Leukemia Research 81 (2019) 19–24

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Clinical presentation and prognosis of immunoglobulin light-chain amyloidosis with high percentage of bone marrow plasma cells

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ARTICLE INFO

Keywords:
Light-chain amyloidosis
Bone marrow plasma cells
Outcome

ABSTRACT

Objective: To summarize the clinical features and outcomes in Chinese patients with immunoglobulin light-chain (AL) amyloidosis with ≥10% bone marrow plasma cells (BMPCs).
Methods: We retrospectively compared the clinical features and outcomes between patients with ≥10% BMPCs (high-BMPC group; n = 56) and those with < 10% BMPCs (low-BMPC group; n = 311).
Results: Patients in the high-BMPC group had significantly higher levels of N-terminal pro-brain natriuretic peptide, significantly lower levels of 24 h urine protein, and significantly higher levels of difference between the involved and uninvolved serum free light chains (485.3 versus 121.1 mg/L, P < 0.001). Patients in the high-BMPC group had significantly higher early mortality within 3 months of diagnosis (21.4% versus 10.9%, P = 0.018). In a 3-month landmark analysis, median progression-free survival durations were 17.3 and 34.5 months (P = 0.01), and the median overall survival durations were 24.4 months and not reached in the high- and low-BMPC groups, respectively (P = 0.005).
Conclusion: Patients with AL amyloidosis and ≥10% BMPCs have higher mortality within 3 months of diagnosis and poorer prognosis compared with patients with < 10% BMPCs.

1. Introduction

Primary systemic light-chain (AL) amyloidosis is characterized by the presence of monoclonal plasma cells and deposition of misfolded immunoglobulin light chain in various organs [1]. The outcome of patients with AL amyloidosis is highly dependent on the spectrum and severity of organ involvement, especially cardiac involvement [2,3]. Patients with Mayo 2004 stages 1–3 have median overall survival (OS) durations of 27.2, 11.1, and 4.1 months, respectively [2]. Moreover, difference between the involved and uninvolved serum free light chain (dFLC) is a powerful tool for assessing tumor burden and defining prognosis, and has thus been added to the revised 2012 staging prognostic system [3,4]. In addition to dFLC, previous studies reported that measurement of monotypic bone marrow plasma cells (BMPCs) by multiparameter flow cytometry had prognostic value in patients with AL amyloidosis [5,6]. Furthermore, some studies showed that patients with > 10% BMPCs were more likely to have cardiac involvement but less likely to have kidney involvement, and had a poorer prognosis than patients with ≤10% BMPCs [7,8]. In this study, we aimed to analyze the correlations between the percentage of BMPCs, clinical features, and outcomes in a cohort of Chinese patients with AL amyloidosis.

2. Materials and methods

2.1. Patients

Clinical and laboratory data, treatment, hematologic and organ responses, and follow-up information were analyzed retrospectively for 367 patients with newly diagnosed AL amyloidosis at Peking Union Medical College Hospital, China, between January 2009 and December 2017. Multiple myeloma, as defined by the CRAB (hypercalcemia, renal failure, anemia, and lytic bone lesions) criteria, had been excluded in all these patients [9]. The diagnosis of AL amyloidosis was confirmed by the presence of Congo red-positive fibril deposition on biopsy and green birefringence under polarized light. Information on monoclonal protein on serum protein electrophoresis, serum/urine immunofixation

Abbreviations: AL amyloidosis, immunoglobulin light-chain amyloidosis; BMPCs, bone marrow plasma cells; dFLC, difference between the involved and uninvolved serum free light chain; ASCT, autologous stem cell transplantation

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https://doi.org/10.1016/j.leukres.2019.04.002
Received 24 January 2019; Received in revised form 20 March 2019; Accepted 6 April 2019
Available online 08 April 2019

Table 1
Baseline clinical characteristics of the patients (n = 367). cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; 24hUP, 24 h urine protein; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; dFLC, difference between involved and uninvolved free light chains; BMPCs, bone marrow plasma cells.

Characteristics	Low-BMPC group (n = 311)	High-BMPC group (n = 56)	P value
Gender (male/female), n	208/103	32/24	0.158
age, years (median, range)	57(37–84)	58.5(20–78)	0.840
involved light chain type(κ/λ), n	89/222	17/39	0.791
laboratory examination			
cTnI, ug/L (median, range)	0.050(0–1.945)	0.062(0–11.800)	0.369
NT-proBNP, pg/ml, (median, range)	2028(7–103277)	4540(50–24156)	0.010
24hUP, g, (median, range)	2.78(0–27.92)	1.02(0–8.540)	< 0.001
eGFR < 60 ml/min/1.73m^2, n (%)	65(20.9%)	5(8.9%)	0.036
ALP, U/L, (median, range)	85(25–2637)	86(39–770)	0.986
dFLC, mg/L, (median, range)	121.1(0.6–4263.0)	485.3(17.0–4953.5)	< 0.001
BMPCs, %, (median, range)	3.5(0–9.5)	13(10.0–34.5)	< 0.001
Organ involvement			
heart involvement, n (%)	219(70.4%)	46(82.1%)	0.071
kidney involvement, n (%)	226(72.7%)	35(62.5%)	0.122
liver involvement, n (%)	66(21.2%)	14(25.0%)	0.528
Number of important organ involved, n(%)			0.288
0	8(2.6%)	3(5.4%)	
1	124(39.9%)	20(35.7%)	
2	150(48.2%)	24(42.9%)	
3	29(9.3%)	9(16.1%)	
Mayo stage 2004: n (%)			0.183
Stage 1	77(28.5%)	8(16%)	
Stage 2	100(37%)	22(44%)	
Stage 3	93(34.4%)	20(40%)	
Mayo stage 2012: n (%)			0.001
Stage 1	88(35.6%)	3(6.5%)	
Stage 2	54(21.9%)	12(26.1%)	
Stage 3	58(23.5%)	16(34.8%)	
Stage 4	47(19%)	15(32.6%)	

electrophoresis, or free light chain measurement using Freelite™ (The Binding Site, Birmingham, UK) was available for all patients. AL amyloidosis subtype was identified by laser micro-dissection/mass spectrometry, immunofluorescence, or immunohistochemistry [10]. Amyloid-related organ involvement was assessed according to the 2005 consensus criteria and based on biopsy of the affected organ, biopsy at an alternate site [11]. Only heart, kidney, and liver were included, to estimate the number of important organs involved. Mayo stage was determined when available, using both the 2004 and 2012 criteria [2,3]. The study was approved by the Peking Union Medical College Hospital Ethic's Committee.

2.2. BMPCs

Bone marrow samples were obtained by aspiration at diagnosis and were used to produce Wright Giemsa-stained bone marrow smears according to standard procedures. BMPCs were identified under optical microscopy by senior experienced cytologists, and 200 bone marrow nucleated cells were systematically counted in random areas. Patients were then assigned to the high-BMPC group (BMPCs ≥10%) or low-BMPC group (BMPCs < 10%) according to their initial percentage of BMPCs. We did not count plasma cells in bone marrow biopsy stained with CD138. And if the bone marrow aspiration was diluted, we would repeat the aspiration to ensure the quality of sample in our clinical practice.

2.3. Organ and hematologic response assessment

Hematologic response and organ response were evaluated after each cycle of treatment or every 3 months after completion of treatment. Hematologic response was based on consensus criteria [12], according to the dFLC: complete response (CR), very good partial response (VGPR), partial response (PR), and no response (NR). CR was defined as a normal ratio of serum FLC with negative serum and urinary immunofixation electrophoresis; VGPR was defined as a dFLC of < 40 mg/L; and PR was defined as a dFLC reduction of 50%. The overall hematologic response rate was defined as the ratio of patients who achieved a hematologic response equal to or better than PR. Organ response was evaluated according to the consensus guidelines for the conduct and reporting of clinical trials in systemic AL amyloidosis [13,14].

2.4. Follow-up

The last follow-up was on January 31, 2018. OS was defined as the time from diagnosis to death from any cause or last follow-up, and progression-free survival (PFS) was defined as the time from diagnosis until progression or death. Early death was defined as death within 3 months of diagnosis.

2.5. Statistical analysis

Continuous data were presented as median and range. Categorical variables were compared between two groups using χ^2 or Fisher's exact test (in case of expected numbers < 5), and continuous variables were compared using Mann–Whitney tests. Survival curves were plotted according to the Kaplan–Meier method, and compared between groups using the log-rank test. Statistical analysis was performed using SPSS software (v23.0; IBM, Armonk, NY, USA). All statistical tests were two-sided with a P value < 0.05 considered significant.

3. Results

3.1. Baseline characteristics

The 367 patients with AL amyloidosis included 56 (15.3%) in the high-BMPC group and 311 (84.7%) in the low-BMPC group. The baseline demographics and clinical characteristics of the two groups are summarized in Table 1. There was no significant difference in median age at diagnosis, sex, or involved light chain type between the two groups. Levels of the cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP) were significantly higher in patients in the high-BMPC group (4540 versus 2028 pg/ml, P = 0.01), but 24 h urine protein was significantly lower (1.02 versus 2.78 g, P < 0.001). The median dFLC was significantly higher in the high-BMPC group compared with the low-BMPC group (485.3 versus 121.1 mg/L, P < 0.001).

3.2. Organ involvement and Mayo risk stratification

There was no significant difference in organ involvement, including heart, kidney, and liver, between the two groups. The Mayo 2004 and Mayo 2012 staging system scoring distributions were available for 320 (87.2%) and 293 (79.8%) patients, respectively. There was a significant difference in stage distribution according to the Mayo 2012 staging system (P = 0.001) but not according to the Mayo 2004 staging system. Three (6.5%), 12 (26.1%), 16 (34.8%), and 15 (32.6%) patients in the high-BMPC group were diagnosed with Mayo 2012 stages 1–4 disease, respectively, compared with 88 (35.6%), 54 (21.9%), 58 (23.5%), and 47 (19%) patients in the low-BMPC group (Table 1).

3.3. Treatment

Sixty-seven (18.3%) patients did not receive any chemotherapy due to poor economic or physical conditions or early death. The first-line treatment regimens used by the 367 patients are presented in Table 2. There was no significant difference in treatment choice between the two groups (P = 0.081). Bortezomib-based treatment was the most frequently used first-line treatment in both groups, used by 123 (39.5%) patients in the low-BMPC group and 27 (48.2%) patients in the high-BMPC group. Melphalan-based regimens were used in 63 (20.3%) patients in the low-BMPC group compared with 12 (21.4%) in the high-BMPC group. Thirty-five (11.2%) and five (8.9%) patients in the low- and high-BMPC groups, respectively, chose immunomodulatory drugs, including thalidomide- and lenalidomide-based treatment as first-line therapy. Autologous stem cell transplantation (ASCT) was administered to 34 (10.9%) and one (1.8%) patients in the low- and high-BMPC groups, respectively.

3.4. Hematologic and organ responses

Among the patients who received therapy, 258 (86%) were evaluable for hematologic response and organ response, while the other 42 (14%) could not be evaluated due to unavailable laboratory results after chemotherapy. Five patients in the high-BMPC group (12.5%) achieved CR, nine (22.5%) achieved VGPR, and six (15%) achieved PR, compared with 88 (40.4%) CR, 48 (22.0%) VGPR, and 20 (9.2%) PR in the low-BMPC group. The overall hematologic response rate was significantly lower in the high-BMPC group compared with the low-BMPC group (50.0% versus 71.6%, P = 0.007). The organ response rate was also significantly lower in the high- compared with the low-BMPC group (27.5% versus 45.4%, P = 0.035). The best hematologic and organ responses in the available patients are listed in Table 3.

Table 2
First-line treatment of 367 patients. ASCT, autologous stem cell transplantation.

First-line therapy	Low-BMPC group(n = 311)	High-BMPC group(n = 56)
Bortezomib-based	123(39.5%)	27(48.2%)
Melphalan-based	63(20.3%)	12(21.4%)
Lenalidomide-based	15(4.8%)	0(0%)
Thalidomide-based	20(6.4%)	5(8.9%)
ASCT	34(10.9%)	1(1.8%)
No therapy	56(18.0%)	11(19.6%)

Table 3
Hematologic and organ responses of 258 evaluable patients. CR, complete response; VGPR, very good partial response; PR, partial response; NR, no response.

Response	Low-BMPC group(n = 218)	High-BMPC group(n = 40)	P value
Best hematologic response, n (%)			0.004
CR	88(40.4%)	5(12.5%)	
VGPR	48(22%)	9(22.5%)	
PR	20(9.2%)	6(15%)	
NR	62(28.4%)	20(50%)	
Overall hematologic response, n (%)	156(71.6%)	20(50%)	0.007
Organ response, n (%)	99(45.4%)	11(27.5%)	0.035
cardiac response, n (%)	43/141(30.5%)	8/32(25%)	
renal response, n (%)	74/166(44.6%)	5/24(20.8%)	
liver response, n (%)	12/47(25.5%)	3/12(25%)	

3.5. Survival

After a median follow-up time of 21.7 months (range, 1.1–120.8) for surviving patients, 30 (53.6%) patients died in the high-BMPC group and 108 (34.7%) died in the low-BMPC group, including 12 (21.4%) and 34 (10.9%) who died within 3 months of diagnosis in the high- and low-BMPC groups, respectively. The incidence of early mortality within 3 months of diagnosis was significantly higher in the high-BMPC group (P = 0.018). In a 3-month landmark analysis, the median PFS was 17.3 months in the high-BMPC group compared with 34.5 months in the low-BMPC group (P = 0.01) (Fig. 1A), while the median OS was 24.4 months in the high-BMPC group but was not reached in the low-BMPC group (P = 0.005; Fig. 1B). Among 300 (81.7%) patients who received chemotherapy, the median PFS was 12.9 months in the high-BMPC group compared with 31.9 months in the low-BMPC group (P < 0.001; Fig. 1C), and the median OS was 17.6 months in the high-BMPC group but was not reached in the low-BMPC group (P < 0.001; Fig. 1D).

Among patients who did not receive novel drugs (bortezomib or lenalidomide) as part of their first-line therapy, both PFS and OS were significantly lower in the high- compared with the low-BMPC group (13.9 versus 29.4 months, P = 0.0075 and 18.2 versus 59.9 months, P = 0.0386, respectively) (Fig. 2A and B). Among the patients who did receive novel drug-based first-line therapy, there was still a significant difference between the groups in terms of PFS and OS (PFS: 10.2 months in the high-BMPC group versus 22.3 months in the low-BMPCs group, P = 0.0149; OS: 16.2 months in the high-BMPC group versus not reached in the low-BMPC group, P = 0.0495; Fig. 2C and D).

To elucidate interactions between BMPCs and other variables, a multivariate Cox proportional hazards model was built, which included the Mayo 2004 staging system, dFLC, BMPCs and history of ASCT. BMPCs ≥10% retained its independent prognostic value for worse PFS (HR = 1.835; 95% CI, 1.198–2.810; P = 0.005) and OS (HR = 1.655; 95% CI, 1.033–2.650; P = 0.036). But history of ASCT did not have prognostic value for PFS (P = 0.247) nor OS (P = 0.098) in the multivariate analyses.

4. Discussion

AL amyloidosis is usually considered to present a low tumor burden

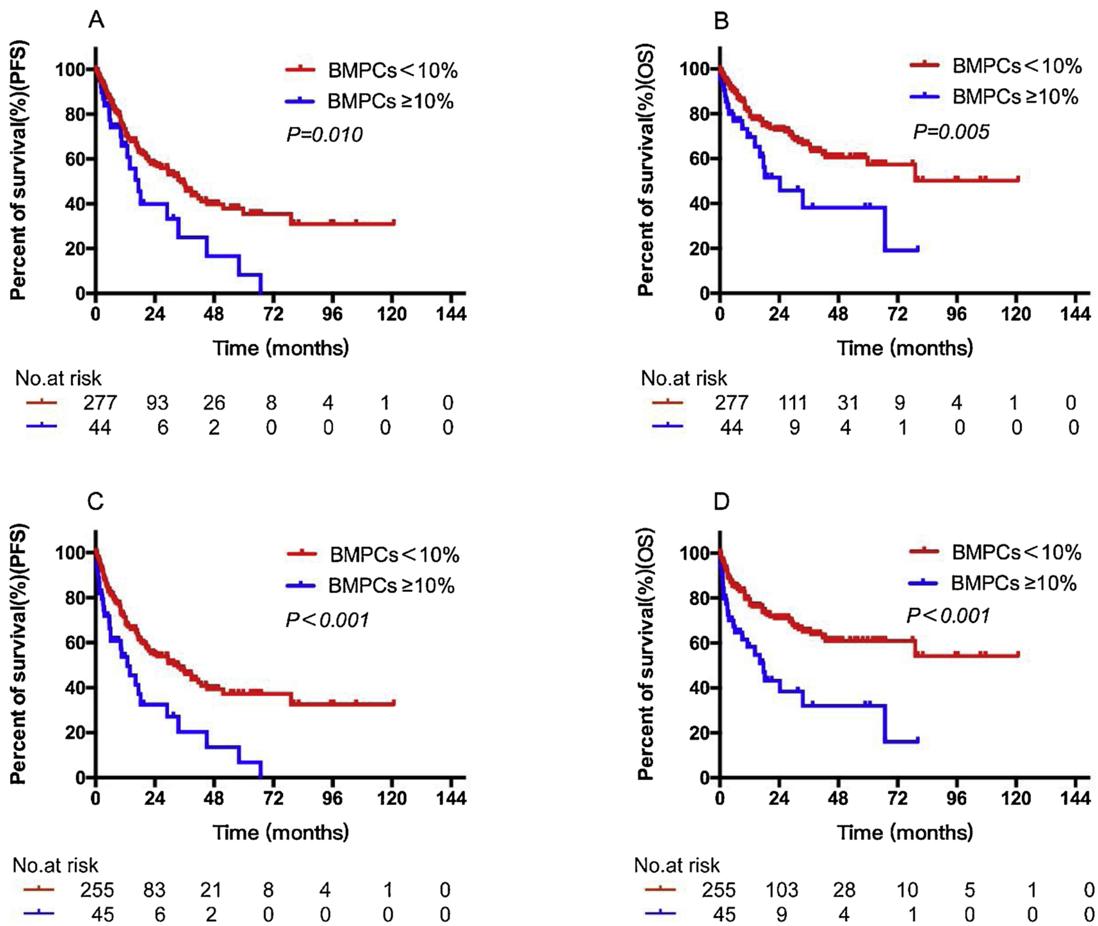

Fig. 1. Survival outcomes according to a BMPC threshold of 10%. (A) PFS and (B) OS among patients who survived for more than 3 months. (C) PFS and (D) OS among patients who received chemotherapy.

with a median BMPC infiltration of 7%–10% compared with multiple myeloma. Previous authors suggested that increased BMPCs had prognostic value and were associated with high FLCs and organ involvement in AL amyloidosis [8,15,16]. However, BMPCs as a prognostic factor or as a parameter for directing therapy in AL amyloidosis have largely been ignored in routine clinical practice. The current study showed that patients with AL amyloidosis and ≥10% BMPCs had distinct clinical characteristics, higher early mortality within 3 months of diagnosis, and a poorer prognosis than patients with < 10% BMPCs.

A study from Spain showed that cardiac involvement was more frequent in patients with > 10% BMPCs, but kidney involvement was more frequent in patients with ≤10% BMPCs [8]. In our cohort, patients in the high-BMPC group had significantly higher levels of NT-proBNP and lower levels of 24 h urine protein. Furthermore, patients with ≥10% BMPCs showed a trend towards more cardiac involvement and less kidney involvement (82.1% of patients with cardiac involvement in the high-BMPC group versus 70.4% in the low-BMPC group, P = 0.071; 62.5% of patients with kidney involvement in the high-BMPC group versus 72.7% in the low-BMPC group, P = 0.122). This might be due to a positive correlation between BMPCs and dFLC [8], and the direct cardiotoxicity of a high level of free light chain [17,18], but the biological basis of this phenomenon needs further investigation.

In addition, a Spanish study found that patients with > 10% BMPCs showed a trend towards higher early mortality within 1 year of diagnosis (27% versus 11%, P = 0.08) [8]. Similarly, our cohort showed significantly higher early mortality within 3 months of diagnosis in patients in the high- compared with the low-BMPC group (21.4% versus 10.9%, P = 0.018). The higher early mortality might be due to the more frequent cardiac involvement in patients with > 10% BMPCs.

The prognosis of AL amyloidosis depends mainly on the presence and degree of cardiac involvement, as well as the tumor burden. Tumor burden is usually measured by the dFLC, which was included in the revised 2012 staging prognostic system, together with cardiac biomarkers, due to their proven independent prognostic value [3]. BMPCs are a source of free light chains and are therefore positively correlated with dFLC [8]. A previous study from the Mayo Clinic reported that patients with AL amyloidosis who had > 10% BMPCs had a similar prognosis to AL amyloidosis patients with CRAB, but poorer than that of AL amyloidosis patients with < 10% BMPCs (16 versus 10.6 versus 46 months, respectively, P < 0.001) [7]. Another study from Spain showed that the median PFS was 48 months among patients with ≤10% BMPCs compared with 18 months for those with > 10% BMPCs (P = 0.02), and the median OS was also significantly higher in the ≤10% compared with the > 10% BMPC group (not reached versus 33 months, P = 0.046) [8]. In the current cohort, patients with ≥10% BMPCs had shorter PFS and OS. Among patients who survived 3 months, the median PFS durations in the low- and high-BMPC groups were 34.5 and 17.3 months, respectively (P = 0.01), while the median OS was not reached in the low-BMPC group, compared with 24.4 months in the high-BMPC group (P = 0.005).

A Spanish study [8] found that the presence of > 10% of BMPC infiltration was associated with significantly shorter PFS and OS among patients who did not receive a novel drug (bortezomib or lenalidomide) as first-line therapy, but there was no significant difference in PFS or OS between the high- and low-BMPC groups among those who did receive novel drugs. They therefore suggested that treatment with so-called novel drugs might overcome the negative prognostic impact of a high BMPCs infiltration [8]. However, there were significant differences in

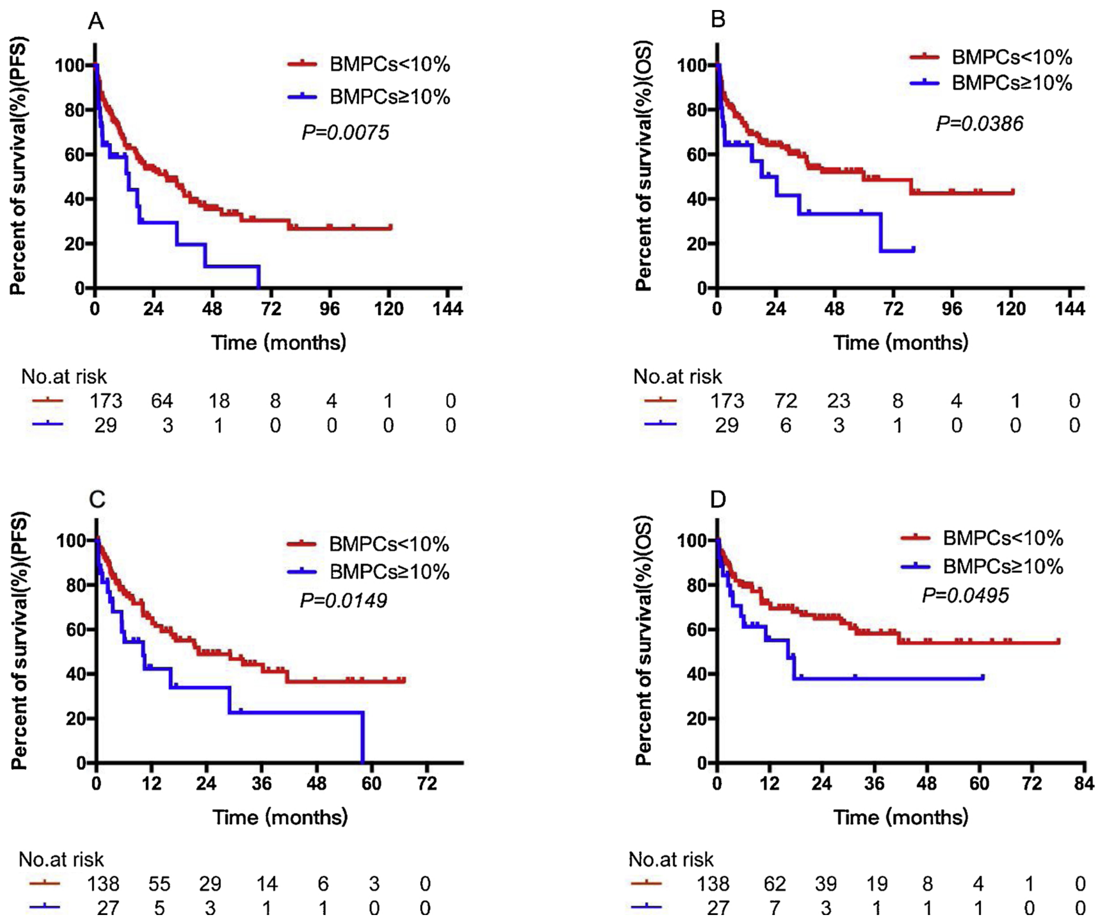

Fig. 2. Survival outcomes according to a BMPC threshold of 10%. (A) PFS and (B) OS among patients who did not receive novel drugs (bortezomib or lenalidomide). (C) PFS and (D) OS among patients who received novel drugs.

PFS and OS between the high- and low-BMPC groups in the present cohort, irrespective of the use of novel drugs, suggesting that bortezomib or lenalidomide-based therapy might not overcome the negative prognostic impact of high BMPCs. A study from Boston including 546 patients with AL amyloidosis who underwent ASCT showed that > 10% and < 30% BMPCs were not poor prognosis factors. The median OS for patients with ≤10% and > 10% BMPCs was 7.86 and 6.8 years, respectively (P = 0.7) [19]. Because relatively few patients in our cohort received ASCT, we did not compare post-transplant survival between the two groups. However, the current study was a retrospective study from a single center, and the results therefore need to be confirmed by other studies.

In conclusion, we compared the distinct clinical characteristics and outcomes between patients with ≥10% and those with < 10% BMPCs in a cohort of Chinese patients with AL amyloidosis. Our results suggest that patients with a higher percentage of BMPCs have a poorer prognosis and are more likely to suffer early mortality than patients with a lower percentage of BMPCs.

Declarations of interest

None.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 81570195, for LJ), Beijing Natural Science Foundation (Grant No. 7182128, for LJ), Foundation for Distinguished Young Physician of Peking Union Medical College Hospital (Grant No. JQ201501, for LJ), the CAMS Innovation Fund for Medical Sciences (Grant No. 2016-12M-1-002, for LJ), and The National Key Research and Development Program of China (Grant No. 2016YFC0901503, for LJ).

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