (14.0%)		
	⩾3	26 (26.0%)		
Pathology	All	58 (58.0%)		
	Anaplasia or blast cell	16 (16.0%)		
Ki-67 (%)	All	30 (15~60)		
	Anaplasia or blast cell	70 (55~80)		
Radiotherapy	Yes	21 (21.0%)		
Surgery	Yes	30 (30.0%)		
FISH		n = 75	n = 130	
	1q21 gain	29 (38.7%)	69 (53.1%)	.050
	IgH/MAF	4 (5.3%)	12 (9.2%)	.321
	IgH/FGFR3	15 (20.0%)	25 (19.2%)	1.000
	IgH/CCND1	12 (16.0%)	24 (18.5%)	.863
	TP53	9 (12.0%)	21 (16.2%)	.388
Phenotype		n = 80	n = 136	
	CD19	5 (6.3%)	3 (2.2%)	.150
	CD20	4 (5.0%)	16 (11.8%)	.098
	CD27	18 (22.5%)	35 (25.7%)	.594
	CD28	8 (10.0%)	14 (10.3%)	.945
	CD56	51 (63.8%)	98 (72.1%)	.202

Abbreviations: EMD-B, bone-related extramedullary disease; non-EMD, no extramedullary disease; FISH, fluorescence in situ hybridization.

EMD–B characteristics

A total of 100 patients with EMD-B were enrolled. Of these, paravertebral lesions accounted for the largest proportion, up to 43%, followed by sternum and ribs (32%), cranium (25%), and other appendicular skeletal (total 37%) lesions. In addition, 60/14/26 (60%/14%/26%) patients had 1, 2, and ⩾3 involved sites of EMD-B, respectively. The pathology results of the extramedullary tumor were available in 58 (58%) patients through fine needle aspiration biopsy or surgical resection, with a median Ki-67 index of 30% (15%~60%). Sixteen samples were identified as anaplastic or blast plasma cells with a median Ki-67 index of 70% (55%~80%). Five (31.3%) of the 16 patients died, and the median OS was 22 months. For local treatment options, 21 (21%) received radiotherapy and 30 (30%) underwent surgical resection. Neither could effectively influence survival according to the Cox regression results.

FISH—including 1q21 gain, t(14; 16), t(4; 14), t(11; 14), and del(17p)—was tested in 75 patients with EMD-B and 130 non-EMD patients. There was a marginally lower percentage of 1q21 gain in the EMD-B group than in the non-EMD group (38.7% vs 53.1%, *P* = .050). No other significant differences were seen (Table 2). Immunophenotypes of myeloma cells in bone marrow tested by flow cytometry were available in 80 patients with EMD-B and 136 patients with non-EMD. In the EMD-B group, CD20 and CD56 tended to have lower expression levels than in the non-EMD group (CD20: 5.0% vs 11.8%, *P* = .098; CD56: 63.8% vs 72.1%, *P* = .202).

A Cox regression model was performed on the 100 patients with EMD-B (Table 3). The results of univariate and multivariate analyses showed that age (⩾60 years, *P* = .006), paravertebral lesions (*P* = .043), and immunoglobulin D (IgD) M-protein (*P* = .014) may have adverse effects on survival. The number of EMD-Bs did not affect prognosis (*P* = .700).

Table 3. Cox regression analysis of all patients with EMD-B (n = 100).

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	P	HR	95% CI	*P*	HR	95% CI
Age	.004	3.010	(1.434-6.317)	.006	3.063	(1.379-6.801)
Paravertebral	.143	1.699	(0.835-3.455)	.043	2.113	(1.024-4.358)
ISS III	.048	2.362	(1.006-5.548)	.274		
IgD	.001	8.255	(2.257-30.188)	.014	5.276	(1.397-19.923)
ASCT	.007	0.291	(0.119-0.714)	.051		

Abbreviations: ISS, International Staging System; ASCT, autologous stem cell transplantation.

Table 4. Cox regression analysis of all patients before and after propensity score matching.

BEFORE PSM (N = 300)						
	SINGLE-FACTOR ANALYSIS			MULTI-FACTOR ANALYSIS		
	P	HR	95% CI	*P*	HR	95% CI
EMD-B	.252	1.28	(0.84-1.98)	.035	1.62	(1.03-2.52)
Age ≥60 years	.006	1.73	(1.17-2.56)	.125		
BMPC ≥47.5%	.002	1.94	(1.26-2.99)	.006	1.83	(1.19-2.86)
LDH ≥185 U/L	.002	1.91	(1.27-2.87)	.011	1.74	(1.13-2.69)
ASCT	.002	0.48	(0.30-0.77)	.003	0.51	(0.29-0.77)
AFTER PSM (N = 209)						
	SINGLE-FACTOR ANALYSIS			MULTI-FACTOR ANALYSIS		
	P	HR	95% CI	*P*	HR	95% CI
EMD-B	.046	1.66	(1.01-2.73)	.022	1.80	(1.09-2.98)
BMPC ≥47.5%	.001	2.28	(1.38-3.75)	.005	2.08	(1.25-3.46)
Ca ≥2.50 mmol/L	.008	2.24	(1.24-4.03)	.028	1.96	(1.08-3.58)
ASCT	.016	0.46	(0.25-0.86)	.026	0.49	(0.26-0.92)

Abbreviations: ASCT, autologous stem cell transplantation; BMPC, bone marrow plasma cell; Ca, calcium; CI, confidence interval; EMD-B, bone-related extramedullary disease; HR, hazard ratio; LDH, lactate dehydrogenase; PSM, propensity score matching.

Outcome analysis

OS was analyzed by the Cox proportional hazards regression before and after PSM for all patients (Table 4). EMD-B at new diagnosis (HR = 1.62, 95% CI: [1.03, 2.52], *P* = .035) and BMPC ≥47.5% (HR = 1.83, 95% CI: 1.19-2.86, *P* = 0.006) were adverse risk predictors. Autologous stem cell transplantation (HR = 0.51, 95% CI: 0.29-0.77, *P* = .003) was a protective factor. The above factors were consistent before and after pairing.

The median follow-up time was 46 months (0-118 months). Before matching, 31 (31.0%) patients in the EMD-B group and 70 (35.0%) patients in the non-EMD group died. No significant differences were found in the Kaplan-Meier curves between the 2 groups (EMD-B vs non-EMD: PFS 28 months vs 31 months, *P* = .376; OS 55 months vs 76 months, *P* = .248)

(Figure 1A and C). After being matched, 27 (64.9%) patients in EMD-B group and 43 (67.4%) patients in non-EMD group died. The median PFS (EMD-B vs non-EMD: PFS 26 months vs 31 months, *P* = .251) was comparable between the 2 groups (Figure 1D). The median OS time of the EMD-B group was significantly shorter than that of the non-EMD group (EMD-B vs non-EMD: OS 52 months vs 96 months, *P* = .043) (Figure 1B).

Subgroup analysis

The association between NDMM with EMD-B and OS was further investigated in clinically relevant subgroups (Figure 2). For all matched patients, the adverse risk of death was significantly higher in the EMD-B group than in the non-EMD group (HR = 1.66, 95% CI: 1.01-2.74, *P* = .045). The *P* value
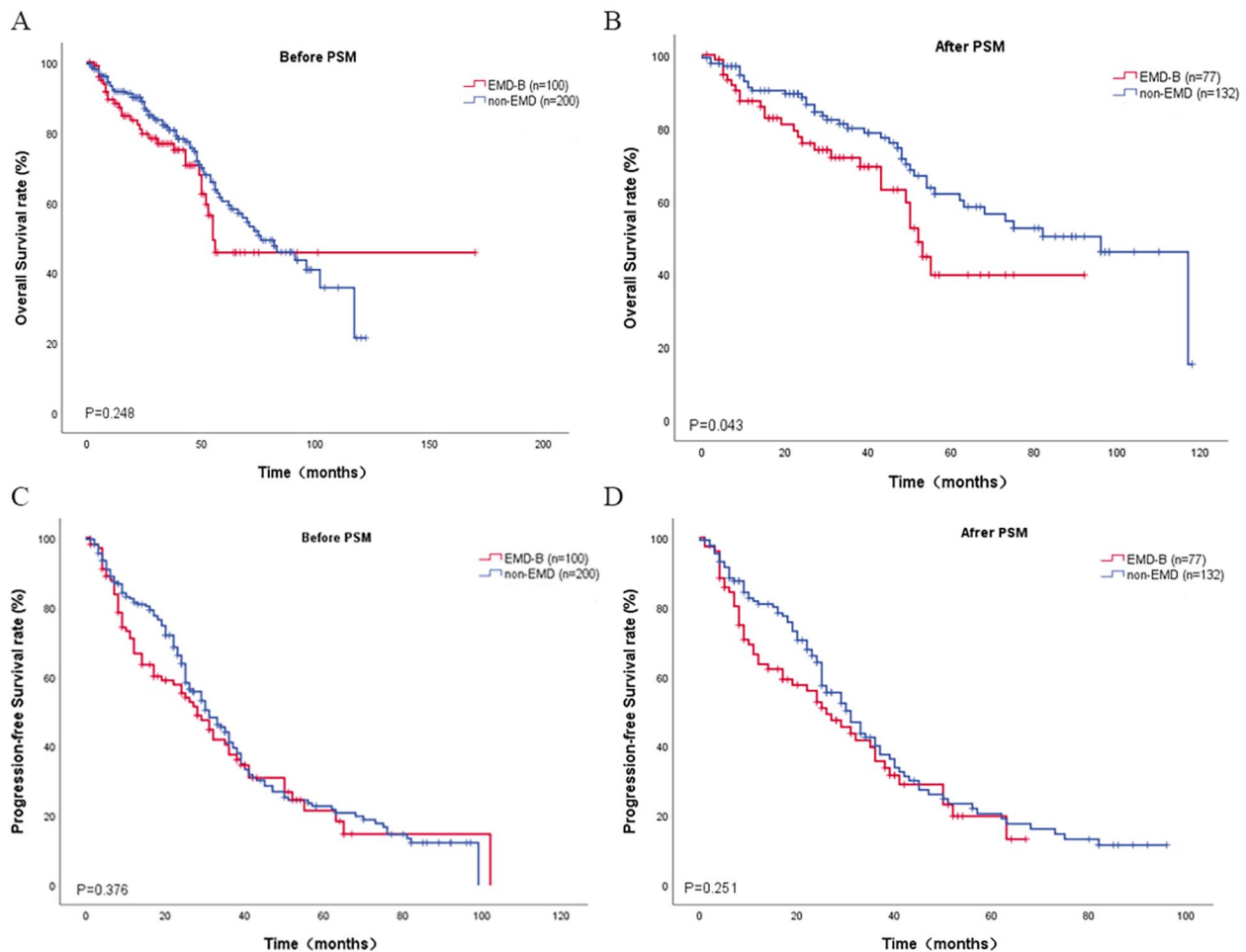
Figure 1. Kaplan-Meier curve of patients with extramedullary disease with bone-related (EMD-B) and multiple myeloma patients without extramedullary disease (non-EMD). (A) Overall survival (OS) before propensity score matching (PSM), (B) OS after matching, (C) progression-free survival (PFS) before matching, and (D) PFS after matching.

was significant for men, age $\geqslant 60$ years, BMPC proportion $<47.5\%$, no ASCT, and ISS stage III patients. Kaplan-Meier curves of each subgroup are listed in the Supplementary Figure. Patients with EMD-B had poorer median OS than those without EMD in the "male" subgroup (50 months vs 117 months, $P=.002$) (Supplementary Figure A), "age older than 60 years" subgroup (43 months vs 82 months, $P=.001$) (Supplementary Figure C), "BMPC less than 47.5%" subgroup (53 months vs 117 months, $P=.022$) (Supplementary Figure E), and "ISS stage III" subgroup (38 months vs 75 months, $P=.034$) (Supplementary Figure G). There were no significant differences in the "female" ($P=.816$), "age younger than 60 years" ($P=.836$), or "BMPC more than 47.5%" ($P=.658$) or "ISS stage I and II" ($P=.303$) subgroups (Supplementary Figure B, D, F, and H). This means that patients in the above former subgroups presented poorer outcomes when diagnosed with EMD-B.

Treatment and effectiveness

Induction therapy. A total of 31/46 (40%/60%) patients in the EMD-B group and 56/76 (42%/58%) patients in the

non-EMD group received PI + IMiD/PI + chemotherapy–based induction regimens. The treatment effectiveness is listed in Table 5. For the EMD-B group, the overall response rate (ORR) was 66.2%, and the CR/VGPR/PR/MR rates were 20.8%/23.4%/22.1%/5.2%, respectively. For the non-EMD group, the ORR was 75.8%, and the CR/VGPR/PR/MR rates were 30.3%/22.0%/23.5%/2.30%, respectively. No significant differences were found (ORR: $P=.138$). Furthermore, induction regimens were divided into 2 groups: PI + IMiDs and PI + chemotherapy–based regimens. With PI + IMiD–based regimens, the ORR was 64.5% in the EMD-B group and 73.2% in the non-EMD group ($P=.396$). The CR/VGPR/PR/MR rates were 19.4%/32.2%/12.9%/0% in the EMD-B group and 26.8%/26.8%/19.6%/0% in the non-EMD group ($P=.659$), respectively. With PI + chemotherapy–based regimens, ORR was 67.4% in the EMD-B group and 77.6% in the non-EMD group ($P=.213$), and the CR/VGPR/PR/MR rates were 21.7%/17.4%/28.3%/8.7% in the EMD-B group and 32.9%/18.4%/26.3%/3.9% in the non-EMD group ($P=0.573$), respectively. Different induction regimens did not impact effectiveness.
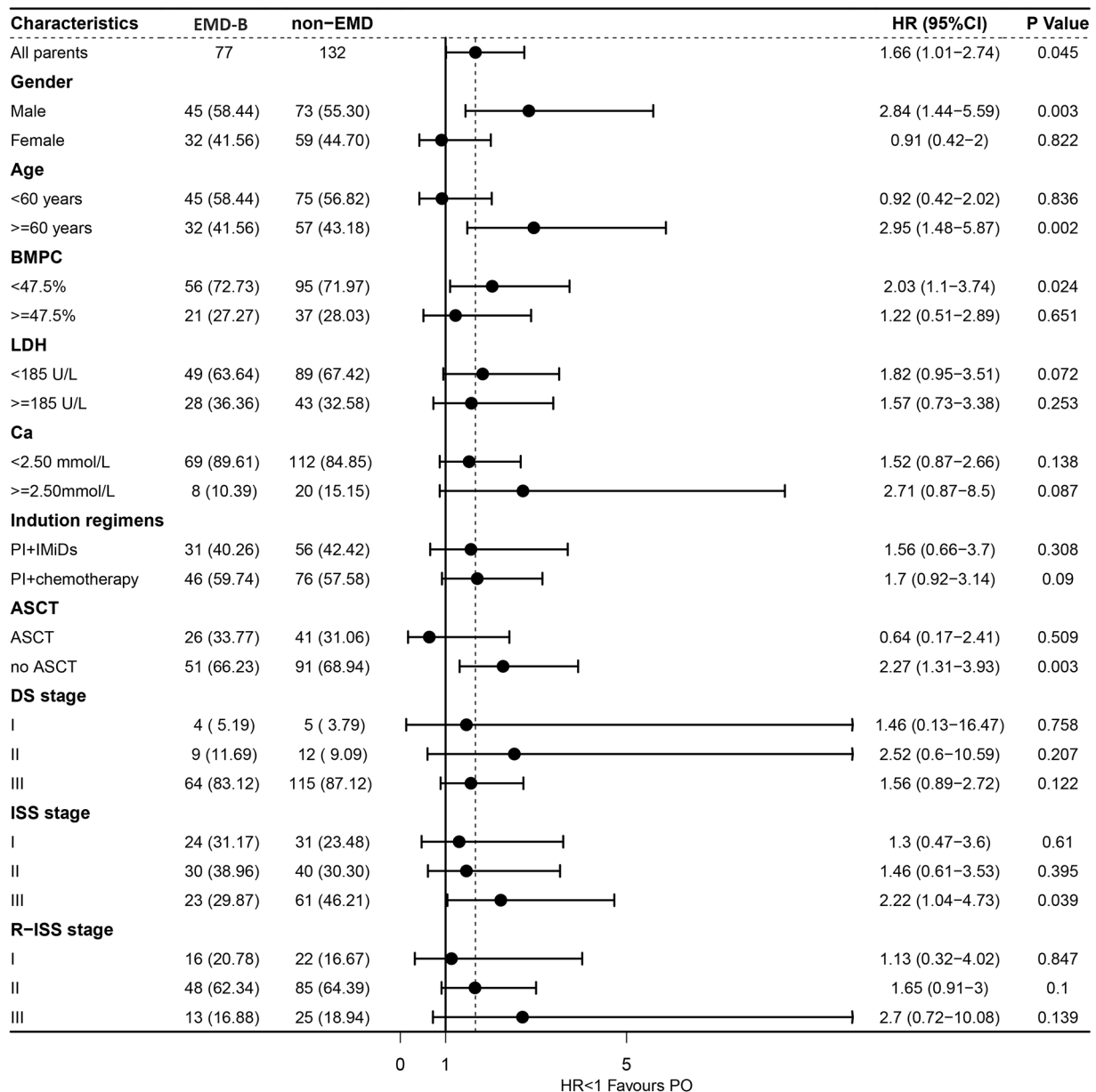
Characteristics	EMD-B	non−EMD		HR (95%CI)	P Value
All parents	77	132		1.66 (1.01−2.74)	0.045
Gender					
Male	45 (58.44)	73 (55.30)		2.84 (1.44−5.59)	0.003
Female	32 (41.56)	59 (44.70)		0.91 (0.42−2)	0.822
Age					
<60 years	45 (58.44)	75 (56.82)		0.92 (0.42−2.02)	0.836
>=60 years	32 (41.56)	57 (43.18)		2.95 (1.48−5.87)	0.002
BMPC					
<47.5%	56 (72.73)	95 (71.97)		2.03 (1.1−3.74)	0.024
>=47.5%	21 (27.27)	37 (28.03)		1.22 (0.51−2.89)	0.651
LDH					
<185 U/L	49 (63.64)	89 (67.42)		1.82 (0.95−3.51)	0.072
>=185 U/L	28 (36.36)	43 (32.58)		1.57 (0.73−3.38)	0.253
Ca					
<2.50 mmol/L	69 (89.61)	112 (84.85)		1.52 (0.87−2.66)	0.138
>=2.50mmol/L	8 (10.39)	20 (15.15)		2.71 (0.87−8.5)	0.087
Indution regimens					
PI+IMiDs	31 (40.26)	56 (42.42)		1.56 (0.66−3.7)	0.308
PI+chemotherapy	46 (59.74)	76 (57.58)		1.7 (0.92−3.14)	0.09
ASCT					
ASCT	26 (33.77)	41 (31.06)		0.64 (0.17−2.41)	0.509
no ASCT	51 (66.23)	91 (68.94)		2.27 (1.31−3.93)	0.003
DS stage					
I	4 (5.19)	5 (3.79)		1.46 (0.13−16.47)	0.758
II	9 (11.69)	12 (9.09)		2.52 (0.6−10.59)	0.207
III	64 (83.12)	115 (87.12)		1.56 (0.89−2.72)	0.122
ISS stage					
I	24 (31.17)	31 (23.48)		1.3 (0.47−3.6)	0.61
II	30 (38.96)	40 (30.30)		1.46 (0.61−3.53)	0.395
III	23 (29.87)	61 (46.21)		2.22 (1.04−4.73)	0.039
R−ISS stage					
I	16 (20.78)	22 (16.67)		1.13 (0.32−4.02)	0.847
II	48 (62.34)	85 (64.39)		1.65 (0.91−3)	0.1
III	13 (16.88)	25 (18.94)		2.7 (0.72−10.08)	0.139

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HR<1 Favours PO

Figure 2. Subgroup analysis on association between extramedullary disease with bone-related (EMD-B) and overall survival.
ASCT indicates autologous stem cell transplantation; BMPC, bone marrow plasma cell; Ca, calcium; CI, confidence interval; DS, Durie-Salmon System; HR, hazard ratio; IMiDs, immunomodulator drugs; ISS, International Staging System; LDH, lactate dehydrogenase; Non-EMD, no extramedullary disease; PI, proteasome inhibitor; PSM, propensity score matching; R-ISS, Revised International Staging System.

Autologous hematopoietic stem cell transplantation. A total of 26 (34%) patients in the EMD-B group and 41 (31%) patients in the non-EMD group underwent ASCT following induction. For patients not receiving ASCT, the ORR was 60.8% in the EMD-B group and 71.4% in the non-EMD group (*P* = .193). The CR rate of the EMD-B group was 15.7%, which was significantly lower than 31.9% in the non-EMD group (*P* = .035). For patients receiving ASCT, the ORRs were 76.9% in the EMD-B group and 85.4% in the non-EMD group (*P* = .701). Complete remission rates were increased and became comparable between the 2 groups (EMD-B vs non-EMD: 42.3% vs 48.8%, *P* = .626) (Table 5). For survival analysis of patients not receiving ASCT, the median OS time was significantly shorter in the EMD-B group than in the non-EMD group (49 months vs 75 months, *P* = .003). After receiving ASCT, there were no significant differences (EMD-B vs non-EMD: not reached vs 96 months, *P* = .505) (Figure 3). Furthermore, patients with EMD-B were divided into the ASCT group and no ASCT group. Survival analysis showed a significantly better median OS in the ASCT group than in the no ASCT group (ASCT vs no ASCT: not reached vs 49 months, *P* = .003) (Figure 4).

Discussion

The EMD-B is generally considered to have the same nature as intramedullary lesions in therapeutic response and long-term outcomes. However, their heterogeneities have rarely

Table 5. Treatment efficiency group by EMD-B and induction regimens.

| | ALL PATIENTS | | INDUCTION REGIMENS | | | | TRANSPLANTATION | | | |
| | | | PI + IMID | | PI + CHEMOTHERAPY | | ASCT | | NO ASCT | |
	EMD-B (N=77)	NON-EMD (N=132)	EMD-B (N=31)	NON-EMD (N=56)	EMD-B (N=46)	NON-EMD (N=76)	EMD-B (N=26)	NON-EMD (N=41)	EMD-B (N=51)	NON-EMD (N=91)
ORR	51 (66.2%)	100 (75.8%)	20 (64.5%)	41 (73.2%)	31 (67.4%)	59 (77.6%)	22 (84.6%)	37 (90.2%)	31 (60.8%)	65 (71.4%)
CR	16 (20.8%)	40 (30.3%)	6 (19.4%)	15 (26.8%)	10 (21.7%)	25 (32.9%)	11 (42.3%)	20 (48.8%)	8 (15.7%)	29 (31.9%)
VGPR	18 (23.4%)	29 (22.0%)	10 (32.3%)	15 (26.8%)	8 (17.4%)	14 (18.4%)	5 (19.2%)	8 (19.5%)	10 (19.6%)	17 (18.7%)
PR	17 (22.1%)	31 (23.5%)	4 (12.9%)	11 (19.6%)	13 (28.3%)	20 (26.3%)	6 (23.1%)	9 (22.0%)	13 (25.5%)	19 (20.9%)
MR	4 (5.2%)	3 (2.3%)	0 (0%)	0 (0%)	4 (8.7%)	3 (3.9%)	3 (11.5%)	1 (2.4%)	2 (3.9%)	2 (2.2%)
SD/PD/NE	22 (28.6%)	29 (22.0%)	11 (35.5%)	15 (26.8%)	11 (23.9%)	14 (18.4%)	1 (3.8%)	3 (7.3%)	18 (35.3%)	24 (26.4%)

Abbreviations: ASCT, autologous stem cell transplantation; CR, complete remission; EMD-B, bone-related extramedullary disease; IMID: immunomodulatory drug; MR, minimal response; NE, not evaluated; Non-EMD-B, no extramedullary disease; ORR, overall response rate; PD, progressed disease; PI, proteasome inhibitor; PR, partial response; SD, stable disease; VGPR, very good partial response.

been discussed. A previously reported meta-analysis enrolling 2332 myeloma patients including 243 with EMD-B demonstrated that patients with EMD-B had a median PFS of 24.3 months (95% CI: 21.2-28.2), with no significant differences compared with non-EMD patients (25.2 months, $P = .10$). There was a significantly lower 5-year OS rate in EMD-B versus non-EMD (51% vs 59%, HR [95% CI: 1.39 [1.13-1.70], $P = .001$).[10] Çiftçiler et al[11] also reported a poorer prognosis of transplant-eligible patients with EMD at diagnosis on 5-year OS ($P = .02$) than non-EMD. Consistent with these results, we found poor OS in patients with EMD-B (median OS: EMD-B vs non-EMD 52 months vs 96 months, $P = .043$) after adjustment by PSM.

At the same time, we analyzed the impact of EMD-B on survival through a Cox regression model. Single-factor analysis suggested age $\geqslant 60$ years, BMPC $\geqslant 47.5\%$, LDH $\geqslant 185$ U/L to be risk factors for OS, and ASCT was the only protective factor. We found that EMD-B was not significant in single-factor analysis, but did make sense in multifactor analysis, which means that interference factors—for example, age—cover up the real impact of EMD-B. In addition, the Cox regression analysis was also used after matching, which identified EMD-B as a risk predictor of OS as well as the protective effect of ASCT.

We analyzed the prognostic factors of 100 patients with EMD-B. It was surprising to find paravertebral lesions as an independent risk factor for OS (HR = 2.11, 95% CI: [1.02, 4.36], $P = .043$), especially in the setting of IgD type and age. No similar conclusion has ever been reported. A study of EBMT demonstrated that the number of EMD-Bs did not affect survival (3-year PFS: 50.5% vs 36.0%, $P = .71$; 3-year OS: 77.2% vs 91.7%, $P = .27$). We obtained the same result from the Cox regression analysis ($P = .700$). Cytogenetic data were also collected, but we did not find any differences. Other studies reported that some FISH detectable abnormalities may have an association with EMD. TP53 mutation/p53 deletion was found more frequently in patients with EMD-S (34.5% vs 11.9%). It might be important to assess the cytogenetic abnormalities of the EMD sample because marked dissociation has been found between bone marrow and mass tissue.[8] In addition to cytogenetic abnormalities, some antigens on myeloma cell surfaces are thought to have a more apparent correlation with EMD. CD56 is an adhesion molecule with decreased expression in patients with EMD. We found a lower rate of CD56 expression in the EMD-B group than in the non-EMD group (63.8% vs 72.1%), but without significance, which may be due to the limited sample size.

Management of MM has improved, most notably with the application of novel agents, but a few studies focus on plasmacytomas. Generally in clinical settings, patients eligible for transplantation receive PI-containing induction therapy to reduce the tumor burden before high-dose conditioning. Several groups have reported the effectiveness of bortezomib
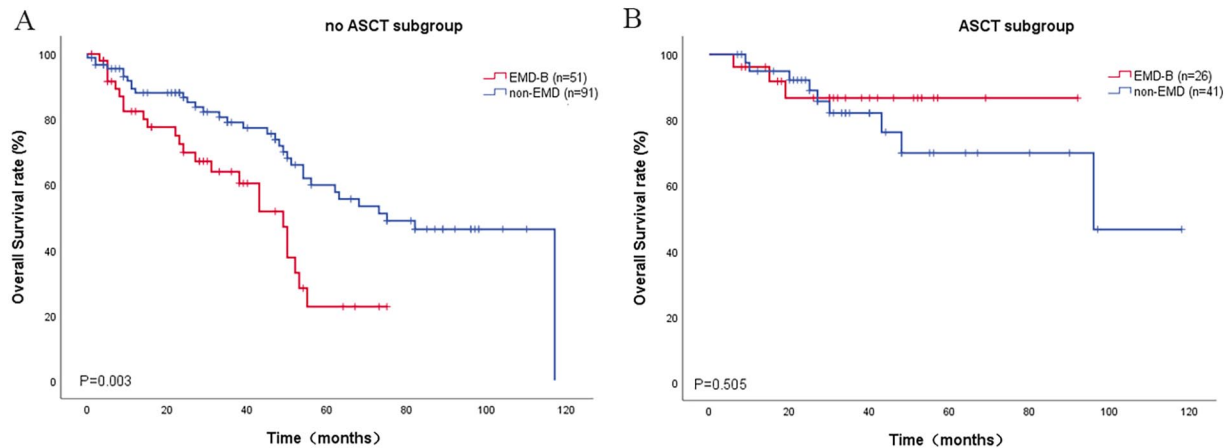
Figure 3. Kaplan-Meier curve of patients with extramedullary disease with bone-related (EMD-B) versus multiple myeloma patients without extramedullary disease (non-EMD). (A) Not receiving transplantation and (B) having received transplantation. ASCT indicates autologous stem cell transplantation.
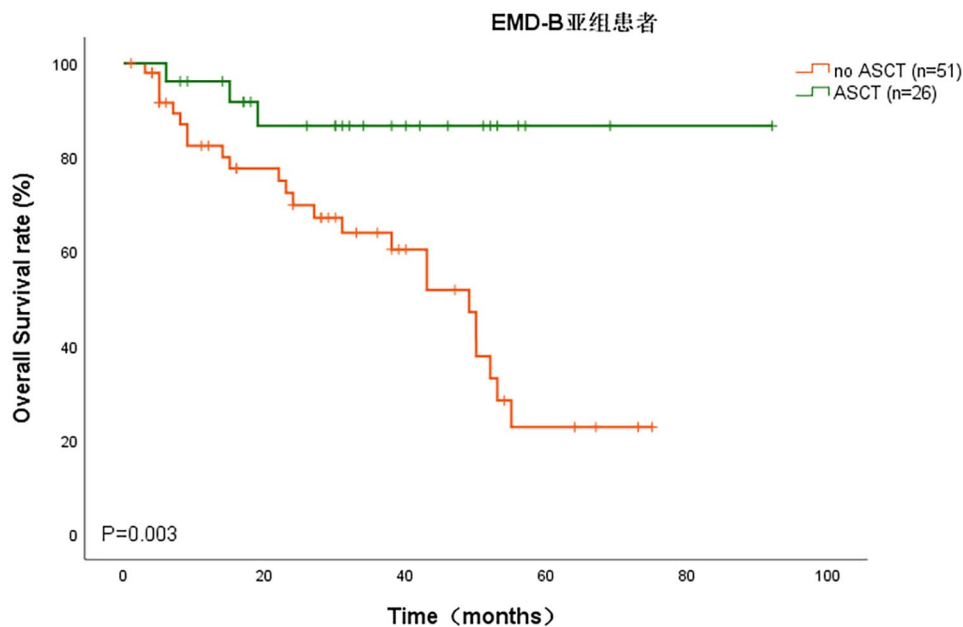

Figure 4. Kaplan-Meier curve of OS according to receiving ASCT or not in patients with extramedullary disease with bone-related (EMD-B).

on EMD.[10,12,13] PI-based induction is followed by ASCT as a backbone for transplant-eligible patients. Proteasome inhibitor + immunomodulatory drug–based (usually lenalidomide)[10] regimens or high-dose chemotherapy were generally chosen for others on personalized principles.[14] In our study, PI + IMiD did not show better effectiveness than PI + chemotherapy. Both were less efficient in the EMD-B group than in the non-EMD group (PI + IMiD: HR = 1.56, 95% CI: 0.66-3.70; PI + chemotherapy: HR = 1.70, 95% CI: 0.92-3.14).

The ASCT is the only way to eliminate tumor cells, including myeloma stem cells. Several studies have reported that ASCT is beneficial to patients with EMD. Varettoni et al[2] showed significantly poorer PFS in EMD patients using conventional chemotherapy compared with non-EMD (18 months vs 30 months, *P* = .03), which could be overcome by ASCT. From a study in the Balkan Myeloma Study Group and

Barcelona University, researchers demonstrated that ASCT can prolong the median PFS from 28.1 to 51.7 months in patients with EMD-B as well as from 11.4 to 46.5 months in patients with EMD-S (*P* < .001). Multivariate analysis showed that EMD-B (HR [95% CI]: 0.44 [0.21-0.92]), EMD occurrence at diagnosis (HR [95% CI]: 0.34 [0.23-0.51]), ISS-I (HR [95% CI]: 0.45 [0.28-0.73]), and ASCT (HR [95% CI]: 0.58 [0.38-0.89]) were protective factors of OS for patients with EMD.[7] However, non-EMD patients were not included in this study, so it is unclear whether ASCT can overcome the poor prognosis of EMD or the differences between EMD-B and non-EMD. In another retrospective study, 271 consecutive MM patients receiving ASCT were analyzed. Forty-four patients presented with EMD while not distinguishing EMD-B or EMD-S, in whom a significantly shorter median PFS (18 months vs 44 months, *P* < .001) and OS (32 months vs

100 months, $P < .001$) were found. Achievement of CR was an important positive predictor for both PFS and OS.[15] The study from EBMT analyzed a total of 3744 adult MM patients who had received ASCT. A total of 543 (14.5%) patients had EMD-B with a median PFS of 36 months. Similar 3-year PFS (50.0% vs 47.9%, $P = .78$) and 3-year OS (77.7% vs 80.1%, $P = .09$) were found between EMD-B and non-EMD patients. Autologous stem cell transplantation can significantly improve the 3-year PFS of patients with only 1 involved site (EMD-B: $P = .86$, EMD-S: $P = .88$), whereas it was not equally effective on OS.[3] Furthermore, research showed that tandem ASCT could not further improve the outcome of EMD-B patients compared with single ASCT (3-year PFS: 54.3% vs 59.4%, $P = .44$; 3-year OS: 80.3% vs 82.6%, $P = .88$).[3] However, Gagelmann et al reported that tandem ASCT can improve OS (HR [95% CI]: 0.46 [0.24-0.89], $P = .02$) and PFS (HR [95% CI]: 0.64 [0.42-0.96], $P = .03$) of NDMM patients with EMD and high-risk cytogenetics versus single ASCT.[16] Based on the above data, ASCT might be a recommended option in treating patients with EMD. In our study, we demonstrate that ASCT could significantly increase the CR rate as well as improve OS in newly diagnosed myeloma patients with EMD-B.

Our study has some limitations. First, this is a single-center, retrospective analysis, medical records are not as precise and scientific as prospective studies, and patients enrolled have selection bias. Thus, our sample size is not enough to make a convincing conclusion. Further investigations are needed to determine the optimal strategy for EMD-B management. Finally, our cases lack new treatment options around these years, and the minimal residual disease and pathologic data can be further improved and analyzed.

Conclusions

According to the results of our study, EMD-B is an independent risk predictor of survival in newly diagnosed MM patients, especially for those who are men, older, have a lower BMPC burden, and do not receive ASCT and ISS stage III. Their poor prognosis can be overcome by ASCT.

Author Contributions

YW, AL, and WC contributed to conception and design of the study. YW, TX, and JY organized the database. YW performed the statistical analysis. YW and AL wrote the first draft of the manuscript. All authors contributed to manuscript revision and approved the submitted version.

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Supplemental Material

Supplemental material for this article is available online.

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