Newly diagnosed multiple myeloma patients with CD56 expression benefit more from autologous stem cell transplantation

Chuanying Geng
Capital Medical University
Huixing Zhou
Capital Medical University
Huijuan Wang
Capital Medical University
Yanchen Li
Capital Medical University
Yun Leng
Capital Medical University
Zhiyao Zhang
Capital Medical University
Yuan Jian
Capital Medical University
Guangzhong Yang
Capital Medical University
Wenming Chen (13910107759@163.com)
Capital Medical University

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Abstract

Background

Several studies showed that lack of CD56 expression was a poor prognostic factor for patients with newly diagnosed multiple myeloma (NDMM). However, other studies were not able to confirm the prognostic value of CD56 in NDMM. This study aimed to evaluate the prognostic value of CD56 expression for patients with NDMM who received autologous stem cell transplantation (ASCT).

Methods

We retrospectively analyzed 394 patients with NDMM under 66 years old and the propensity score matching technique was used to reduce the bias between two groups.

Results

CD56 expression was observed in 265 (67.3%) patients, and 175 (44.4%) patients received ASCT. 44.9% (119/265) CD56 positive patients received ASCT; and 43.4% (56/129) CD56 negative patients received ASCT. Univariate and multivariate analyses showed that ASCT was correlated with longer OS ($p < 0.001$) and PFS ($p < 0.001$) for CD56 positive patients. ASCT may improve PFS of CD56 negative patients in univariate analysis, but it had no impact on PFS in multivariate analysis. Moreover, ASCT could not improve OS of CD56 negative patients in univariate and multivariate analysis ($p > 0.05$). In the propensity score matching analysis, 216 patients with CD56 expression were identified, 108 patients had received ASCT and 108 patients had no ASCT. Among 129 patients without CD56 expression, 80 patients, 40 in each group, were identified. Among 216 matched patients with CD56 expression, patients with ASCT had longer OS (87.6 vs.56.1 months, $p < 0.001$) and PFS (40.4 vs.27.6 months, $p = 0.003$). However, ASCT had no impact on OS and PFS for matched patients without CD56 expression ($p > 0.05$).

Conclusions

These results demonstrated that ASCT may improve OS and PFS of patients with CD56 expression and had little impact on survival of CD56 negative patients.

Background

Multiple myeloma (MM) is a common hematological malignancy which originates from clonal plasma cells [1]. MM remains an incurable disease until nowadays, and autologous stem cell transplantation (ASCT) is the standard treatment for newly diagnosed MM (NDMM), despite the advent of novel agents [2–3]. For a heterogenous disease, survival interval for patients varies significantly, from a few months to more than ten years [4]. It is important to identify prognostic factors for MM. During several decades, it

has developed many useful prognostic factors, including Durie-Salmon (DS) stage, International Staging System (ISS), lactate dehydrogenase (LDH) level, high-risk cytogenetics abnormalities [5–6]. It has been reported that certain immunophenotypes of plasma cells may impact MM prognosis and clinical characteristics. CD56 was an isoform of the neural cell adhesion molecule which was able to mediate the adhesion of MM cells to the extracellular matrix. Studies showed that CD56 expression could be detected in 55 ~ 85% patients with MM [7–13]. CD56 expression was constant over the course of MM and it was significantly linked to the degree of both bone marrow and peripheral blood involvement [14]. CD56 expression by plasma cells also correlated with the presence of lytic bone lesions in MM [15]. Sahara N et al [16] reported that MM with CD56 negative had a poor prognosis with higher chance of extramedullary disease, Bence Jones protein, renal insufficiency, thrombocytopenia, and plasma cell morphology. CD56 expression level was lower in advanced stages than earlier stages [13]. Lack of CD56 expression was a poor prognostic factor for patients with NDMM [7–8, 17]. Expression of CD56 was associated with better response to bortezomib treatment and was a promising candidate biomarker for predicting response to therapeutic regimens contained bortezomib [18]. However, other studies reported that lack of CD56 expression was not risk factors for survival in patients with MM [10–11, 19–21].

We found that ASCT may improve the overall survival (OS) and progression-free survival (PFS) of patients with CD56 expression and had no impact on survival of CD56 negative patients in novel-agent era. So, we retrospectively analyzed 394 patients with NDMM under 66 years old in Beijing Chao-Yang Hospital, Capital Medical University. This study aimed to evaluate the prognostic value of CD56 expression for patients with NDMM who received ASCT.

Methods

Patients

We recorded baseline data of NDMM patients in Beijing Chaoyang Hospital, Capital Medical University from February 1, 2011 to October 1, 2021 by searching the Electronic Medical Record System (EMRS). The International Myeloma Working Group (IMWG) criteria of MM was used to confirm patients with NDMM and all patients were followed up until March 1, 2022 [3]. We followed the patients through the EMRS without disturbing patients in any way. Bone marrow specimen testing was a routine examination for the diagnosis and evaluation of MM in our center. The CD56 expression was detected by flow cytometry. Cytogenetic abnormalities were detected by Fluorescence in situ hybridization (FISH), including t(4; 14), t(14; 16) and del17p13. This study followed to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Beijing Chaoyang Hospital.

Response And Outcome Measures

Response and outcome measures

Patient responses were confirmed according to the IMWG criteria [22]. The main indexes included stringent complete remission (sCR), complete remission (CR), very good partial remission (VGPR), partial remission (PR), minimal remission (MR), stable disease (SD) and progressive disease (PD) based on the assessment of serum and urine protein electrophoresis, immunofixation, serum-free light chain assay, and bone marrow (BM) aspiration and biopsy. If the patients had extramedullary disease at diagnosis, ^{1} F-FDG PET/CT was necessary for response analysis. Primary endpoints were PFS and OS. The time from diagnosis to disease progression or death was defined as the estimated PFS, and the time from diagnosis to death from any cause or last exposure date was defined as the estimated OS. Patients who could not be followed up were censored at last contact.

Statistical analysis

Statistical analysis was carried out through SPSS 23.0 software. Categorical variables were analyzed by Chi-square test or Fisher's exact test. PFS and OS were estimated according to Kaplan-Meier method and the survival differences were compared by two-tailed log-rank test. The COX proportional hazards regression analyses were used to assess the prognostic impact, and results were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Propensity score matching techniques were used to balance the distribution of factors with prognostic value in previous studies or in this study. P values less than < 0.05 were considered statistically significant, and all tests were two-sided.

Results

Patient characteristics

A total of 394 patients with NDMM under 66 years old were enrolled, CD56 expression was detected in 265 (67.3%) patients and 175 (44.4%) patients received ASCT after induction therapy containing novel agents with 12 months. There were 119/265 (44.9%) and 56/129 (43.4%) received ASCT in CD56 positive and negative patients, respectively. Table 1 summarized the characteristics of 394 patients. The male-to-female ratio was 1.28 (221/173) and the median age was 55 (range 24–65) years old. The most common monoclonal protein was IgG type (49.2%) and 185 (47.0%) were at ISS stage III. All patients received induction therapy combining novel agents, 190 (48.2%) patients received bortezomib-based regimens, 41 (10.4%) combining immunomodulatory drugs (IMiDs), 163 (41.4%) combining bortezomib and IMiDs. After induction therapy, 175 (44.4%) patients received ASCT. As shown in Table 1, there were statistically significant differences between CD56 positive and negative patients in MM subtype, corrected serum calcium level (CsCa), lactate dehydrogenase (LDH), t(14; 16) and t(4; 14).

Table 1
Baseline clinical and biological characteristics of MM patients

	all patients	CD56 positive	CD56 negative	
Characteristics	n = 394	n = 265	n = 129	
	n (%)	n (%)	n (%)	p value
Sex				
Male	221(56.1)	143(54.0)	78(60.5)	0.22
Female	173(43.9)	122(46.0)	51(39.5)	
MM subtype				
IgG	194(49.2)	143(54.0)	51(39.5)	0.00
IgA	76(19.3)	58(21.9)	18(14.0)	
IgD	21(5.3)	4(1.5)	17(13.2)	
Light chain only	89(22.6)	54(20.4)	35(27.1)	
Non-secretory	14(3.6)	6(2.3)	8(6.2)	
ISS stage				
I	78(19.8)	48(18.1)	30(23.3)	0.17
II	131(33.2)	96(36.2)	35(27.1)	
III	185(47.0)	121(45.7)	64(49.6)	
Hemoglobin				
< 100 g/L	244(61.9)	168(63.4)	76(58.9)	0.39
≥ 100 g/L	150(38.1)	97(36.6)	53(41.1)	
Serum creatinine				
≤ 2mg/dL	321(81.5)	219(82.6)	102(79.1)	0.39
> 2mg/dL	73(18.5)	46(17.4)	27(20.9)	
Corrected serum calcium				
≤ 2.75 mmol/L	343(87.1)	223(84.2)	120(93.0)	0.01
> 2.75 mmol/L	51(12.9)	42(15.8)	9(7.0)	
Lactate dehydrogenase				
≤ 250 U/L	336(85.3)	233(87.9)	103(79.8)	0.03

	all patients	CD56 positive	CD56 negative	
> 250 U/L	58(14.7)	32(12.1)	26(20.2)	
Cytogenetic abnormalities by FISH				
del(17p13)				
abnormality	38(9.6)	27(10.2)	11(8.5)	0.60
non-abnormality	356(90.4)	238(89.8)	118(91.5)	
t(14; 16)				
abnormality	15(3.8)	2(0.8)	13(10.1)	0.00
non-abnormality	379(96.2)	263(99.2)	116(89.9)	
t(4; 14)				
abnormality	69(17.5)	66(24.9)	3(2.3)	0.00
non-abnormality	325(82.5)	199(75.1)	126(97.7)	
Induction regimes				
Bortezomib based	190(48.2)	128(48.3)	62(48.1)	0.44
IMiD based	41(10.4)	31(11.7)	10(7.8)	
Bortezomib and IMiD based	163(41.4)	106(40.0)	57(44.2)	
ASCT				
Yes	175(44.4)	119(44.9)	56(43.4)	0.78
No	219(55.6)	146(55.1)	73(56.6)	
Abbreviations: IMiD: immunomodulatory; ASCT: autologous stem cell transplant				

Multivariate Analysis For Survival

Univariate analysis found seven factors associated with OS and they were hemoglobin (HGB) < 100 g/L, LDH > 250 U/L, serum creatinine (SCr) > 2mg/dL, CsCa > 2.75mmol/L, del(17p13), t(14; 16), ISS III stage and ASCT. Multivariate analysis was performed for CD56, t(4; 14) and these eight covariates. It was showed that ASCT was a favorable factor for OS (HR = 0.43, 95%CI: 0.30–0.63, p < 0.001) and PFS (HR = 0.51, 95%CI: 0.38–0.68, p < 0.001) of patients with NDMM (Table 2). Among CD56 positive patients, univariate analyses showed that ASCT was a favorable factor for OS (HR = 0.36, 95%CI: 0.22–0.58, p < 0.001) and PFS (HR = 0.53, 95%CI: 0.37–0.74, p < 0.001); the favorable effect of ASCT on OS (HR = 0.30, 0.18–0.50, p < 0.001) and PFS (HR = 0.51, 0.36–0.72, p < 0.001) was confirmed in multivariate analyses

(Table 2). Among CD56 negative patients, univariate analyses showed that ASCT was a favorable factor for PFS (HR = 0.54, 95%CI: 0.33–0.90, p = 0.02), but had no statistic impact on OS (p = 0.75); and multivariate analyses showed that ASCT had no effect on PFS (p = 0.08) and OS (p = 0.78) (Table 2).

Table 2
Cox analysis (univariate and multivariate) of ASCT

	all		**CD56 positive**		**CD56 negative**	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Univariate						
OS	0.00	0.47(0.32–0.68)	0.00	0.36(0.22–0.58)	0.75	
PFS	0.00	0.53(0.40–0.70)	0.00	0.53(0.37–0.74)	0.02	0.54(0.33–0.90)
Multivariate						
OS	0.00	0.43(0.30–0.63)	0.00	0.30(0.18–0.50)	0.78	
PFS	0.00	0.51(0.38–0.68)	0.00	0.51(0.36–0.72)	0.08	
Abbreviations: HR: hazard ratio; 95% CI: 95%confidence interval; ASCT: autologous stem cell transplant						

Matched Pairs Of Patients

Among CD56 positive patients, ASCT and non-ASCT patients were matched for ISS stage, HGB, SCr, CsCa, LDH, del(17p13), t(14; 16) and t(4; 14). A total of 216 patients were identified by propensity score matching technique, with 108 patients in each group. It was showed that there was no significantly difference in matched groups of ASCT and non-ASCT patients with respect to these characteristics (Table 3). Among CD56 negative patients, ASCT and non-ASCT patients were matched for above similar factors and 80 patients, 40 in each group, were identified. These two matched groups also had no difference in these factors (Table 3).

Table 3
Baseline clinical and biological characteristics of matched patients

Characteristics	CD56 positive		CD56 negative	
	ASCT	non-ASCT	ASCT	non-ASCT
	n = 108	n = 108	n = 40	n = 40
	n (%)	n (%)	n (%)	n (%)
ISS stage				
I	22(20.4)	16(14.8)	9(22.5)	8(20.0)
II	41(38.0)	50(46.3)	15(37.5)	16(40.0)
III	45(41.7)	42(38.9)	16(40.0)	16(40.0)
Hemoglobin				
< 100 g/L	63(58.3)	69(63.9)	24(60.0)	24 (60.0)
≥ 100 g/L	45(41.7)	39(36.1)	16(40.0)	16 (40.0)
Serum creatinine				
≤ 2mg/dL	96(88.9)	95(88.0)	34(85.0)	36 (90.0)
> 2mg/dL	12(11.1)	13(12.0)	6(15.0)	4 (10.0)
Corrected serum calcium				
≤ 2.75 mmol/L	93(86.1)	89(82.4)	37(92.5)	37 (92.5)
> 2.75 mmol/L	15(13.9)	19(17.6)	3(7.5)	3 (7.5)
Lactate dehydrogenase				
≤ 250 U/L	97(89.8)	93(86.1)	33(82.5)	33 (82.5)
> 250 U/L	11(10.2)	15(13.9)	7(17.5)	7 (17.5)
Cytogenetic abnormalities by FISH				
del(17p13)				
abnormality	12(11.1)	12(11.1)	3(7.5)	2 (5.0)
non-abnormality	96(88.9)	96(88.9)	37(92.5)	38 (95.0)
t(14; 16)				
abnormality	0(0.0)	0(0.0)	7(17.5)	4 (10.0)
non-abnormality	108(100.0)	108(100.0)	33(82.5)	36 (90.0)

Characteristics	CD56 positive		CD56 negative	
	ASCT	non-ASCT	ASCT	non-ASCT
	n = 108	n = 108	n = 40	n = 40
	n (%)	n (%)	n (%)	n (%)
t(4; 14)				
abnormality	29(26.9)	30(27.8)	0(0.0)	0(0.0)
non-abnormality	79(73.1)	78(72.2)	40(100.0)	40(100.0)

Response Analysis

All patients were monitored for best response after ASCT and consolidation therapy. Among the 216 matched patients with CD56 expression, 200 (92.6%) patients achieved at least PR. Seventy-four patients (34.3%) achieved sCR, 28 (13.0%) CR, 61 (28.2%) VGPR, and 37 (17.1%) PR. Patients received ASCT had the higher sCR rate (46.3%) than those without ASCT (22.2%) in the matched groups ($p < 0.001$, Table 4). Among the 80 matched patients without CD56 expression, 77 (96.3%) patients achieved at least PR. Thirty-two patients (40.0%) achieved sCR, 10 (12.5%) CR, 20 (25.0%) VGPR, and 15 (18.8%) PR. Patients received ASCT also had the higher sCR rate (57.5%) than those without ASCT (22.5%) in the matched groups ($p = 0.004$, Table 4).

Table 4
Best response rate of matched patients

Response	CD56 positive		CD56 negative	
	ASCT	non-ASCT	ASCT	non-ASCT
	n = 108	n = 108	n = 40	n = 40
	n (%)	n (%)	n (%)	n (%)
sCR	50(46.3)	24(22.2)	23(57.5)	9(22.5)
CR	18(16.7)	10(9.3)	5(12.5)	5(12.5)
VGPR	31(28.7)	30(27.8)	10(25.0)	10(25.0)
PR	7(6.5)	30(27.8)	2(5.0)	13(32.5)
SD	2(1.9)	12(11.1)	0(0.0)	2(5.0)
PD	0(0.0)	2(1.9)	0(0.0)	1(2.5)

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

Survival Analysis

The median follow-up time for all patients was 30.0 (range 1.3-114.7) months. It was showed that ASCT could improve OS and PFS of patients (Fig. 1B and 2B). Among CD56 positive patients, the median OS were 87.6 (95% CI, 66.5-108.7) months and 54.1 (95% CI, 41.3–66.9) for patients with and without ASCT, respectively ($p < 0.001$, Fig. 1C); the median PFS were 40.1 (95% CI, 33.7–46.5) months and 25.8 (95% CI, 17.2–34.4) for patients with and without ASCT, respectively ($p < 0.001$, Fig. 2C). After matching, CD56 positive patients who received ASCT also had longer OS (87.6 vs.56.1 months, $p < 0.001$) and PFS (40.4 vs.27.6 months, $p = 0.003$) than those CD56 positive patients who had no ASCT (Fig. 1D and 2D). Among CD56 negative patients, the median OS were 56.2 (95% CI, 38.5–73.9) months and 53.9 (95% CI, 37.0-70.8) for patients with and without ASCT respectively ($p = 0.748$, Fig. 1C); the median PFS estimated were 35.5 (95% CI, 26.1–44.9) months and 22.0 (95% CI, 17.7–26.3) for patients with and without ASCT respectively ($p = 0.016$, Fig. 2C). After matching, CD56 negative patients received ASCT also had similar OS (49.2 vs.48.7 months, $p = 0.569$) and PFS (35.4 vs.22.9 months, $p = 0.082$) with those CD56 negative patients who had no ASCT (Fig. 1D and 2D).

Discussion

In our study, we evaluated the prognostic value of CD56 expression for patients with NDMM undergoing ASCT. We found that ASCT might improve the OS and PFS of patients with CD56 expression and had

little impact on survival of CD56 negative patients in novel-agent era.

CD56 is a neural cell adhesion molecule associated with the axon growth during normal embryogenesis. It is expressed in most of the malignant plasma cells and is very common on myeloma cells. Several studies showed CD56 expression could be detected in 55 ~ 85% patients with MM [7–13]. Pan Y et al [7] retrospectively analyzed 50 patients with NDMM and found 74% MM patients with CD56 expression. Skerget M et al [8] also detected CD56 expression in 110 patients with NDMM and reported that CD56 expression rate was 71%. Another study assessed 34 patients with NDMM and reported that 29 (85.3%) patients had CD56 expression [13]. Our study showed that 67.3% patients presented CD56 expression which was similar with previous studies.

The prognostic value of CD56 expression in NDMM have been assessed in several studies. It was showed that lack of CD56 expression of NDMM was a poor prognostic factor. Pan Y et al [7] analyzed the prognostic value of CD56 expression in 50 patients with NDMM and found that CD56 was a favorable prognostic factor for OS in multivariate analysis. Moreover, CD56-positive patients had higher overall response rates (ORR) than CD56-negative patients after induction therapy. Skerget M et al [8] analyzed 110 patients with NDMM and showed that the median PFS of CD56 positive patients was longer than CD56 negative patients. One multicenter study which enrolled 35 patients with NDMM carrying t(14;16) and 124 patients without t(14;16) as a control indicated that lack of CD56 expression was a poor prognostic factor for MM patients with t(14;16) in novel-agent era [17]. However, some studies failed to confirm the result. Greipp PR et al [10] conducted a study of 68 untreated patients with MM from a single institution and found that lack of CD56 expression was not a prognostic factor in MM. One prospective, long-term study enrolled 204 MM patients also found that CD56 expression carried no distinct adverse prognosis [11]. Hundemer M et al [20] analyzed CD56 expression of patients with NDMM who received ASCT by flow cytometry and indicated that CD56 was not a prognostic factor. Other studies could not also consider CD56 expression as a prognostic factor for MM [19, 21].

At present, ASCT remains the standard treatment after induction therapy for eligible patients with NDMM [2]. Comparing with standard therapy, patients received ASCT had an increase in the CR rate and a longer OS (54 vs. 42 months) [23]. We also found that ASCT may improve remission rates of CD56 positive and negative patients. It was consistent with previous reported results. There were two studies evaluating prognostic value of CD56 on survival of MM patients undergoing ASCT and they found that CD56 was not related to the outcome of patients received ASCT [20, 21]. In this study, we found that CD56 expression was not related to OS and PFS of NDMM patients by Kaplan-Meier survival analysis (Fig. 1A and 2A). We divided the patients into four groups using CD56 and ASCT, and found that ASCT improved the survival of CD56 positive patients, but did not significantly improve the survival of CD56 negative patients. The result was inconsistent with the conclusions of these two studies. The reason might be different induction therapy regimens. In our study, all patients received induction therapy combining novel agents followed by single course of melphalan 200 mg/m^2 as intensive chemotherapy prior to transplant of autologous peripheral blood stem cells. Patients of other two studies received conventional chemotherapy before ASCT. Both of these studies had not enrolled CD56 positive and negative patients

who had not received ASCT. They did not evaluate the effect of ASCT on survival of CD56 positive or negative patients with NDMM. In our study, ASCT could significantly prolong OS and PFS of CD56 positive patients. However, ASCT had no impact on survival of CD56 negative patients. It suggested that NDMM patients with CD56 expression may benefit more from ASCT than CD56 negative patients in novel-agent era.

The study is limited for the database from a single center and the retrospective nature. We are a large MM center in China, and some data of patients might be referred to other medical centers, which might affect to assess the prognostic value of CD56 expression. Finally, follow-up of patients is insufficient, and further larger population studies are needed to verify the results.

In conclusion, our study suggested that ASCT could significantly prolong OS and PFS of CD56 positive patients, but had little impact on survival of CD56 negative patients. It needs further study to confirm these results in the future.

Declarations

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Authors' contributions

CG, GY and WC designed the analysis and wrote the manuscript. HW, YL, YL, YJ and HZ collected and interpreted the data. ZZ performed the statistical analysis. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval and consent to participate

This study followed to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Beijing Chaoyang Hospital. The requirement for informed consent was waived by the Medical Ethics Committee of Beijing Chaoyang Hospital due to the retrospective nature of the data.

We followed the patients through the electronic medical record system without disturbing the patients in any way or interfering with the treatment of the patients.

Consent for publication

Not applicable

Competing interests

No potential conflict of interest was reported.

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Figures

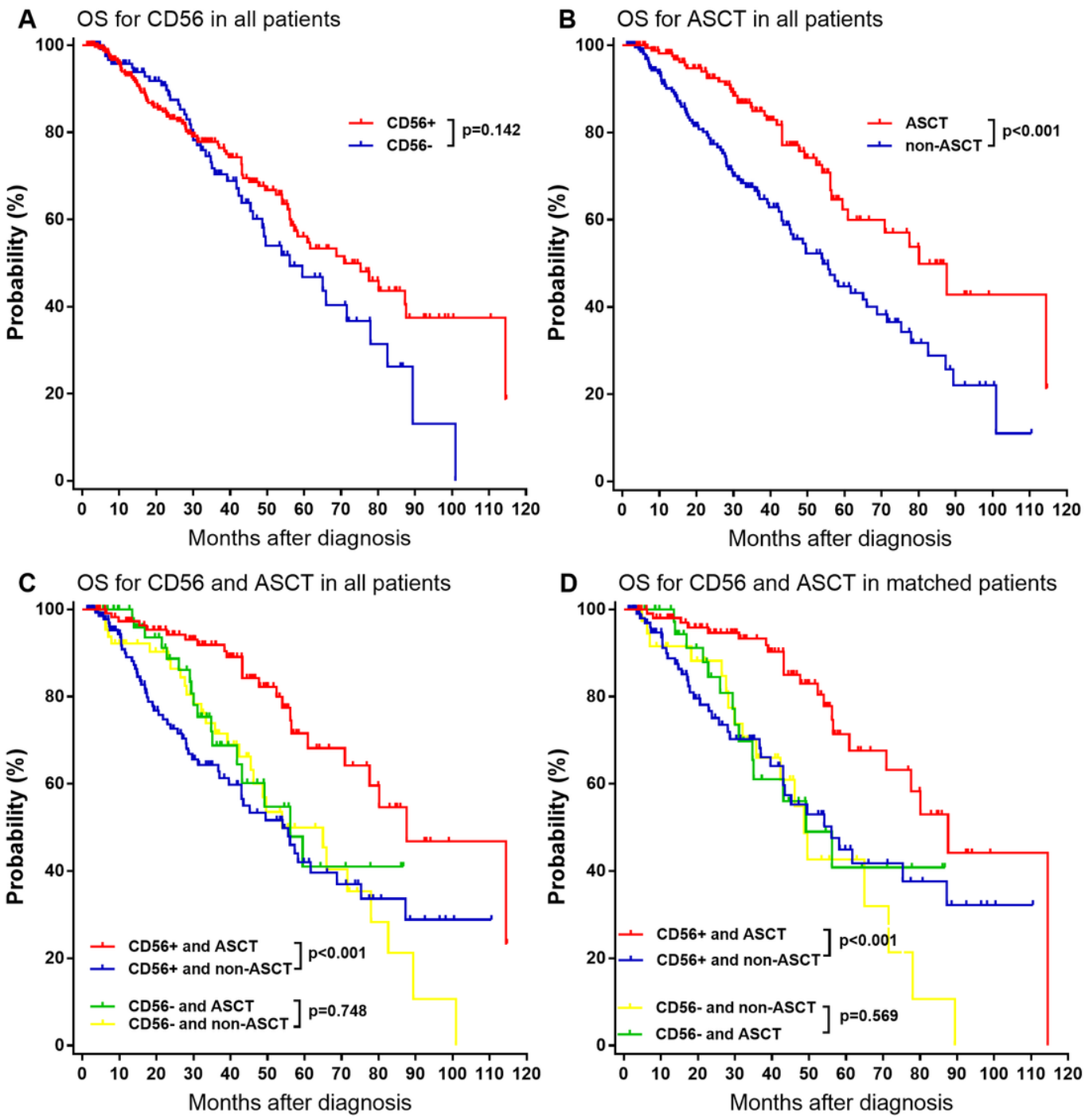

Figure 1

Kaplan-Meier survival curves on OS of patients with NDMM. (A) all patients. (B) all patients. (C) all patients. (D) matched patients.

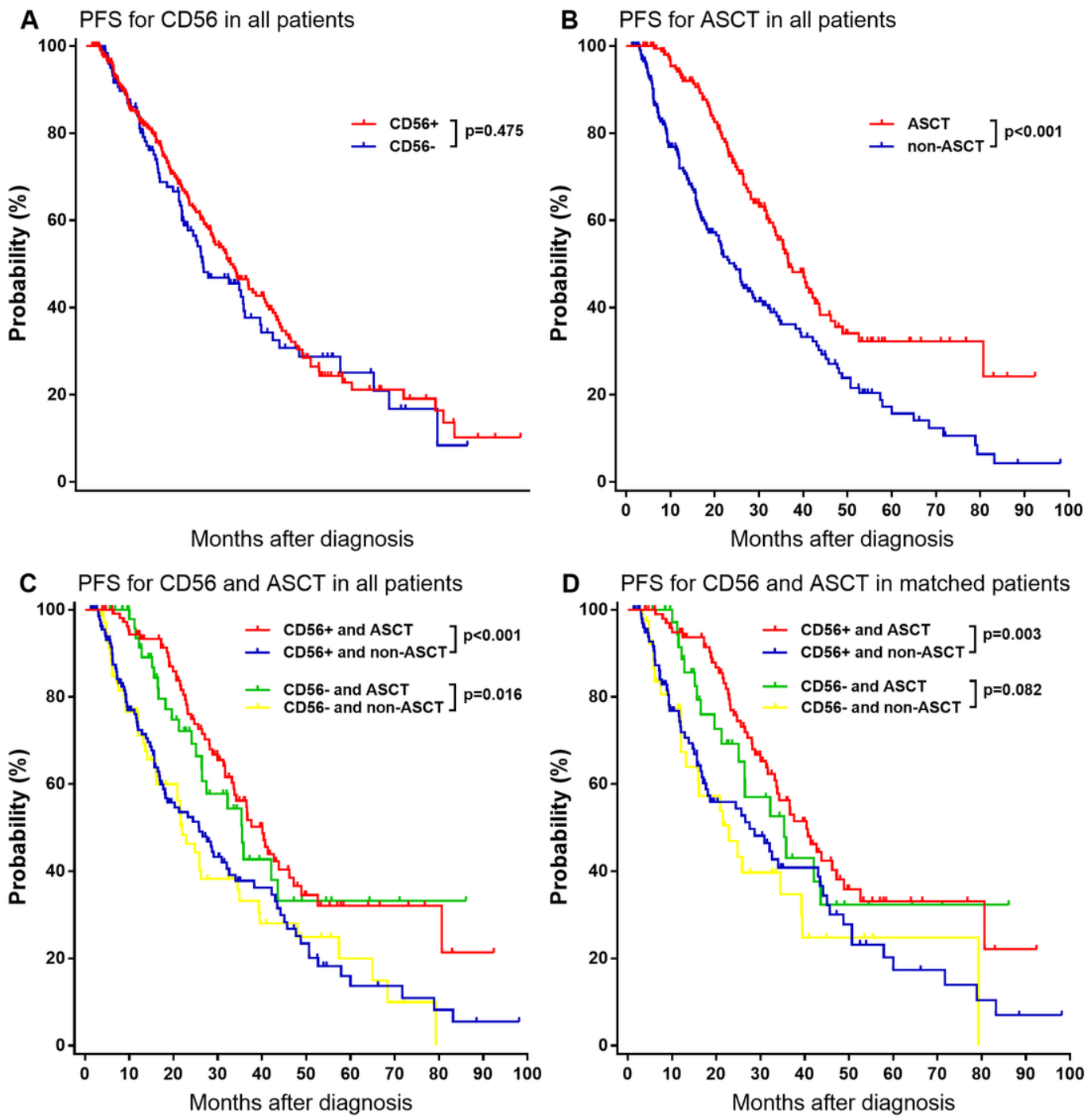

Figure 2

Kaplan-Meier survival curves on PFS of patients with NDMM. (A) all patients. (B) all patients. (C) all patients. (D) matched patients.