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ORIGINAL RESEARCH

Clinical Characteristics and Prognostic Value of Circulating Plasma Cells in Newly Diagnosed Multiple Myeloma Patients in China

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Background: Newly diagnosed multiple myeloma (MM) patients with circulating plasma cells (CPC) had worse prognosis, and it was important to investigate the prognostic value of CPC for newly diagnosed MM.

Methods: We retrospectively enrolled 718 patients with newly diagnosed MM and used propensity score matching to reduce the effect of different distributions of prognostic factors on the outcome.

Results: We totally analyzed 718 patients included 103 (14.3%) patients with CPC and 615 (85.7%) patients without CPC. Median overall survival (OS) (35.1 months vs 57.4 months, p <0.001) and progression-free survival (PFS) (17.2 months vs 25.8 months, p =0.002) were significantly shorter in patients with CPC compared with that of patients without CPC. Univariate Cox proportional hazards regression analysis showed that CPC was associated with shorter OS (HR=1.740, 95% CI: 1.293–2.342, p<0.001) and PFS (HR=1.486, 95% CI: 1.149–1.921, p=0.003). However, it was showed that CPC was not an independent poor prognostic factor for OS (p=0.243) and PFS (p=0.228) in multivariable analyses. In the propensity score matching analysis, patients with CPC had similar OS (p=0.309) and PFS (p=0.686) to patients without CPC.

Conclusion: Our study suggested that newly diagnosed MM patients with CPC had poor outcome, but CPC was not an independent poor prognostic factor for patients with newly diagnosed MM.

Keywords: multiple myeloma, circulating plasma cells, survival, prognosis

Introduction

In recent years, with the application of new treatment measures, the survival of MM patients has been significantly prolonged.[1–3] However, MM is a very heterogeneous disease and the survival of patients ranged from a few months to more than ten years. Therefore, screening accurate prognostic indicators to assess the prognosis of patients and formulating accurate individualized treatment plan is an important issue in the diagnosis and treatment of MM. The presence of circulating plasma cells (CPC) in peripheral blood of MM patients was a marker of highly proliferative myeloma disease. It had been suggested that MM patients who had more than 5% CPCs in their peripheral blood had the same short survival as those with plasma cell leukemia.[4] Klimienė I et al[5] believed that the adherent immunophenotype of bone marrow MM cells determines the presence of CPCs in peripheral blood and disease progression. The loss of adhesion molecule expression may cause PCs to leave the bone marrow environment and enter peripheral blood. Other studies also suggested that CPC was associated with some prognostic factors of MM and high level of CPC was a poor prognostic factor for MM.[6–10]

Although current studies suggest that CPCs is a poor prognostic factor for MM, the impact of CPCs on survival has been insufficiently studied. In particular, there are few studies on large samples of Chinese population. This retrospective study enrolled consecutive patients with newly diagnosed MM who received novel agent-based first-line therapy such as

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proteasome inhibitors and immunomodulatory drugs in Beijing Chaoyang Hospital, Capital Medical University between May 1, 2009 and October 1, 2021. We investigated clinical characteristics and the prognostic value of CPC in new diagnosed MM patients.

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. CPCs of peripheral blood smear were less than 20% in all patients and patients were diagnosed according to the definition of multiple myeloma by the IMWG and followed up to August 1, 2022.[11] We retrospectively collected and followed up patients through the Electronic Medical Record System (EMRS) without disturbing patients in any way. Peripheral blood smear examination and bone marrow specimen examination are routine examinations in the diagnosis and evaluation of MM in our center. This standardized method quantified plasma cells in Wright-Giemsa-stained blood smears. EDTA-anticoagulated blood is thinly smeared and stained. Three cytologists independently analyzed ≥100 nucleated cells under 100-fold oil infusion, and identified plasma cells. The results are expressed as (plasma cells/always nucleated cells) ×100%, and the differences are resolved by reassessment. Cytogenetic abnormalities including del (17 p), t(14; 16) and t(4; 14) were detected by the method of fluorescence in situ hybridization (FISH) in myeloma cells which were purified with anti-CD138 + magnetic beads. The study was approved by the Medical Ethics Committee of Beijing Chaoyang Hospital in accordance with the Declaration of Helsinki.

Response and Outcome Measures

During the induction therapy phase, response assessments were recommended every 1–2 treatment cycles, while during the maintenance therapy phase, evaluations should be conducted at 3–6 months to monitor disease stability and treatment efficacy. Follow-up was conducted by reviewing outpatient and inpatient medical records and telephone calls. Patient outcomes included strict complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), disease stability (SD), and disease progression (PD), as defined by IMWG criteria.[12] The primary endpoints of this study 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 death from time of diagnosis to death or last follow-up date. Patients who could not be followed up were reviewed at the last follow-up.

Statistical Analysis

All data in this study were analyzed by SPSS 23.0 software. The χ^2-test or Fisher test were used to test categorical variables. Kaplan Meier method was used to draw survival curves, and Log rank test was used to evaluate the difference between survival curves. To mitigate Type I error inflation from multiple comparisons, we implemented the Bonferroni correction by adjusting the conventional significance threshold ($\alpha = 0.05$) according to the number of preplanned pairwise comparisons ($n = 3$). This yielded a corrected significance level of $p < 0.0167$ ($0.05 \div 3$). Consequently, statistical significance for all two-tailed analyses was defined as $p < 0.0167$. The survival outcomes of MM patients were comprehensively evaluated using stepwise Cox proportional hazards regression modeling to identify independent prognostic factors influencing disease progression. Both univariate and multivariate analyses were performed to assess potential predictors while controlling for confounding variables. The magnitude and direction of associations were quantified through hazard ratios (HRs) accompanied by 95% confidence intervals (CIs), with statistical significance determined at α=0.05. Propensity score matching technique could be used to control the distribution of confounding factors between groups and reduce the interference of confounding factors on results. In this study, propensity score matching technique was used to match patients with and without CPC in a 1:1 ratio to balance the distribution of prognostic factors between groups. The caliper width was set to 0.2 of the standard deviation of the propensity score. P<0.05 was considered statistically significant.

Results

Patient Characteristics

Of 718 patients enrolled in this study, 103 (14.3%) had CPCs in the peripheral blood (Table 1). The age ranged from 33 to 87 years, the median age was 62 years, and the male to female ratio was 1.21(392/326). The proportion of patients with IgG-type MM (48.3%) was the highest, and 351 (48.9%) were at International Scoring System (ISS) stage III. All patients received induction regimens containing at least one new drug, of which 174 (24.2%) patients received autologous stem cell transplantation (ASCT) after induction therapy. Patients without CPC had significantly longer OS

Table 1 Baseline Clinical and Biological Characteristics of MM Patients

Characteristics	All Patients n=718 n (%)	CPC Negative n=615 n (%)	CPC Positive n=103 n (%)	p value
Sex				
Male	392(54.6)	342(55.6)	50(48.5)	0.200
Female	326(45.4)	273(44.4)	53(51.5)	
Age				
≦65 years	460(64.1)	391(63.6)	69(67.0)	0.579
>65 years	258(35.9)	224(36.4)	34(33.0)	
MM subtype				
IgG	347(48.3)	290(47.2)	57(55.3)	0.572
IgA	163(22.7)	141(22.9)	22(21.4)	
IgD	36(5.0)	31(5.0)	5(4.9)	
Light chain only	157(21.9)	140(22.8)	17(16.5)	
Non-secretory	15(2.1)	13(2.1)	2(1.9)	
ISS stage				
I	108(15.0)	105(17.1)	3(2.9)	0.000
II	259(36.1)	228(37.1)	31(30.1)	
III	351(48.9)	282(45.9)	69(67.0)	
Hemoglobin				
< 100 g/L	467(65.0)	372(60.5)	95(92.2)	0.000
≥ 100 g/L	251(35.0)	243(39.5)	8(7.8)	
Serum creatinine				
≤ 2mg/dL	565(78.7)	493(80.2)	72(69.9)	0.026
> 2mg/dL	153(21.3)	122(19.8)	31(30.1)	
Corrected serum calcium				
≤ 2.75 mmol/L	630(87.7)	548(89.1)	82(79.6)	0.009
> 2.75 mmol/L	88(12.3)	67(10.9)	21(20.4)	
Lactate dehydrogenase				
≤ 250 U/L	614(85.5)	543(88.3)	71(68.9)	0.000
> 250 U/L	104(14.5)	72(11.7)	32(31.1)	
Cytogenetic abnormalities by fish				
del(17p13)				
Abnormality	73(10.2)	62(10.1)	11(10.7)	0.086
Non-abnormality	645(89.8)	553(89.9)	92(89.3)	
t(14; 16)				
Abnormality	26(3.6)	16(2.6)	10(9.7)	0.002
Non-abnormality	692(96.4)	599(97.4)	93(90.3)	
t(4; 14)				
Abnormality	137(19.1)	101(16.4)	36(35.0)	0.000
Non-abnormality	581(80.9)	514(83.6)	67(65.0)	

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients n=718 n (%)	CPC Negative n=615 n (%)	CPC Positive n=103 n (%)	p value
Induction regimes				
Bortezomib based	386(53.8)	339(55.1)	47(45.6)	0.075
IMiD based	69(9.6)	61(9.9)	8(7.8)	
Bortezomib and IMiD based	263(36.6)	215(35.0)	48(46.6)	
ASCT				
Yes	174(24.2)	152(24.7)	22(21.4)	0.535
No	544(75.8)	463(75.3)	81(78.6)	

Abbreviations: CPC, circulating plasma cells; ISS, International Scoring System; IMiD, immunomodulatory; ASCT, autologous stem cell transplant.

and PFS than that of patients with CPC. However, there was no difference in OS and PFS between patients with 1–4% CPC and at least 5% CPC (Figure 1A–C). To assess the effect of CPC on the prognosis of newly diagnosed MM patients, we divided the patients into two groups according to the presence or absence of CPC in peripheral blood. As shown in Table 1, there were statistically significant differences between patients with and without CPC in ISS stage, hemoglobin (HGB), serum creatinine (SCr), Corrected serum calcium (CsCa), lactate dehydrogenase (LDH), t(14; 16) and t(4; 14).

Multivariate Analysis for Survival

Univariate Cox proportional risk regression analysis showed that eleven factors associated with OS: age > 65 years, HGB ≥100g/L, LDH >250 U/L, SCr >2mg/dl, CsCa >2.75 mmol/L, CPC positive, del(17p13), t(14; 16), t(4; 14), ISS stage and ASCT (Table 2). Multivariate analysis was performed for these eleven covariates. CPC in the multivariate analysis was not independently associated with shorter OS (p=0.243). Other factors that were independently associated with OS in the multivariate analysis included age >65 years, HGB ≥100g/L, LDH >250U/L, CsCa >2.75mmol/L, del(17p13), t (14; 16), t(4; 14) and ASCT (Table 2). A multivariate analysis for PFS was performed in same models and showed that CPC was also not significantly associated with PFS (p=0.228) (Table 3).

Response

Patients with and without CPC were matched for age, HGB, LDH, SCr, CsCa, del(17p13), t (14; 16), t(4; 14), ISS stage and ASCT. A total of 196 patients were screened out of 718 patients, 98 in each group. The results showed that there was no significant difference in any factor between negative and positive matched groups (Table 4). Response analysis showed that 624 (86.9%) patients achieved PR or better after during treatment. One hundred and eighty-one patients (25.2%) achieved sCR, 107 (14.9%) achieved CR, 169 (23.5%) achieved VGPR, and 167 (23.3%) achieved PR. It showed that patients with CPC had similar remission rates to patients without CPC (p=0.391, Table 5). Of the 196 matched patients, 165 (84.2%) patients achieved PR or better after induction treatment. Forty-six patients (23.5%) achieved sCR, 22 (11.2%) achieved CR, 51 (26.0%) achieved VGPR, and 46 (23.5%) achieved PR. Patients with CPC also had similar remission rates to patients without CPC (p=0.470, Table 5).

Survival

The median follow-up time for all patients was 29.9 (range 0.3–145.9) months. Among 718 patients, the median OS estimated by the Kaplan-Meier method were 35.1 (95% CI, 24.8–45.4) months and 57.4 (95% CI, 52.4–62.4) for patients with and without CPC respectively (p<0.001, Figure 1B). The median PFS were 17.2 (95% CI, 10.0–24.4) months and 25.8 (95% CI, 23.8–27.8) for all patients with and without CPC respectively (p=0.002, Figure 1D). The median OS estimated by the Kaplan-Meier method were 38.4 (95% CI, 25.4–51.4) months and 43.2 (95% CI, 36.8–49.6) for

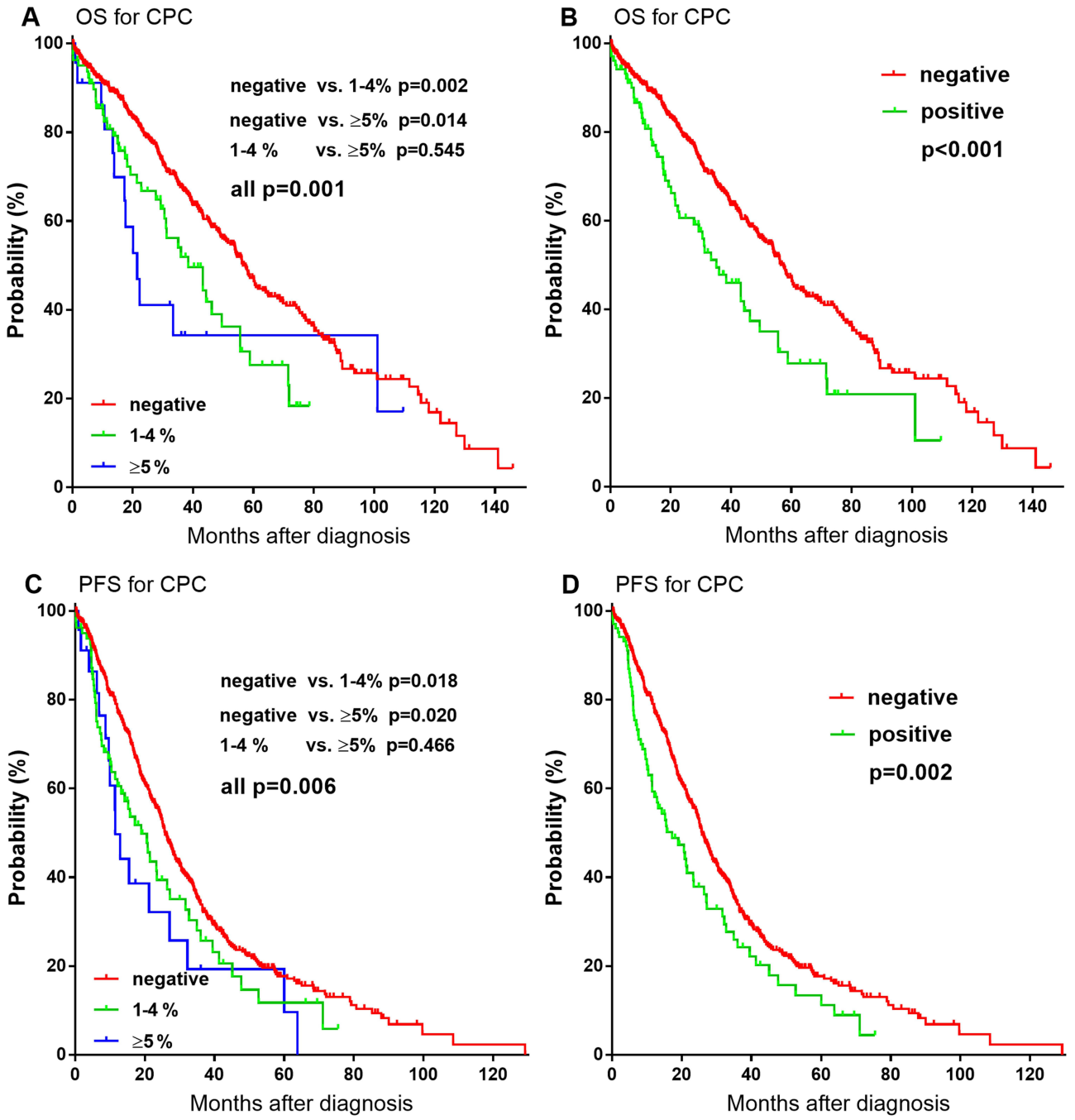

Figure 1 The OS and PFS of newly diagnosed MM patients with different levels of CPC. OS for all patients with 1–4%, ≥5% and without CPC, and there was no difference in OS between patients with 1–4% and ≥5% CPC **(A)**. OS for all patients with and without CPC **(B)**. PFS for all patients with 1–4%, ≥5% and without CPC, and there was no difference in PFS between patients with 1–4% and ≥5% CPC **(C)**. PFS for all patients with and without CPC **(D)**.

matched patients with and without CPC respectively (p=0.309, Figure 2A). The median PFS were 17.2 (95% CI, 10.4–24.0) months and 21.7 (95% CI, 16.2–27.2) for matched patients with and without CPC respectively (p=0.686, Figure 2B).

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Table 2 Cox Analysis (Univariate and Multivariate) of Prognostic Factors for OS

	Univariate			Multivariate		
	HR	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age >65years	1.645	1.316–2.056	0.000	1.360	1.071–1.728	0.012
HGB ≥100g/L	0.553	0.431–0.708	0.000	0.697	0.539–0.900	0.006
LDH >250U/L	2.349	1.784–3.093	0.000	2.090	1.577–2.769	0.000
SCr > 2mg/dL	1.738	1.361–2.218	0.000			0.083
CsCa >2.75mmol/L	2.307	1.744–3.053	0.000	2.263	1.700–3.013	0.000
CPC positive	1.740	1.293–2.342	0.000			0.243
del(17p13)	1.687	1.216–2.339	0.002	1.728	1.242–2.405	0.001
t(14; 16)	1.841	1.112–3.048	0.018	2.027	1.222–3.363	0.006
t(4; 14)	1.354	1.037–1.766	0.026	1.366	1.045–1.785	0.022
ISS stage						
I	1.000	Ref				
II	1.784	1.158–2.747	0.009			0.317
III	2.594	1.705–3.945	0.000			0.071
Induction regimes						
Bortezomib based	1.000	Ref				
IMiD based	1.002	0.709–1.415	0.993			
Bortezomib and IMiD based	0.926	0.714–1.201	0.563			
ASCT	0.403	0.293–0.554	0.000	0.462	0.329–0.650	0.000

Abbreviations: CPC, circulating plasma cells; HGB, hemoglobin; LDH, lactate dehydrogenase; SCr, serum creatinine; CsCa, corrected serum calcium; ISS, International Scoring System; 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 >65 years	1.414	1.172–1.707	0.000			0.156
HGB ≥100g/L	0.648	0.530–0.791	0.000			0.059
LDH >250U/L	1.946	1.525–2.484	0.000	1.954	1.528–2.499	0.000
SCr > 2mg/dL	1.349	1.090–1.670	0.006			0.702
CsCa >2.75mmol/L	2.093	1.631–2.686	0.000	1.888	1.468–2.427	0.000
CPC positive	1.486	1.149–1.921	0.003			0.228
del(17p13)	1.322	0.982–1.781	0.066			0.070
t(14; 16)	1.366	0.852–2.192	0.195			0.133
t(4; 14)	1.509	1.207–1.886	0.000	1.463	1.170–1.830	0.001
ISS stage						
I	1.000	Ref				
II	1.391	1.009–1.919	0.044			0.458
III	1.848	1.356–2.520	0.000			0.147
Induction regimes						
Bortezomib based	1.000	Ref				
IMiD based	1.111	0.826–1.495	0.484			
Bortezomib and IMiD based	0.933	0.755–1.154	0.525			
ASCT	0.463	0.365–0.586	0.000	0.456	0.360–0.579	0.000

Abbreviations: CPC, circulating plasma cells; HGB, hemoglobin; LDH, lactate dehydrogenase; SCr, serum creatinine; CsCa, corrected serum calcium; ISS, International Scoring System; IMiD, immunomodulatory; ASCT, autologous stem cell transplant.

Table 4 Baseline Characteristics Between Matched Patients with and Without CPC

Characteristics	All Patients n=196 n (%)	CPC Negative n=98 n (%)	CPC Positive n=98 n (%)	p value
Age				
≦65 years	128(65.3)	64(65.3)	64(65.3)	1.000
>65 years	68(34.7)	34(34.7)	34(34.7)	
ISS stage				
I	6(3.1)	3(3.1)	3(3.1)	0.952
II	60(30.6)	29(29.6)	31(31.6)	
III	130(66.3)	66(67.3)	64(65.3)	
Hemoglobin				
< 100 g/L	182(92.9)	92(93.9)	90(91.8)	0.579
≥ 100 g/L	14(7.1)	6(6.1)	8(8.2)	
Serum creatinine				
≤ 2mg/dL	138(70.4)	70(71.4)	68(69.4)	0.754
> 2mg/dL	58(29.6)	28(28.6)	30(30.6)	
Corrected serum calcium				
≤ 2.75 mmol/L	157(80.1)	78(79.6)	79(80.6)	0.858
> 2.75 mmol/L	39(19.9)	20(20.4)	19(19.4)	
Lactate dehydrogenase				
≤ 250 U/L	145(74.0)	74(75.5)	71(72.4)	0.625
> 250 U/L	51(26.0)	24(24.5)	27(27.6)	
Cytogenetic abnormalities by fish				
del(17p13)				
Abnormality	23(11.7)	12(12.2)	11(11.2)	0.824
Non-abnormality	173(88.3)	86(87.8)	87(88.8)	
t(14; 16)				
Abnormality	9(4.6)	4(4.1)	5(5.1)	0.733
Non-abnormality	187(95.4)	94(95.9)	93(94.9)	
t(4; 14)				
Abnormality	70(35.7)	34(34.7)	36(36.7)	0.766
non-Abnormality	126(64.3)	64(65.3)	62(63.3)	
ASCT				
Yes	41(20.9)	20(20.4)	21(21.4)	0.861
No	155(79.1)	78(79.6)	77(78.6)	

Abbreviations: CPC, circulating plasma cells; ISS, International Scoring System; IMiD, immunomodulatory; ASCT, autologous stem cell transplant.

Table 5 Best Response Rate of MM Patients

Response	All patients		Matched Patients	
	CPC Negative n=615 n (%)	CPC Positive n=103 n (%)	CPC Negative n=98 n (%)	CPC Positive n=98 n (%)
sCR	158(25.7)	23(22.3)	23(23.5)	23(23.5)
CR	97(15.8)	10(9.7)	13(13.3)	9(9.2)
VGPR	142(23.1)	27(26.2)	26(26.5)	25(25.5)
PR	142(23.1)	25(24.3)	22(22.4)	24(24.5)
SD	56(9.1)	12(11.7)	13(13.3)	11(11.2)
PD	20(3.3)	6(5.8)	1(1.0)	6(6.1)

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

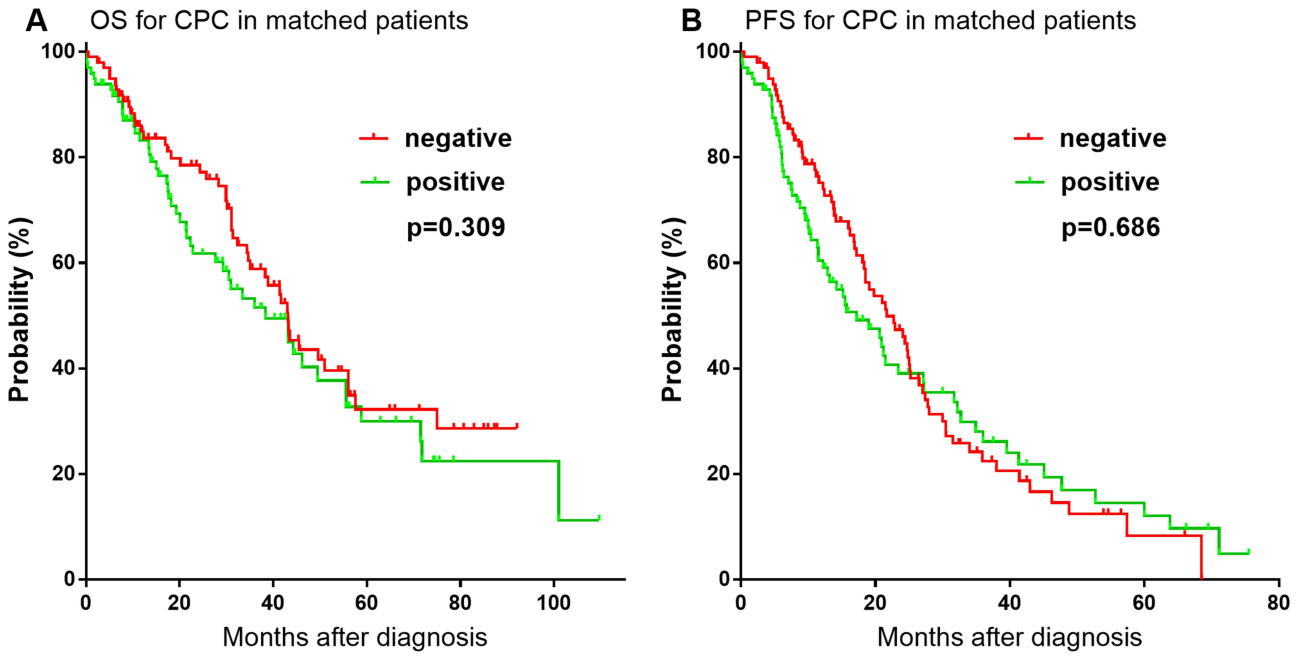

Figure 2 The OS and PFS of matched patients with newly diagnosed MM between negative and positive CPC. OS of matched patients with and without CPC **(A)**. PFS of matched patients with and without CPC **(B)**.

Discussion

The prognostic system of myeloma mainly considers tumor and host factors. Clinical characteristics, cytological characteristics, genetic abnormalities and other indicators of MM patients have important influence on prognosis. Clonal plasma cells mainly proliferate in bone marrow which represent the tumor burden and several studies suggested that small numbers of plasma cells may be detected by cytology, flow cytometry, or slides-based immunofluorescence which were associated with poor prognosis of MM patients.[4,9,10] Wright-Giemsa staining allows for direct morphological assessment of cells, enabling simultaneous evaluation of cell size, nuclear-to-cytoplasmic ratio, and granularity-features critical for distinguishing CPCs from hematopoietic cells or debris in cytological preparations. While flow cytometry offers higher sensitivity for rare-cell detection and multiparametric marker analysis, it requires specialized equipment, costly fluorescent antibodies, and significant technical expertise. In contrast, Wright-Giemsa staining is cost-effective, widely accessible, and compatible with standard light microscopy, making it advantageous for resource-limited settings or studies prioritizing morphological correlation. The flow cytometry could accurately and effectively detect CPCs which could be integrated into modern MM risk stratification model to provide more accurate and individualized diagnosis and treatment for patients.[13] Several studies showed that CPC were associated with some factors which may be prognostic factors for MM. Klimienė I et al[5] assessed the relationship between peripheral blood circulating plasma cells and adhesion molecules, and found that a significant loss of many adhesion molecules (CD49d, CD49e, CD56, CD138) in peripheral blood circulating plasma cells. It showed that loss of adhesion molecule expression enables plasma cells to leave the bone marrow and enter the peripheral blood.[14] Rawstron A et al[15] detected 31 peripheral blood samples of MM patients and found that the number of peripheral blood plasma cells were correlated inversely with CD56 and CD38 expression. Zandecki M et al[6] counted circulating plasma cells on mononuclear cell preparations after Giemsa (morphology) and light chain staining (immunocytochemistry) and observed CPCs in 45.9% (45/98) multiple MM patients which were correlated with a higher percentage of bone marrow PC and β2 microglobulin. Bae MH et al[7] detected circulating plasma cells in 85 patients with MM by five-color flow cytometry and patients with high CPCs had lower hemoglobin and platelets, but higher calcium, M-protein and bone marrow PCs, and had shorter PFS and OS. Gonsalves WI et al[8] used multiparametric flow cytometry to quantitate CPCs in MM patients and found that high CPCs was associated to adverse cytogenetics and poor survival. Granell M et al[4] detected circulating plasma cells by Wright-Giemsa-stained

peripheral blood smears in 482 patients with newly diagnosed myeloma or plasma cell leukemia and found that the presence of 5 to 20% circulating plasma cells was associated with a worse overall survival. Moreover, MM patients with ≥5% circulating plasma cells had lower platelet counts, higher bone marrow plasma cells and similar poor prognosis to patients with plasma cell leukemia. Cheng Q et al[16] enrolled 196 newly diagnosed multiple myeloma patients and found that CPC was an independent poor prognostic factor of PFS and OS, and was a good predictor to distinguish patients with higher tumor burden and lower response rates. Nowakowski GS et al[9] detected the number of circulating PCs per 50,000 mononuclear cells by flow cytometry in 302 patients with newly diagnosed multiple myeloma and reported that 80 (27%) patients had no circulating PC; 106 (35%) patients had 1 to 10 and 115 (38%) patients had more than 10 circulating PCs. Moreover, the number of circulating PCs measured by flow cytometry in patients with newly diagnosed MM was an independent predictor of survival. Witzig TE et al analyzed the % blood monoclonal plasma cells (%BPC) in 254 mm patients and found that patients with high %BPC were less likely to have lytic bone disease and the %BPC was an independent prognostic factors for survival of MM patients. Chakraborty R et al[17,18] detected circulating plasma cells prior to autologous stem cell transplantation (ASCT) by six-color flow cytometry in MM patients undergoing early ASCT and CPCs were detected in 19.3% (162/840) patients and was a poor prognostic for outcome of patients with MM. At present, most studies suggested that high level of CPC was a poor prognostic factor in MM.[19–22]

In this study, we retrospectively analyzed newly diagnosed MM patients with less than 20% CPC detected by peripheral blood smears, and found that the survival time of patients with CPC was significantly shorter, but there was no significant difference in OS and PFS between patients with 1–4% and ≥ 5% CPC. Therefore, we divided the patients into two groups according to the presence or absence of CPC in peripheral blood. This study showed that CPC was associated with some factors such as ISS stage, HGB, LDH, SCr, CsCa, t(14;16) and t(4;14), which had been considered as independent prognostic factors for MM in previous studies. The levels of LDH, SCr and CsCa were higher and the levels of hemoglobin were lower in CPC positive patients. More patients were in ISS stage III and had t (14; 16) and t (4; 14). All these factors suggested progressive MM and a worse prognosis. In our study, patients with CPCs had higher t(4;14) and t(14;16) which may induce poor prognosis. Jin X et al[23] also found that the proportions of high-risk cytogenetic abnormalities including t(4;14) and t(14;16) were higher among CPC-positive patients than among CPC-negative patients. Patients with CPC had a median survival of 35.1 months which was significantly shorter than that of patients without CPC who had a median survival of 57.4 months. Univariate Cox proportional hazards regression analyses suggested that CPC was a poor prognostic factor for newly diagnosed MM. However, multivariable analyses showed that CPC was not an independent poor prognostic factor for patients with newly diagnosed MM. Our study confirmed that CPCs represented an adverse prognostic factor in MM, consistent with previous observations. However, we were unable to validate CPCs as an independent poor prognostic factor in MM. This discrepancy may stem from differences in study population characteristics and/or variations in the multivariate analysis models employed across studies. For eliminating the impact of above factors on prognostic value assessment of CPC, we used propensity-score matched analysis to balance covariate distributions between patients with and without CPC. 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 and without CPC had similar OS after balancing main factors. As a result, CPC may be a poor prognostic factor for patients with newly diagnosed MM, but not an independent poor prognostic factor. Nevertheless, our study suggested that CPC testing can be a simple and effective way to identify high-risk MM patients and help clinicians develop rational treatment plans for newly diagnosed MM patients.

This study has some limitations. It was a retrospective analysis with data from a single MM diagnosis and treatment center and the median follow-up time in this study was short, requiring long-term follow-up to verify the results. In this study, Wright-Giemsa-stained peripheral blood smears were used to count CPCs, which was less sensitive than flow cytometry. To ensure the accuracy of CPC counting, all smears were examined by experienced hematologists for peripheral blood cytology. Our study specifically addressed clinical characteristics of Chinese patients; however, ethnic-specific factors may limit cross-population generalizability. Future multinational studies are needed to validate the prognostic value of CPC in new diagnosed MM patients.

In conclusion, our study demonstrated that the presence of peripheral blood plasma cells was a poor prognostic factor, but nor an independent prognostic factor for patients with newly diagnosed multiple myeloma in China.

Data Sharing Statement

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

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.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No potential conflict of interest was reported by the authors.

References

1. Lakshman A, Kumar SK. Chimeric antigen receptor T-cells, bispecific antibodies, and antibody-drug conjugates for multiple myeloma: an update. *Am J Hematol*. 2022;97(1):99–118. doi:10.1002/ajh.26379
2. Chen Y, Tao S, Zheng X, et al. Research progress on treatment of extramedullary multiple myeloma. *Hematology*. 2021;26(1):985–994. doi:10.1080/16078454.2021.2005310
3. SR G, n F, MA S. Daratumumab for the treatment of multiple myeloma. *Drugs Today* 2021;57(10):591–605. doi:10.1358/dot.2021.57.10.3313853
4. Granell M, Calvo X, Garcia-Guiñón A, et al. Prognostic impact of circulating plasma cells in patients with multiple myeloma: implications for plasma cell leukemia definition. *Haematologica*. 2017;102(6):1099–1104. doi:10.3324/haematol.2016.158303
5. Klimienė I, Radzevičius M, Matuzevičienė R, Sinkevič-Belliot K, Kučinskienė ZA, Pečeliūnas V. Adhesion molecule immunophenotype of bone marrow multiple myeloma plasma cells impacts the presence of malignant circulating plasma cells in peripheral blood. *Int J Lab Hematol*. 2021;43(3):403–408. doi:10.1111/ijlh.13387
6. Zandecki M, Facon T, Preudhomme C, et al. Significance of circulating plasma cells in multiple myeloma. *Leuk Lymphoma*. 1994;14(5–6):491–-496. doi:10.3109/10428199409049709
7. Bae MH, Park C-J, Kim BH, et al. Increased circulating plasma cells detected by flow cytometry predicts poor prognosis in patients with plasma cell myeloma. *Cytometry B Clin Cytom*. 2018;94(3):493–499. doi:10.1002/cyto.b.21606
8. Gonsalves WI, Rajkumar SV, Gupta V, et al. Quantification of clonal circulating plasma cells in newly diagnosed multiple myeloma: implications for redefining high-risk myeloma. *Leukemia*. 2014;28(10):2060–2065. doi:10.1038/leu.2014.98
9. Nowakowski GS, Witzig TE, Dingli D, et al. Circulating plasma cells detected by flow cytometry as a predictor of survival in 302 patients with newly diagnosed multiple myeloma. *Blood*. 2005;106(7):2276–2279. doi:10.1182/blood-2005-05-1858
10. Witzig TE, Gertz MA, Lust JA, Kyle RA, O'Fallon WM, Greipp PR. Peripheral blood monoclonal plasma cells as a predictor of survival in patients with multiple myeloma. *Blood*. 1996;88(5):1780–1787. doi:10.1182/blood.V88.5.1780.1780
11. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538–e548. doi:10.1016/S1470-2045(14)70442-5
12. Durie BG, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467–1473. doi:10.1038/sj.leu.2404284
13. Periago A, Campillo JA, Mrowiec A, et al. Circulating aberrant plasma cells allow risk stratification of patients with myeloma. *Am J Hematol*. 2016;91(9):E353–E355. doi:10.1002/ajh.24431
14. Rawstron AC, Owen RG, Davies FE, et al. Circulating plasma cells in multiple myeloma: characterization and correlation with disease stage. *Br J Haematol*. 1997;97(1):46–55. doi:10.1046/j.1365-2141.1997.72653.x
15. Rawstron A, Barrans S, Blythe D, et al. Distribution of myeloma plasma cells in peripheral blood and bone marrow correlates with CD56 expression. *Br J Haematol*. 1999;104(1):138–143. doi:10.1046/j.1365-2141.1999.01134.x
16. Cheng Q, Cai L, Zhang Y, Chen L, Hu Y, Sun C. Circulating plasma cells as a biomarker to predict newly diagnosed multiple myeloma prognosis: developing nomogram prognostic models. *Front Oncol*. 2021;11:639528. doi:10.3389/fonc.2021.639528
17. Chakraborty R, Muchtar E, Kumar SK, et al. Risk stratification in myeloma by detection of circulating plasma cells prior to autologous stem cell transplantation in the novel agent era. *Blood Cancer J*. 2016;6(12):e512. doi:10.1038/bcj.2016.117

18. Chakraborty R, Muchtar E, Kumar SK, et al. Serial measurements of circulating plasma cells before and after induction therapy have an independent prognostic impact in patients with multiple myeloma undergoing upfront autologous transplantation. *Haematologica*. 2017;102(8):1439–1445. doi:10.3324/haematol.2017.166629
19. Li J, Wang N, Tesfaluul N, Gao X, Liu S, Yue B. Prognostic value of circulating plasma cells in patients with multiple myeloma: a meta-analysis. *PLoS One*. 2017;12(7):e0181447. doi:10.1371/journal.pone.0181447
20. Galieni P, Travaglini F, Vagnoni D, et al. The detection of circulating plasma cells may improve the revised international staging system (R-ISS) risk stratification of patients with newly diagnosed multiple myeloma. *Br J Haematol*. 2021;193(3):542–550. doi:10.1111/bjh.17118
21. Zahran AM, Sayed MM, Shafik EA, Khallaf SM, Mohamed WM, Hetta HF. The frequency and clinical implications of lymphocyte subsets and circulating plasma cells in newly diagnosed multiple myeloma patients. *Egypt J Immunol*. 2019;26(2):117–131.
22. Vagnoni D, Travaglini F, Pezzoni V, et al. Circulating plasma cells in newly diagnosed symptomatic multiple myeloma as a possible prognostic marker for patients with standard-risk cytogenetics. *Br J Haematol*. 2015;170(4):523–531. doi:10.1111/bjh.13484
23. Jin X, Jiang X, Li H, et al. Prognostic implications of circulating plasma cell percentage in multiple myeloma and primary plasma cell leukemia defined by new criteria. *Acta Haematol*. 2025;148(1):48–57. doi:10.1159/000538658