Low Barthel index score is a poor prognostic factor for newly diagnosed multiple myeloma patients

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Abstract

Background: The basic activities of daily life may affect the prognosis of multiple myeloma (MM) patients and the Barthel index (BI) is currently the most widely used tool to evaluate basic activities of daily life, but few studies have evaluated its prognostic value in MM.

Methods: We retrospectively enrolled patients with newly diagnosed MM and analyzed the association between the BI and the survival of newly diagnosed MM patients.

Results: We totally analyzed 538 patients and found that median overall survival (OS) and progression-free survival (PFS) were significantly shorter in the low BI (≤85) group compared with the high BI (>85) group. Univariate Cox proportional hazards regression analysis showed that the low BI was associated with shorter OS and PFS. It was also confirmed that the low BI was poor prognostic factor for OS and PFS in multivariable analyses. In the propensity score matching analysis, patients with low BI also had shorter OS and PFS.

Conclusion: Our study suggested that the low BI was a poor prognostic factor for patients with newly diagnosed MM.

Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by abnormal proliferation of neoplastic plasma cells in bone marrow [1]. New therapeutic measures have greatly improved the survival of patients, but the survival heterogeneity of MM patients is large, and accurate evaluation of patients' prognosis is an important issue in the diagnosis and treatment of MM [2,3]. Staging system based on biochemical markers and cytogenetic abnormalities is a common prognostic indicator of MM, but the physical condition of MM patients also plays an important role in the prognosis [4]. The geriatric assessment (GA) scoring system of International Myeloma Working Group (IMWG), Fried model and Facon model are currently commonly used to evaluate patients' daily basic activity ability, which can screen out patients with MM who are vulnerable and develop personalized treatment regimens [5-7]. The basic activities of daily life may affect the prognosis of MM patients and can be used as a prognostic factor of MM patients. Barthel index (BI) is currently the most widely used tool to evaluate basic activities of daily life, but few studies have evaluated its prognostic value in MM.

We screened MM patients undergoing initial treatment in Beijing Chaoyang Hospital, Capital Medical University, and analyzed the prognostic value of BI in new diagnosed MM patients. We used propensity score matching techniques to balance the distribution of factors to overcome the influence of uneven distribution of prognostic factors on the results of the analysis. The aim of this study was to evaluate the prognostic value of BI for patients with newly diagnosed MM.

Methods

Patients

The baseline data of newly diagnosed MM patients in Beijing Chaoyang Hospital, Capital Medical University from May 1, 2009 to October 1, 2021 were collected. MM patients were diagnosed according to the IMWG diagnostic criteria, and all patients were followed up until May 1, 2022 [8]. We recorded baseline data of newly diagnosed MM patients by searching the Electronic Medical Record System (EMRS). We also followed the patients through the EMRS without disturbing patients in any way. Basel score is one of the routine evaluation indicators for inpatients, which is used to evaluate patients' self-care ability in Beijing Chaoyang Hospital, Capital Medical University. BI scores were calculated before induction therapy. BI consists of 10 items: feeding, bathing, grooming, dressing, defecation, bladder control, using the toilet, chair transfer, walking and climbing stairs. Each project was graded according to the amount of assistance required to complete each activity. Low BI was defined as a BI score of 85 or less and the rest as high BI group. The detection of cytogenetic abnormalities in MM patients by fluorescence in situ hybridization (FISH) was one of the routine tests in our research center. Prior to FISH testing, all patients' plasma cells were purified with anti-CD138 + magnetic beads. Then the aberrations of 17p13, 14q32 (IGH), 16q23 (MAF) and 4p16.3 (FGFR3) were analyzed by DNA probe. A total of 200 interphase nuclei were analyzed and the technical thresholds of cytogenetic abnormalities del (17 p), t (14; 16) and t (4; 14) were 20%, 10% and 10%, respectively.

Response and outcome measures

Patient efficacy was evaluated according to IMWG criteria [9], including strict complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), disease stability (SD), and disease progression (PD). The primary end point were progression free survival (PFS) and overall survival (OS). PFS was defined as from time of diagnosis to disease progression or death, and OS was defined as from time of diagnosis to death from any cause or last follow-up date. Patients who could not be followed up were censored at the date of last follow-up.

Statistical analysis

SPSS 23.0 software was used for statistical analysis. Variables that do not conform to normal distribution were described in the form of median (range). The classification variables were described in the form of sample number and percentage. The categorical variables were tested by the χ^2 or Fisher test. Survival analysis was performed using the Kaplan Meier method, and the comparison between groups was performed using the Log rank test. Univariate and multivariate Cox proportional hazards regression analyses were used to screen for prognostic factors in MM and results were reported as hazard ratios (HR) with 95% confidence intervals (CI). Propensity score matching technique can control the distribution of confounding factors between groups and reduce the interference of confounding factors on the result. In this study, propensity score matching was used to match low and high MM patients at a ratio of 1:1 to balance the distribution of prognostic factors among different groups. The caliper width was set as 0.2 of the Standard Deviation of the propensity score. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

Of 538 patients included in this study, 198 (36.8%) patients had low BIs (Table 1). The age ranged from 30 to 87 years, the median age was 60 years, and the male to female ratio was 1.21(295/243). The proportion of patients with IgG-type MM (49.2%) was the highest, and 269 (50.0%) were at International Scoring System (ISS) stage III. All patients received induction regimens containing at least one new drug (bortezomib, thalidomide, lenalidomide), 279 (51.9%) patients received bortezomib based regimens and 47(8.7%) patients received IMIDs-based regimens and 212(39.4%) patients received bortezomib combined with IMIDs. After induction therapy, 158 (29.4%) patients received autologous stem cell transplant (ASCT). As shown in Table 1, there were statistically significant differences between patients with low and high BI in sex, ISS stage, hemoglobin (HGB), serum creatinine (SCr), Corrected serum calcium (CsCa) and lactate dehydrogenase (LDH).

Table 1
Baseline clinical and biological characteristics of MM patients

	all patients	BI ≦ 85	BI > 85	
Characteristics	n = 538	n = 198	n = 340	
	n (%)	n (%)	n (%)	p value
Sex				
Male	295(54.8)	92(46.5)	203(59.7)	0.003
Female	243(45.2)	106(53.5)	137(40.3)	
Age				
≦ 65 years	376(69.9)	134(67.7)	242(71.2)	0.393
> 65 years	162(30.1)	64(32.3)	98(28.8)	
MM subtype				
IgG	296(49.3)	103(52.0)	162(47.6)	0.877
IgA	113(21.0)	39(19.7)	74(21.8)	
IgD	23(4.3)	7(3.5)	16(4.7)	
Light chain only	123(22.9)	44(22.2)	79(23.2)	
Non-secretory	14(2.6)	5(2.5)	9(2.6)	
ISS stage				
I	85(15.8)	15(7.6)	70(20.6)	0.000
II	184(34.2)	65(32.8)	119(35.0)	
III	269(50.0)	118(59.6)	151(44.4)	
Hemoglobin				
< 100 g/L	350(65.1)	140(70.7)	210(61.8)	0.036
≥ 100 g/L	188(34.9)	58(29.3)	130(38.2)	
Serum creatinine				
≤ 2mg/dL	422(78.4)	141(71.2)	281(82.6)	0.002
> 2mg/dL	116(21.6)	57(28.8)	59(17.4)	
Corrected serum calcium				
≤ 2.75 mmol/L	473(87.9)	158(79.8)	315(92.6)	0.000

	all patients	BI ≦ 85	BI > 85	
> 2.75 mmol/L	65(12.1)	40(20.2)	25(7.4)	
Lactate dehydrogenase				
≤ 250 U/L	467(86.8)	160(80.8)	307(90.3)	0.002
> 250 U/L	71(13.2)	38(19.2)	33(9.7)	
Cytogenetic abnormalities by FISH				
del(17p13)				
abnormality	51(9.5)	17(8.6)	34(10.0)	0.589
non-abnormality	487(90.5)	181(91.4)	306(90.0)	
t(14; 16)				
abnormality	20(3.7)	6(3.0)	14(4.1)	0.520
non-abnormality	518(96.3)	192(97.0)	326(95.9)	
t(4; 14)				
abnormality	99(18.4)	34(17.2)	65(19.1)	0.574
non-abnormality	439(81.6)	164(82.8)	275(80.9)	
Induction regimes				
Bortezomib based	279(51.9)	112(56.6)	167(49.1)	0.085
IMiD based	47(8.7)	20(10.1)	27(7.9)	
Bortezomib and IMiD based	212(39.4)	66(33.3)	146(42.9)	
ASCT				
Yes	158(29.4)	52(26.3)	106(31.2)	0.227
No	380(70.6)	146(73.7)	234(68.8)	
Abbreviations: BI: Barthel index; IMiD: immunomodulatory; ASCT: autologous stem cell transplant				

Multivariate Analysis For Survival

Univariate Cox proportional risk regression analysis showed that ten factors associated with OS: age > 65years, HGB ≥ 100g/L, LDH > 250U/L, SCr > 2mg/dl, CsCa > 2.75mmol/L, BI score ≤ 85, del(17p13), t(14; 16), ISS stage and ASCT (Table 2). Multivariate analysis was performed for these ten covariates and t(4; 14). Low BI in the multivariate analysis was independently associated with shorter OS (HR = 1.813, 95%CI: 1.346–2.442, p < 0.001). Other factors that were independently associated with OS in the

multivariate analysis included LDH > 250U/L, CsCa > 2.75mmol/L, del(17p13), t (14; 16) and ASCT (Table 2). A multivariate analysis for PFS was performed in same models and showed that low BI was also significantly associated with PFS (HR = 1.423, 95%CI: 1.117–1.814, p = 0.004) (Table 3).

Table 2
Cox analysis (univariate and multivariate) of prognostic factors for OS

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age > 65years	1.359	1.008–1.833	0.044			0.905
HGB ≥ 100g/L	0.609	0.439–0.845	0.003			0.180
LDH > 250U/L	2.348	1.659–3.324	0.000	1.989	1.393–2.839	0.000
SCr > 2mg/dL	1.988	1.462–2.702	0.000			0.140
CsCa > 2.75mmol/L	2.443	1.715–3.480	0.000	2.282	1.584–3.287	0.000
BI ≤ 85	1.987	1.493–2.643	0.000	1.813	1.346–2.442	0.000
del(17p13)	2.768	1.840–4.163	0.000	2.986	1.981-4.500	0.000
t(14; 16)	1.694	0.943–3.041	0.078	2.048	1.134–3.699	0.017
t(4; 14)	1.021	0.701–1.488	0.913			0.574
ISS stage			0.000			0.532
I	1.000	Ref				
II	1.797	1.002–3.223	0.049			
III	2.769	1.580–4.855	0.000			
Induction regimes			0.260			
Bortezomib based	1.000	Ref				
IMiD based	1.412	0.930–2.144	0.105			
Bortezomib and IMiD based	1.021	0.717–1.453	0.910			
ASCT	0.380	0.260–0.557	0.000	0.323	0.220–0.476	0.000

	Univariate	Multivariate
Abbreviations: HGB: hemoglobin; LDH: Lactate dehydrogenase; SCr: Serum creatinine; CsCa: corrected serum calcium; BI: Barthel index; IMiD: immunomodulatory; ASCT: autologous stem cell transplant		

Table 3
Cox analysis (univariate and multivariate) of prognostic factors for PFS

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Age > 65years	1.166	0.911–1.492	0.223			0.305
HGB ≥ 100g/L	0.637	0.493–0.824	0.001			0.102
LDH > 250U/L	1.676	1.235–2.275	0.001	1.461	1.064–2.006	0.019
SCr > 2mg/dL	1.727	1.334–2.235	0.000			0.160
CsCa > 2.75mmol/L	2.426	1.779–3.308	0.000	2.186	1.594–2.998	0.000
BI ≤ 85	1.640	1.299–2.070	0.000	1.423	1.117–1.814	0.004
del(17p13)	1.691	1.155–2.476	0.007	1.797	1.226–2.633	0.003
t(14; 16)	1.409	0.807–2.461	0.228			0.203
t(4; 14)	1.110	0.829–1.488	0.482			0.502
ISS stage			0.000			0.077
I	1.000	Ref				
II	1.585	1.025–2.451	0.038			
III	2.502	1.655–3.782	0.000			
Induction regimes			0.178			
Bortezomib based	1.000	Ref				
IMiD based	1.378	0.959–1.980	0.083			
Bortezomib and IMiD based	0.961	0.728–1.267	0.776			
ASCT	0.483	0.366–0.636	0.000	0.470	0.356–0.620	0.000

	Univariate	Multivariate
Abbreviations: HGB: hemoglobin; LDH: Lactate dehydrogenase; SCr: Serum creatinine; CsCa: corrected serum calcium; BI: Barthel index; IMiD: immunomodulatory; ASCT: autologous stem cell transplant		

Response

Patients with low and high BI were matched for LDH, CsCa, del(17p13), t (14; 16), ISS stage and ASCT. A total of 334 patients were screened out of 538 patients, 167 in each group. The results showed that there was no significant difference in any factor between low and high matched groups (Table 4). Response analysis showed that 471 (87.5%) patients achieved partial response (PR) or better after during treatment. One hundred and sixty-eight patients (31.2%) achieved stringent complete response (sCR), 55 (10.2%) achieved complete response (CR), 127 (23.6%) achieved very good partial response (VGPR), and 121 (22.5%) achieved PR. It showed that low BI patients had worse remission rates compared with the high group ($p = 0.001$, Table 5). Of the 334 matched patients, 288 (86.2%) patients achieved PR or better after induction treatment. One hundred and one patients (30.2%) achieved sCR, 35 (10.5%) achieved CR, 80 (24.0%) achieved VGPR, and 72 (21.6%) achieved PR. Patients with low BI had similar remission rates to the high group ($p = 0.165$, Table 5).

Table 4
Baseline characteristics between matched patients with low and high Barthel index

	all patients	BI ≦ 85	BI > 85	
Characteristics	n = 334	n = 167	n = 167	
	n (%)	n (%)	n (%)	p value
Age				
≦ 65 years	230(68.9)	110(65.9)	120(71.9)	0.237
> 65 years	104(31.1)	57(34.1)	47(28.1)	
MM subtype				
IgG	165(49.4)	86(51.5)	79(47.3)	0.675
IgA	76(22.8)	36(21.6)	40(24.0)	
IgD	14(4.2)	5(3.0)	9(5.4)	
Light chain only	73(21.9)	36(21.6)	37(22.2)	
Non-secretory	6(1.8)	4(2.4)	2(1.2)	
ISS stage				
I	29(8.7)	14(8.4)	15(9.0)	0.907
II	129(38.6)	63(37.7)	66(39.5)	
III	176(52.7)	90(53.9)	86(51.5)	
Hemoglobin				
< 100 g/L	233(69.8)	116(69.5)	117(70.1)	0.905
≥ 100 g/L	101(30.2)	51(30.5)	50(29.9)	
Serum creatinine				
≤ 2mg/dL	262(78.4)	130(77.8)	132(79.0)	0.790
> 2mg/dL	72(21.6)	37(22.2)	35(21.0)	
Corrected serum calcium				
≤ 2.75 mmol/L	291(87.1)	146(87.4)	145(86.8)	0.870
> 2.75 mmol/L	43(12.9)	21(12.6)	22(13.2)	
Lactate dehydrogenase				
≤ 250 U/L	291(87.1)	145(86.8)	146(87.4)	0.870

	all patients	BI ≦ 85	BI > 85	
> 250 U/L	43(12.9)	22(13.2)	21(12.6)	
Cytogenetic abnormalities by FISH				
del(17p13)				
abnormality	24(7.2)	13(7.8)	11(6.6)	0.672
non-abnormality	310(92.8)	154(92.2)	156(93.4)	
t(14; 16)				
abnormality	5(1.5)	4(2.4)	1(0.6)	0.176
non-abnormality	329(98.5)	163(97.6)	166(99.4)	
t(4; 14)				
abnormality	64(19.2)	28(16.8)	36(21.6)	0.266
non-abnormality	270(80.8)	139(83.2)	131(78.4)	
ASCT				
Yes	88(26.3)	44(26.3)	44(26.3)	1.000
No	246(73.7)	123(73.7)	123(73.7)	
Abbreviations: BI: Barthel index; IMiD: immunomodulatory; ASCT: autologous stem cell transplant				

Table 5
Best response rate of MM patients

Response	all patients		matched patients	
	BI ≦ 85	BI > 85	BI ≦ 85	BI > 85
	n = 198	n = 340	n = 167	n = 167
	n (%)	n (%)	n (%)	n (%)
sCR	50(25.3)	118(34.7)	48(28.7)	53(31.7)
CR	25(12.6)	30(8.8)	21(12.6)	14(8.4)
VGPR	49(24.7)	78(22.9)	42(25.1)	38(22.8)
PR	42(21.2)	79(23.2)	35(21.0)	37(22.2)
SD	16(8.1)	31(9.1)	12(7.2)	22(13.2)
PD	16(8.1)	4(1.2)	9(5.4)	3(1.8)

Abbreviations: sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

Survival

The median follow-up time for all patients was 27.7 (range 0.3-117.3) months. Among 538 patients, the median OS estimated by the Kaplan-Meier method were 43.2 (95% CI, 33.6–52.8) months and 69.8 (95% CI, 51.2–88.4) for low and high BI patients respectively ($p < 0.001$, Fig. 1A). The median PFS were 24.5 (95% CI, 18.9–30.1) months and 32.7 (95% CI, 27.2–38.2) for all patients with low and high BI respectively (< 0.001, Fig. 2A). The median OS estimated by the Kaplan-Meier method were 48.7 (95% CI, 38.4–59.0) months and 61.6 (95% CI, 49.8–73.4) for matched patients with low and high BI respectively ($p = 0.026$, Fig. 1B). The median PFS were 26.5 (95% CI, 22.1–30.9) months and 28.5 (95% CI, 21.5–35.5) for matched patients with low and high BI respectively ($p = 0.060$, Fig. 2B).

Discussion

In this study, we evaluated the prognostic value of BI score in patients with newly diagnosed MM. Low BIs were recorded in 36.8% patients and we found that the low BI was an independent poor prognostic factor for OS and PFS in patients with newly diagnosed MM. The propensity score matching analysis also showed that patients with low BI had shorter OS and PFS. However, patients with low BI had similar response rate compared with patients high BI.

Multiple myeloma is a hematological malignancy characterized by abnormal proliferation of neoplastic plasma cells in bone marrow, which may lead to systemic bone destruction and various clinical

manifestations. In the past 20 years, with the development of ASCT, proteasome inhibitors, immunomodulatories and immunotherapy, the survival of MM patients has been significantly prolonged [10–12]. However, due to the survival heterogeneity of MM patients, some patients can survive for more than 10 years, while the median survival time of some patients is only 1–2 years. Therefore, accurate evaluation of patients' prognosis is an important issue in the diagnosis and treatment of MM.

At present, the common clinical prognosis assessment system is mainly based on tumor factors and host factors. The clinical characteristics, physical status, tumor load and other indicators of MM patients play important impacts on the prognosis [13–16]. The age is an important prognostic factor for MM patients, studies showed that patients aged < 65 years had longer survival time than patients aged ≥ 65 years. Therefore, IMWG proposed the GA scoring system, which was based on the daily basic activity scale, instrumental activities of daily living ability assessment scale and Charlson comorbidity index scale, and gave comprehensive scores (0 ~ 5 points) according to patients' age, cognition, comorbidity and physical condition. According to the score, 869 newly diagnosed MM patients were divided into fit group (0 points), intermediate fitness group (1 point) and frail group (≥ 2 points). The 3-year OS rates of the 3 groups were 84%, 76% and 57%, respectively [5]. In addition, GA score system could also indicate the incidence of treatment-related toxic reactions, so it could provide certain reference information for the choice of treatment regimen for newly diagnosed MM patients [13, 17–19].

Since the GA score incorporates age into the system, patients over 75 were at most assigned to the moderate healthy group, which will limit treatment options for older patients with better physical performance. Murillo et al. [6] compared GA score with Fried score regardless of age in 98 elderly patients newly diagnosed with MM (median age 79 years) and found that frail patients screened by the latter had a greater decrease in 1-year total OS rate and a higher risk of death. It indicates that the model has better prognostic value and may be used to assess the physical status of MM patients.

It is also controversial that the GA score assumes that patient self-assessment is more reliable than physician assessment. Facon et al. [7] analyzed 1623 newly diagnosed MM patients and developed a scoring system that combined physician evaluation with patient self-evaluation. This system included age, Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group performance status (ECOG PS) and patients were divided into frail and nonfrail groups. Overall response rates were 72% and 79%, respectively, and PFS were 19.4 months and 24.0 months, respectively. Compared with GA score, Facon model had more significant prognostic evaluation advantages, and its method of dividing MM patients into two groups was more convenient for clinical practice than that of dividing MM patients into three groups. This model was also used to assess the general condition of MM patients to develop appropriate treatment [20–23].

Basic activities of daily life have a great impact on the prognosis of MM patients, which can be used as a prognostic factor of MM patients. The inability of patients to perform basic activities without assistance is an important indicator to evaluate host factors. Barthel index (BI) is currently the most widely used tool to evaluate basic activities of daily life, but few studies have evaluated its prognostic value in MM. In our

study, OS and PFS of patients with low BI was significantly shorter than that of other patients. Univariate and multivariate Cox proportional hazards regression analyses also suggested that low BI was a poor prognostic factor for newly diagnosed MM. Moreover, we used propensity-score matched analysis to balance covariate distributions between patients with low and high BI. It showed that the distribution of main factors which could affect outcome of MM patient had no significant difference between the two matched groups. Patients with low BI had significant shorter OS compared with other patients after balancing main factors. PFS was also shorter, though it had no statistical significance. As a result, low BI may be considered an independent poor prognostic factor for patients with newly diagnosed MM.

This study has several limitations. This study was a retrospective analysis with data from a single MM diagnosis and treatment center and the results need to be confirmed by more research centers. The new treatment significantly improved the survival of patients with MM, and the median follow-up time in this study was short, requiring long-term follow-up to verify the results. After the initial treatment in our center, some patients were transferred to other centers for further treatment, leading to the loss of follow-up of some patients, which may affect the results of the study.

In conclusion, our study demonstrated that low BI was an independent poor prognostic factor for patients with newly diagnosed multiple myeloma. It needs further study to confirm its prognostic value of BI for newly diagnosed MM.

Declarations

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Not applicable.

Author Contributions

C G and W C designed the analysis and wrote the manuscript. G Y, H W, H Z, Y L and Y L collected and interpreted the data. Z Z and Y J performed the statistical analysis. All authors reviewed and approved the final version of the manuscript.

Disclosure of interest

The authors report no conflict of interest.

Ethics approval and consent to participate

This study has been approved by the Medical Ethics Committee of Beijing Chaoyang Hospital. No informed consent was required, because the data are anonymized.

Data availability statement

The authors confirm that the data that support the findings of this study are available from Wenming Chen, upon reasonable request.

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Figures

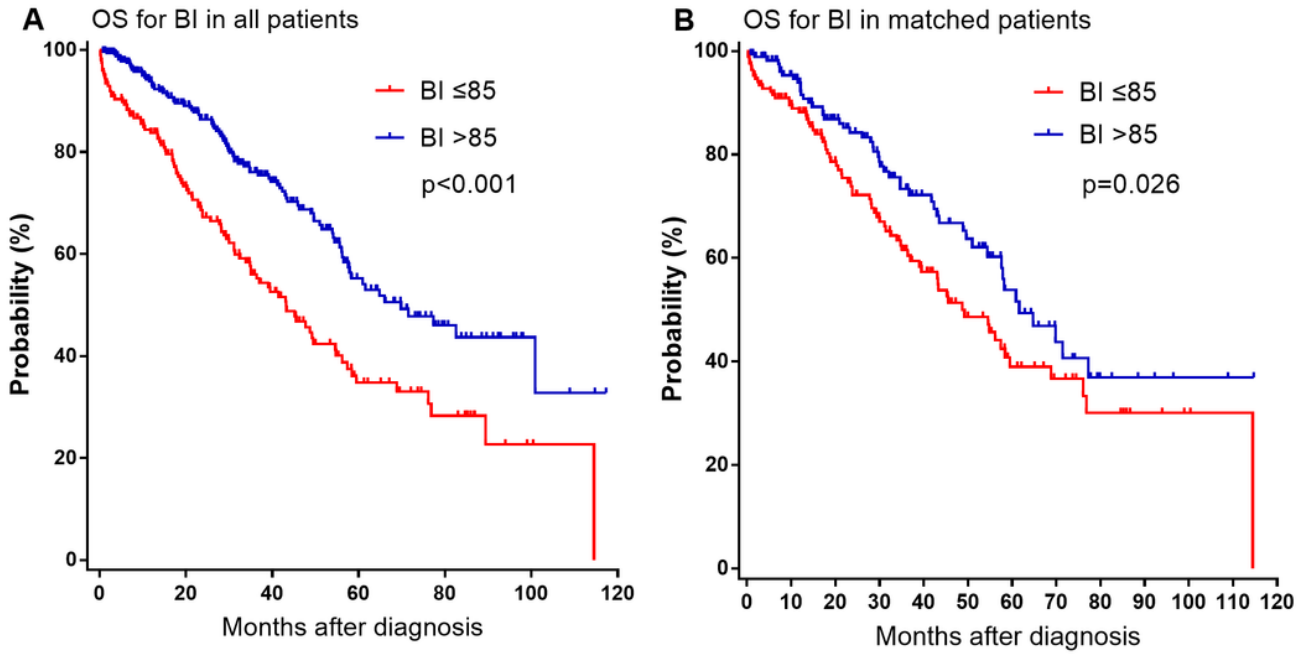

Figure 1

Kaplan-Meier survival curves on OS of patients with newly diagnosed MM. (A) all patients. (B) matched patients.

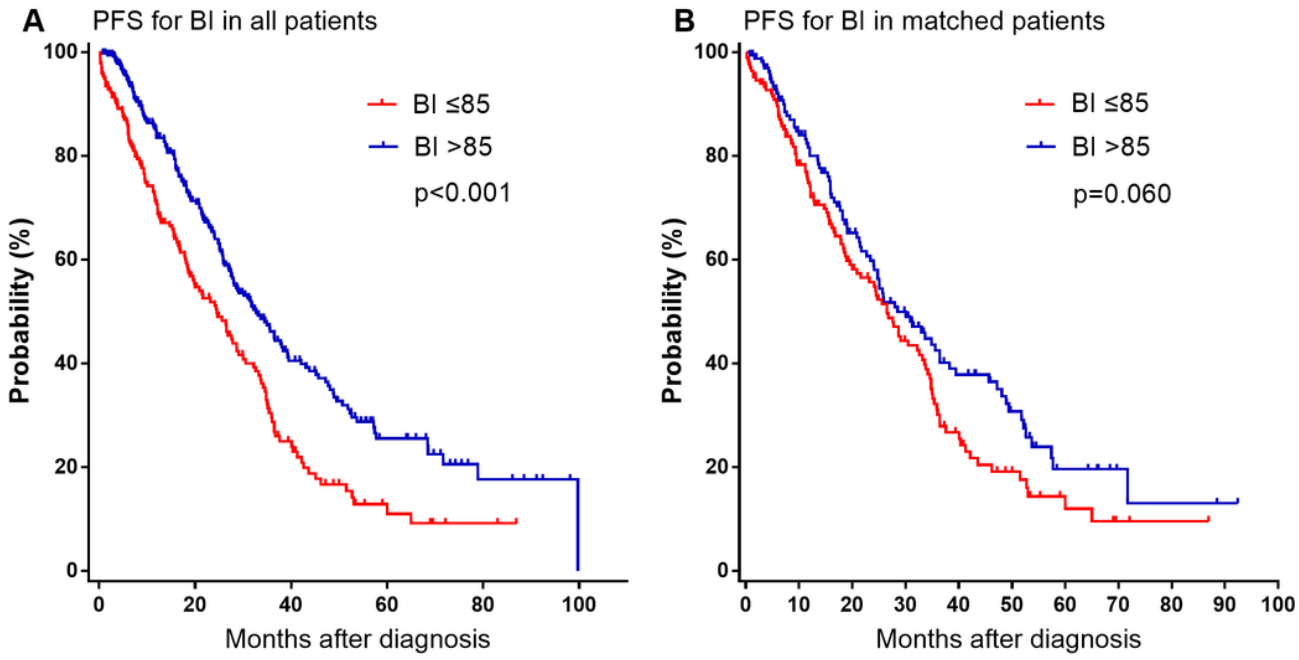

Figure 2

Kaplan-Meier survival curves on PFS of patients with newly diagnosed MM. (A) all patients. (B) matched patients.