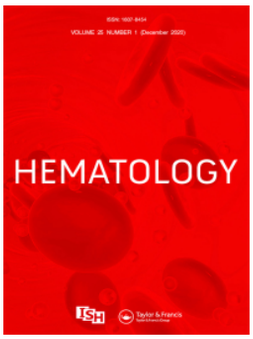

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Time to progression predicts outcome of patients with multiple myeloma that can be influenced by autologous hematopoietic stem cell transplantation

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ABSTRACT

Objectives: Currently, there is limited understanding regarding the prognostic significance of time to progression (TTP) after first remission in multiple myeloma (MM).

Methods: We conducted a retrospective analysis of clinical data from 209 patients with MM. These patients were categorized into ≤ 6 months, ≤ 12 months, ≤ 24 months, > 24 months, 6–12 months, and 12–24 months subgroups based on TTP.

Results: Patients in ≤ 12 months group exhibited shorter median overall survival (OS) and OS-1 compared to those in ≤ 24 months group (61.73 vs 96.10 months, $P = 0.02$; 54.00 vs 74.17 months, $P = 0.048$). ≤ 6 months group exhibited shorter median OS and OS-1 compared to 6–12 months group (33.63 vs 79.60 months, $P = 0.022$; 19.93 vs 65.17 months, $P = 0.015$). Patients in 6–12 months group had shorter median OS and OS-1 compared to those in 12–24 months group (79.60 vs 100.43 months, $P < 0.001$; 65.17 vs 77.17 months, $P = 0.012$).No significant difference in OS was observed between patients in 12–24 months and > 24 months groups. For patients who experienced progression within 12 or 24 months after remission, undergoing autologous hematopoietic stem cell transplantation (ASCT) after progression conferred a median OS and OS-2 advantage over receiving post-progression chemotherapy. Multivariable analysis confirmed that TTP was an independent predictor for OS in patients with MM.

Conclusion: Patients with MM who experience earlier disease progression within 12 months after remission have a worse prognosis, and post-progression ASCT can improve their survival outcomes.

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KEYWORDS
Multiple myeloma; first remission; myeloma progression; time to progression; post-progression treatment; autologous hematopoietic stem cell transplantation; chemotherapy; outcome

Plain language summary

Nowadays, we don't have a very good understanding of how important the time it takes for multiple myeloma (MM) to progress after a patient first responds well to treatment (known as very good partial remission or complete remission) is in predicting how long the patient will live. In this study, we looked at how long it took for MM to progress again after the good response to treatment by analyzing the data of 209 patients with MM. The patients were grouped based on how long it took for their disease to progress again (time to progression, TTP). The study found that patients whose disease progressed within 12 months had a shorter overall survival compared to those who progressed later. It also showed that for patients who experienced progression within 12 or 24 months, getting a specific type of treatment (autologous hematopoietic stem cell transplantation, ASCT) after progression could improve their survival outcomes. Overall, the study suggests that TTP after a good response to treatment is important for predicting survival in patients with MM, and post-progression ASCT can be beneficial for some patients.

Introduction

Multiple myeloma (MM) is a clonal plasma cell disease, the second most common hematologic malignancy [1]. While a widespread adoption of novel agents and autologous stem cell transplant (ASCT) has significantly improved survival in patients with MM [2–4], MM remains incurable with nearly all patients experiencing progression and relapse following initial treatment. Consequently, it becomes crucial to ascertain the prognostic value of MM progression and relapse. A clear understanding of the primary prognostic factors can facilitate risk stratification and aid in making informed treatment decisions.

A comprehensive analysis is required to determine the precise impact of MM progression on prognosis.

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Factors such as the depth and duration of remission, patterns of progression, and treatments administered before and after progression can significantly influence the overall survival (OS) of MM patients [5–7]. Previous studies have reported that early relapse within 12 or 24 months following initial therapy is associated with poorer survival outcomes for patients with MM [5,7–9]. Furthermore, it has been observed that patients with MM experiencing clinical progression exhibit inferior post-progression outcomes compared to those with biochemical progression [10]. However, the real-world prevalence of time to progression (TTP) after achieving very good partial remission (VGPR) or complete remission (CR), as well as its clinical significance on MM patient outcomes, remains poorly understood, especially for patients who experience disease progression within 6 months or between one and two years after remission. Therefore, it is crucial to make more precise grouping based on TTP and investigate the clinical and survival disparities among patients with MM who experience progression at different time intervals following VGPR/CR. This study not only provided a comprehensive and precise stratification based on patient's TTP but also examined the impact of post-progression treatments on clinical outcome. Such an investigation would aid in identifying risk factors more accurately and timely modifications to therapy, ultimately improving patient outcomes.

We designed a retrospective study of patients with MM who experienced disease progression after achieving VGPR or CR with first-line therapy. The primary objective was to investigate the influence of TTP after VGPR or CR on survival in a real-world setting. Additionally, we aimed to elucidate the baseline characteristics of MM patients with varying time intervals from VGPR/CR to MM progression and determine whether any of these baseline characteristics could serve as predictors for the timing of the first MM progression.

Patients and methods

Patients

This retrospective study received approval from the Institutional Review Board of the Third Affiliated Hospital of Soochow University and was conducted in adherence to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participating patients. A total of 402 newly diagnosed patients with MM underwent first-line induction chemotherapy and were able to be evaluated for response assessment at our institution from January 2010 to April 2023. Of these, 258 (63.26%) patients fulfilled the criteria for achieving VGPR or CR according to the recommendations of the International Myeloma Working Group (IMWG) [11]. Subsequently, of the 258, 11 patients did not receive consolidation therapy, 222 patients received consolidation chemotherapy, and sequential ASCT was performed in the other 25 patients who were excluded in this study. During the follow-up period, of the 233, 223 patients either experienced their first MM progression or showed no MM progression with a follow-up duration more than 24 months. Among the 223 patients with MM, 14 individuals were excluded from the analysis. This exclusion encompassed 9 cases that received cellular immunotherapy and 5 cases that accepted CD38 monoclonal antibody therapy after progression. The first-line induction chemotherapy in this study included conventional chemotherapy (e.g. vincristine, melphalan, cyclophosphamide, doxorubicin, and dexamethasone), and proteasome inhibitors (PIs) or/and immunomodulators (IMiDs) based chemotherapy. Post-progression treatments included conventional chemotherapy, PIs or/and IMiDs based chemotherapy, and ASCT with maintenance therapy. Patients meeting any of the following criteria were also excluded from the study: those with monoclonal gammopathies of undetermined significance, smoldering MM, solitary plasmacytoma, primary refractory disease, or insufficient data to determine the occurrence of disease progression or relapse. Ultimately, a total of 209 patients with MM were included in this study (Figure 1). Among the 209 patients who did not undergo ASCT as first-line treatment, 38 were older than 70 years, 35 had significant comorbidities despite being under 70 years, 53 had ASCT deferred, and 83 declined the procedure.

We retrospectively collected clinical and laboratory data at the time of diagnosis, as well as information regarding treatment regimens and treatment response. High risk cytogenetics was limited to del17p, t(4;14), and t(14;16). All patients were followed up until April 23, 2023, or until their death. Follow-up was conducted through telephone calls and verification of medical records. The starting point of TTP was the time of achieving the best response (VGPR or CR). OS was defined as the duration from the time of diagnosis to the last follow-up or death from any cause. OS-1 was defined as the period from the occurrence time of MM progression after the first VGPR or CR to the last follow-up or death. OS-2 was defined as the period from the initial time of post-progression treatment to the last follow-up or death. According to the IMWG criteria [11], progression or relapse was determined by the presence of CRAB symptoms (hypercalcemia, renal failure, anemia, and bone lesions) or new extramedullary plasmacytoma, or an increase of 25% or more from the nadir of measurable monoclonal protein levels or free light chain difference in the serum or urine.

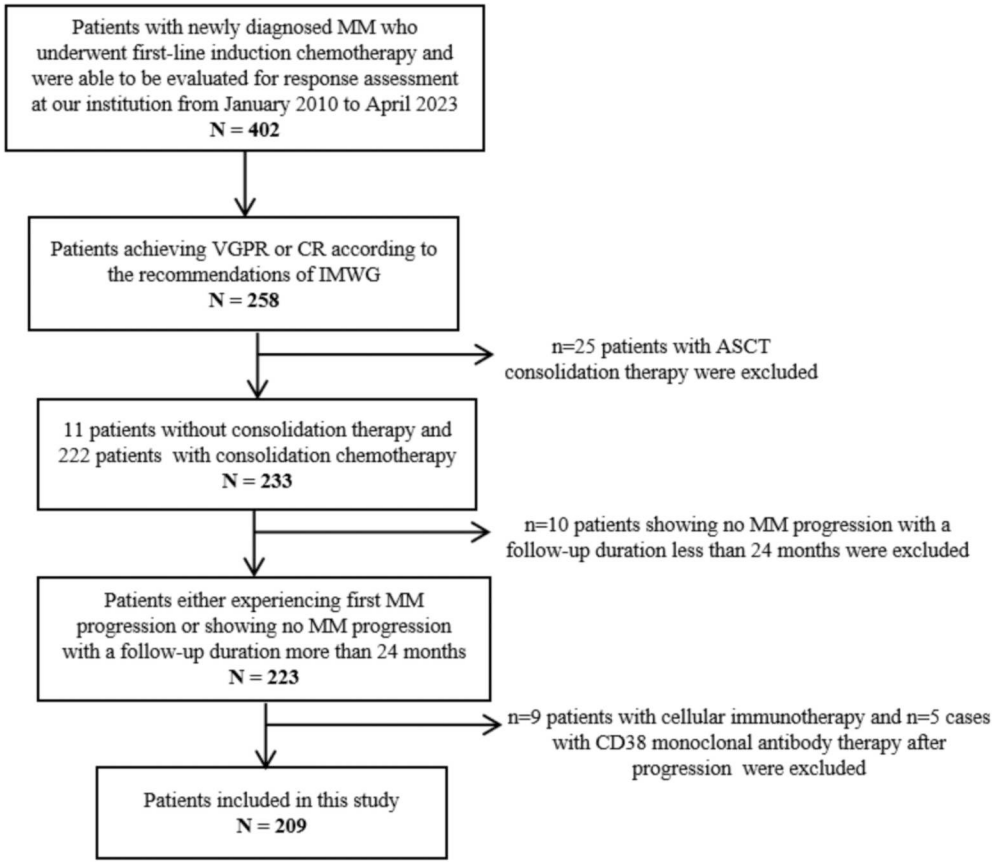


Figure 1. Cohort selection process.

Based on the time elapsed from achieving VGPR or CR to MM progression, the patients were categorized into four groups: ≤ 6 months, ≤ 12 months, ≤ 24 months, and > 24 months, with the latter group including patients with MM who did not experience disease progression during more than 24 months of follow-up. Furthermore, patients who progressed between 6 and 24 months after achieving VGPR/CR were subdivided into 6–12 months group (6 months < TTP ≤ 12 months), and 12–24 months group (12 months < TTP ≤ 24 months).

Statistical analysis

Continuous variables were categorized based on cut-off values determined by receiver operating characteristic (ROC) curve analysis. Categorical variables were represented as numeric values (percentages). The χ^2 test and Fisher's exact test were used to compare the differences of categorical variables. Survival analysis was conducted using Kaplan–Meier method and log-rank test. Univariable and multivariable survival analysis, as well as MM progression assessments, were performed using Cox proportional hazards model, the results of which are reported as hazard ratios with 95% confidence intervals (CIs). Two-sided *P* values < 0.05 were considered to be statistically significant. Statistical analysis was performed with IBM SPSS 23.0 (IBM Inc., Armonk, USA) and Prism software (version 7, GraphPad).

Results

Baseline characteristics

The baseline characteristics of patients at the time of MM diagnosis are presented in Table 1. A total of 209 patients were included in the final analysis and were divided into four groups based on the time from achieving VGPR/CR to MM progression: ≤ 6 months (13 cases), ≤ 12 month (57 cases), ≤ 24 months (97 cases), and > 24 months (112 cases). The median age of patients in the four groups was 68, 64, 63, and 62 years, respectively, showing a gradual decrease. Among the four groups, no significant differences were observed in the categorical distribution of hemoglobin (HGB) level, blood calcium level, β2-microglobulin, serum creatinine (Scr) level, lactate dehydrogenase (LDH), albumin (ALB) level, bone disease, cytogenetic risk, treatment after progression, and treatment response before progression. However, the ≤ 6 months group had the highest proportion of patients with high Eastern Cooperative Oncology Group (ECOG) scores compared to the other three groups. Patients in the ≤ 12 months group were more likely to have high-risk features,

Table 1. Correlations between MM progression and clinical features in patients with MM who have achieved VGPR/CR.

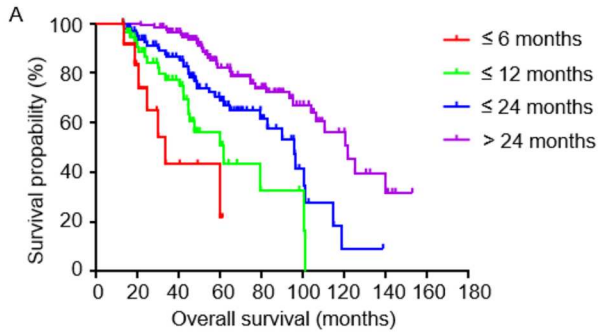
Patient features	TTP ≤ 6 months (*N* = 13) *n* (%)	TTP ≤ 12 months (*N* = 57) *n* (%)	TTP ≤ 24 months (*N* = 97) *n* (%)	TTP > 24 months (*N* = 112) *n* (%)	χ^2	*P*
Age (median, years)	68	64	63	62	16.305	**0.001**
< 68	3 (23.08)	33 (57.89)	56 (57.73)	83 (74.11)		
≥ 68	10 (76.92)	24 (42.11)	41 (42.27)	29 (25.89)		
ECOG					15.362	**0.001**
≤1	4(30.77)	30(52.63)	55 (57.29)	83 (74.11)		
≥2	9(69.23)	27(47.37)	41 (42.71)	29 (25.89)		
ISS stage					10.071	**0.018**
I-II	7(53.85)	24(42.11)	42 (43.30)	70(62.5)		
III	6(46.15)	33(57.89)	55 (56.70)	42(37.5)		
BMPC%					9.345	**0.023**
< 35.25	8(72.73)	32(57.14)	41(42.71)	67(62.04)		
≥ 35.25	3(27.27)	24(42.86)	55(57.29)	41(37.96)		
HGB (g/L)					0.912	0.832
<81.5	4(30.77)	22(38.60)	39(40.21)	39(34.82)		
≥ 81.5	9(69.23)	35(61.40)	58(59.79)	73(65.18)		
Ca^{2+} (mmol/L)					2.013	0.57
< 2.505	10(30.77)	34(59.65)	55(56.70)	68(60.71)		
≥ 2.505	3(69.23)	23(40.35)	42(43.30)	44(39.29)		
β_2-MG (mg/L)					0.9	0.825
<4.78	5(38.46)	28(49.12)	48(50)	51(45.54)		
≥4.78	8(61.54)	29(50.88)	48(50)	61(54.46)		
Scr (mmol/L)					4.011	0.258
<137.5	6(46.15)	41(71.93)	71(73.20)	81(72.32)		
≥137.5	7(53.85)	16(28.07)	26(26.80)	31(27.68)		
LDH (U/L)					4.338	0.226
<151.5	2(15.38)	17(29.82)	40(41.24)	39(34.82)		
≥151.5	11(84.62)	40(70.18)	57(58.76)	73(65.18)		
ALB (g/L)					1.596	0.675
<27.45	1(7.69)	13(22.81)	23(23.71)	27(24.11)		
≥27.45	12(92.31)	44(77.19)	74(76.29)	85(75.89)		
CRP (mg/L)					24.32	**<0.001**
<5.845	6(46.15)	19(33.33)	41(42.27)	77(68.75)		
≥5.845	7(53.85)	38(66.67)	56(57.73)	35(31.25)		
Bone disease					1.438	0.709
Yes	11(84.62)	46(80.70)	77(79.38)	83(74.11)		
No	2(15.38)	11(19.30)	20(20.62)	29(25.89)		
Cytogenetic abnormalities					6.923	0.071
Standard risk	7(53.85)	31(54.39)	56(57.73)	80(71.43)		
High risk	6(46.15)	26(45.61)	41(42.27)	32(28.57)		
First-line induction chemotherapy					289.729	**<0.001**
Conventional chemotherapy	5(38.46)	18(31.58)	25(25.77)	23(20.54)		
Doublet	2	5	6	6		
Triplet	3	13	19	17		
PIs or/and IMiDs based chemotherapy	8(61.54)	39(68.42)	72(74.23)	89(79.46)		
Doublet	3	15	22	29		
Triplet	4	22	46	56		
Quads	1	2	4	4		
Treatment after progression					6.661	0.345
Conventional chemotherapy	3(23.07)	13(22.81)	16(16.49)	15(13.39)		
PIs or/and IMiDs based chemotherapy	8(61.54)	28(49.12)	52(53.61)	73(65.18)		
ASCT	2(15.38)	16(28.07)	29(29.90)	24(21.43)		
Treatment response					1.485	0.686
CR	6(46.15)	24(42.11)	38(39.18)	53(50.56)		
VGPR	7(53.85)	33(57.89)	59(60.82)	59(49.44)		

ALB: albumin, ASCT: autologous hematopoietic stem cell transplantation, BMPC: bone marrow plasmacyte, β_2-MG: β_2-microglobulin, Ca^{2+}: calcium, CI: confidence interval, CR: complete remission, CRP: C-reactive protein, Doublet: 2-drug combination, ECOG: eastern cooperative oncology group, HGB: hemoglobin, IMiDs: immunomodulatory drugs, ISS: international staging system, LDH: lactate dehydrogenase, PIs: proteasome inhibitors, Quads: 4-drug combination, Scr: serum creatinine, Triplet: 3-drug combination, TTP: time to progression, VGPR: very good partial remission.

including ISS stage and C-reactive protein (CRP). The ≤ 24 months group showed the highest proportion of plasma cells in the bone marrow. Of the 209 patients, 48 (22.97%) received first-line conventional induction chemotherapy, 161 (77.03%) opted for first-line induction chemotherapy based on PIs and/or IMiDs. A significant difference in first-line induction chemotherapy was observed across the four groups. Following the first progression of MM, 31 patients (14.83%) continued with conventional chemotherapy, 125 patients (59.81%) chose PIs and/or IMiDs-based chemotherapy, and 53 patients (25.36%) underwent autologous stem cell transplantation (ASCT). No significant differences were found in the distribution of post-progression treatment modalities across the four groups.

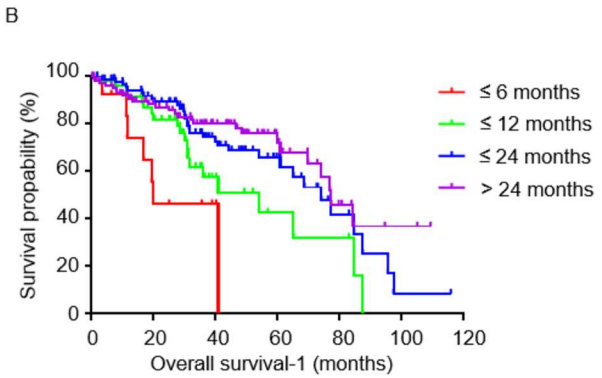
Survival

A total of 209 patients with MM who achieved VGPR/CR after first-line therapy were followed up for a median duration of 69.06 months (95% CI: 60.57–77.57 months). During the follow-up, 186 (89%) cases



Groups	P value
≤ 6 months vs ≤ 12 months	0.084
≤ 12 months vs ≤ 24 months	**0.020**
≤ 24 months vs > 24 months	< **0.001**

Group	N	Events	Median survival (95% CI, months)
≤ 6 months	13	7 (53.85%)	33.63(20.79-46.41)
≤ 12 months	57	23 (40.35%)	61.73(38.93-84.54)
≤ 24 months	97	37 (38.14%)	96.10(81.18-111.02)
> 24 months	112	31 (27.68%)	121.73(105.69-137.77)



Groups	P value
≤ 6 months vs ≤ 12 months	0.065
≤ 12 months vs ≤ 24 months	**0.048**
≤ 24 months vs > 24 months	0.339

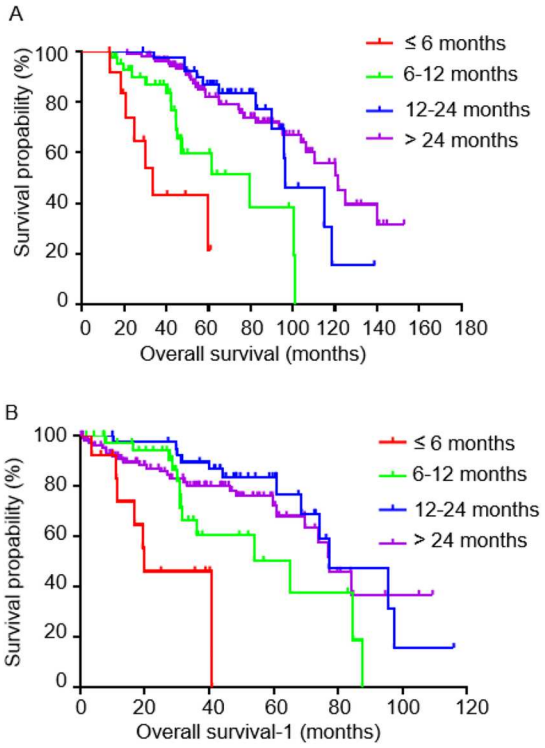
Group	N	Events	Median survival-1 (95% CI, months)
≤ 6 months	13	7 (53.85%)	19.93(8.05-31.81)
≤ 12 months	57	23 (40.35%)	54.00(18.01-63.72)
≤ 24 months	97	37 (38.14%)	74.17(60.67-87.66)
> 24 months	112	31 (27.68%)	77.37(68.43-85.43)

Figure 2. OS and OS-1 of myeloma patients in TTP ≤ 6 months, ≤ 12 months, ≤ 24 months, and > 24 months groups. OS curve (A) and OS-1 curve (B) by Kaplan – Meier survival analysis. CI: confidence interval. OS: overall survival. OS-1: the starting point from the occurrence time of MM progression. TTP: time to progression.

experienced MM progression, with 103 (55.38%) cases progressing after VGPR and 83 (44.62%) cases progressing after CR. There were 66 deaths, of which 5 cases were due to causes unrelated to MM. As depicted in Figure 2(A) and (B), the median OS and OS-1 for patients in the ≤ 6 months group were 33.63 (95% CI: 20.79–46.41) and 19.93 (95% CI: 8.05–31.81) months, compared to 61.73 (95% CI: 38.93–84.54) months and 54.00 (95% CI: 18.01–63.72) months in the ≤ 12 months group ($P = 0.084$ and $P = 0.065$). Patients in the ≤ 12 months group had a shorter median OS and OS-1 compared to those in the ≤ 24 months group [61.73 (95% CI: 38.93–84.54) vs 96.10 (95% CI: 81.18–111.02) months, $P = 0.02$; 54.00 (95% CI: 18.01–63.72) vs 74.17 (95% CI: 60.67–87.66) months, $P = 0.048$, Figure 2(A) and (B)], as well as a shorter median OS for patients in the ≤ 24 months vs > 24 months group [96.10 (95% CI: 81.18–111.02) vs 121.73 (95% CI: 105.69–137.77) months, $P < 0.001$; Figure 2(A)] while there was no significant difference in OS-1 between ≤ 24 months and > 24 months groups [74.17 (95% CI: 60.67–87.66) vs 77.37 (95% CI: 68.43–85.43) months, $P = 0.339$; Figure 2(B)].

Furthermore, to analyse the patients with 6 months < TTP ≤ 24 months, we specifically subdivided them into two additional groups: 6–12 months (44 cases) and 12–24 months (40 cases). Comparing the ≤ 6 months group with the 6–12 months group, the median OS and OS-1 for patients in the ≤ 6 months group were 33.63 (95% CI: 20.79–46.41) months and 19.93 (95% CI: 8.05–31.81) months, while for patients in the 6–12 months group, they were 79.60 (95% CI: 37.98–121.22) months and 65.17 (95% CI: 21.18–86.82) months [$P = 0.022$ and $P = 0.015$, Figure 3(A) and (B)]. Furthermore, compared to the 6–12 months group, patients in the 12–24 months group showed longer median OS and OS-1 [100.43 (95% CI: 76.09–117.05) vs 79.60 (95% CI: 37.98–121.22) months, $P < 0.001$; 77.17 (95% CI: 54.65–99.68) vs 65.17 (95% CI: 21.18–86.82) months, $P = 0.012$, Figure 3(A) and (B)]. In addition, the median OS and OS-1 for patients in the > 24 months group were 121.73 (95% CI: 105.69–137.77) months and 77.37 (95% CI: 68.43–85.43) months, while they were 100.43 (95% CI: 76.09–117.05) months and 77.17 (95% CI: 54.65–99.68) months for patients in the 12–24 months group [$P = 0.683$ and $P = 0.535$, Figure 3(A) and (B)].

Considering the impact of both first-line induction chemotherapy and post-progression treatment on survival, we compared survival outcomes in patients treated with PIs and/or IMiDs-based induction chemotherapy between 2-drug and 3-drug combination groups, when sample sizes permitted. In patients with TTP ≤ 24 months, those in the triplet group showed a significant median OS advantage compared to the doublet group [99.38 (95% CI: 85.07–113.69) vs 64.7 (95% CI: 50.81–78.59) months, $P = 0.013$, Figure S1A]. In contrast, for patients with TTP > 24 months, no significant difference in OS was observed between the two groups [125.07 (95% CI: 79.15–170.99) vs. 127.09 (95% CI: 113.90–140.29) months, $P = 0.129$, Figure S1B]. Then, we categorized patients



Groups	P value
≤ 6 months vs 6-12 months	**0.022**
6-12 months vs 12-24 months	< **0.001**
12-24 months vs > 24 months	0.683

Group	N	Events	Median survival (95% CI, months)
≤ 6 months	13	7 (53.85%)	33.63(20.79-46.41)
6-12 months	44	16 (36.36)	79.60(37.98-121.22)
12-24 months	40	14 (35.00)	100.43(76.09-117.05)
> 24 months	112	31 (27.68%)	121.73(105.69-137.77)

Groups	P value
≤ 6 months vs 6-12 months	**0.015**
6-12 months vs 12-24 months	**0.012**
12-24 months vs > 24 months	0.535

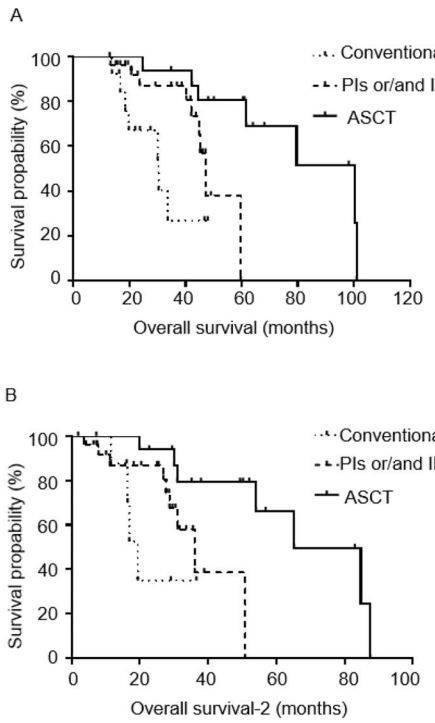
Group	N	Events	Median survival-1 (95% CI, months)
≤ 6 months	13	7 (53.85%)	19.93(8.05-31.81)
6-12 months	44	16 (36.36)	65.17(21.18-86.82)
12-24 months	40	14 (35.00)	77.17(54.65-99.68)
> 24 months	112	31 (27.68%)	77.37(68.43-85.43)

Figure 3. OS and OS-1 of myeloma patients in TTP ≤ 6, 6 months < TTP ≤ 12, 12 months < TTP ≤ 24 months, and TTP > 24 months groups. OS curve (A) and OS-1 curve (B) by Kaplan–Meier survival analysis. 6 −12 months: 6 months < TTP ≤ 12 months, 12 −24 months: 12 months < TTP ≤ 24 months. CI: confidence interval. OS: overall survival. OS-1: the starting point from the occurrence time of MM progression. TTP: time to progression. VGPR: very good partial remission. CR: complete remission.

into three groups based on their post-progression treatment: conventional chemotherapy group, PIs or/and IMiDs based chemotherapy group, and ASCT group. For patients who experienced progression within 12 months after VGPR/CR, those in the ASCT group had a significant median OS and OS-2 advantage compared to those in the conventional chemotherapy group [100.43 (95% CI: 64.51–136.36) vs 30.37 (95% CI: 17.37–43.36) months, $P = 0.002$; 65.17 (95% CI: 38.63–91.71) vs 19.43 (95% CI: 13.38–20.49) months, $P = 0.004$, Figure 4(A) and (B)] or in the PIs or/and IMiDs based chemotherapy group [100.43 (95% CI: 64.51–136.36) vs 47.20 (95% CI: 43.40–51.00) months, $P = 0.022$; 65.17 (95% CI: 38.63–91.71) vs 36.07 (95% CI: 27.03–45.10) months, $P = 0.021$, Figure 4(A) and (B)]. Additionally, the PIs or/and IMiDs based chemotherapy group demonstrated a longer median OS compared to the conventional chemotherapy group [47.2 (95% CI: 43.40–51.00) vs 30.37 (95% CI: 17.37–43.36) months, $P = 0.036$, Figure 4(A)], while there was no difference in OS-2 between the two groups [36.07 (95% CI: 27.03–45.10) vs 19.43 (95% CI: 13.38–20.49) months, $P = 0.269$, Figure 4(B)]. Similarly, for patients who progressed within 24 months after VGPR/CR, the ASCT group exhibited a superior median OS of 101.00 (95% CI: 94.19–107.81) months and a superior median OS-2 of 84.73 (95% CI: 67.22–102.24) months compared to 33.63 (95% CI: 21.10–46.17) months and 21.43 (95% CI: 9.29–34.58) months in the conventional chemotherapy group or 80.10 (95% CI: 61.64–98.56) months and 60.87 (95% CI: 37.99–83.75) months in the PIs or/and IMiDs based chemotherapy group [OS: $P < 0.001$ and $P = 0.004$, Figure 5(A); OS-2: $P < 0.001$ and $P = 0.002$, Figure 5(B)]. Furthermore, PIs or/and IMiDs-based chemotherapy also improved the median OS and OS-2 compared to conventional chemotherapy [80.10 (95% CI: 61.64–98.56) vs 33.63 (95% CI: 21.10–46.17) months, $P = 0.002$; 60.87 (95% CI: 37.99–83.75) vs 21.43 (95% CI: 9.29–34.58) months, $P = 0.008$; Figure 5(A) and (B)].

Univariable and multivariable analysis for OS and myeloma progression

A univariable analysis demonstrated that TTP after VGPR or CR strongly predicted OS in patients with MM. Additionally, factors such as age, ECOG performance status, ISS stage, serum creatinine level, cytogenetic abnormalities and post-progression treatment were also found to be associated with OS (Table 2). Variables that were statistically significant in the univariable analysis were included in the multivariable analysis. Three different Cox proportional hazards models were constructed based on TTP. The multivariable analysis in all three models confirmed the positive effects of standard-risk cytogenetics, ASCT, and longer TTP durations (>6 months, >12 months, and >24 months) on OS (Table 2). Furthermore, the univariable analysis indicated that ECOG performance status, ISS



Groups	P value
PIs or/and IMiDs based chemotherapy vs conventional chemotherapy	**0.036**
ASCT vs conventional chemotherapy	**0.002**
ASCT vs PIs or/and IMiDs based chemotherapy	**0.022**

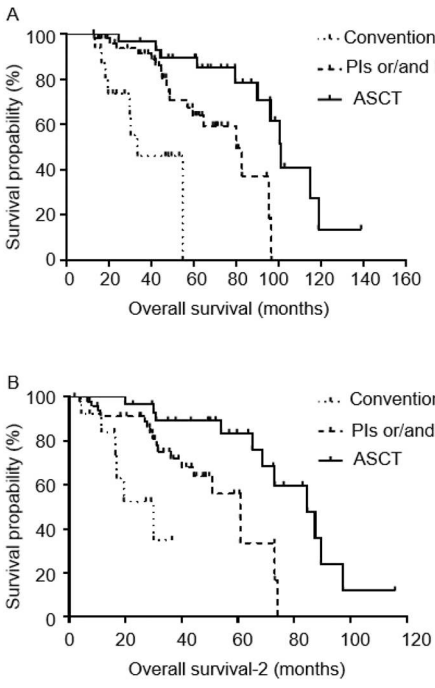
Group	N	Events	Median survival (95% CI, months)
Conventional chemotherapy	13	7 (53.85%)	30.37(17.37-43.36)
PIs or/and IMiDs based chemotherapy	28	9 (32.14%)	47.20(43.40-51.00)
ASCT	16	7 (43.75%)	100.43(64.51-136.36)

Groups	P value
PIs or/and IMiDs based chemotherapy vs conventional chemotherapy	0.269
ASCT vs conventional chemotherapy	**0.004**
ASCT vs PIs or/and IMiDs based chemotherapy	**0.021**

Group	N	Events	Median survival-2 (95% CI, months)
Conventional chemotherapy	13	7 (53.85%)	19.43(13.38-20.49)
PIs or/and IMiDs based chemotherapy	28	9 (32.14%)	36.07(27.03-45.10)
ASCT	16	7 (43.75%)	65.17(38.63-91.71)

Figure 4. OS and OS-2 of myeloma patients who progressed within 12 months after VGPR/CR in different post-progression treatments groups. OS curve (A) and OS-2 curve (B) by Kaplan–Meier survival analysis. ASCT: autologous hematopoietic stem cell transplantation. CI: confidence interval. IMiDs: immunomodulatory drugs. OS: overall survival. OS-2: the starting point from the initial time of post-progression treatment. PIs: proteasome inhibitors. VGPR: very good partial remission. CR: complete remission.

stage, CRP level, cytogenetic abnormalities, and first-line induction chemotherapy significantly influenced MM progression within 24 months after VGPR/CR. Specifically, poor ECOG status, ISS stage III, high CRP level, and first-line conventional induction chemotherapy independently increased the risk of MM progression according to the multivariable analysis (Table 3).



Groups	P value
PIs or/and IMiDs based chemotherapy vs conventional chemotherapy	**0.002**
ASCT vs conventional chemotherapy	**< 0.001**
ASCT vs PIs or/and IMiDs based chemotherapy	**0.004**

Group	N	Events	Median survival (95% CI, months)
Conventional chemotherapy	16	8 (50.00%)	33.63(21.10-46.17)
PIs or/and IMiDs based chemotherapy	52	18 (34.62%)	80.10(61.64-98.56)
ASCT	29	11 (37.93%)	101.00(94.19-107.81)

Groups	P value
PIs or/and IMiDs based chemotherapy vs conventional chemotherapy	**0.008**
ASCT vs conventional chemotherapy	**< 0.001**
ASCT vs PIs or/and IMiDs based chemotherapy	**0.002**

Group	N	Events	Median survival-2 (95% CI, months)
Conventional chemotherapy	16	8 (50.00%)	21.43(9.29-34.58)
PIs or/and IMiDs based chemotherapy	52	18 (34.62%)	60.87(37.99-83.75)
ASCT	29	11 (37.93%)	84.73(67.22-102.24)

Figure 5. OS and OS-2 of myeloma patients who progressed within 24 months after VGPR/CR in different post-progression treatments groups. OS curve (A) and OS-2 curve (B) by Kaplan–Meier survival analysis. ASCT: autologous hematopoietic stem cell transplantation. CI: confidence interval. IMiDs: immunomodulatory drugs. OS: overall survival. OS-2: the starting point from the initial time of post-progression treatment. PIs: proteasome inhibitors. VGPR: very good partial remission. CR: complete remission.

Table 2. Univariable and multivariable analysis of prognostic factors for OS in patients with MM who achieved VGPR/CR.

			Model1		Model2		Model3	
	Univariable analysis		Multivariable analysis		Multivariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (< 68 vs ≥ 68)	2.322 (1.391–3.877)	**0.001**	0.842 (0.424-1.672)	0.623	1.107 (0.581-2.110)	0.758	0.939 (0.492-1.789)	0.847
ECOG (≤1 vs ≥2)	2.523 (1.538–4.138)	**<0.001**	1.729 (0.908-3.291)	0.095	1.474 (0.786-2.763)	0.226	1.678 (1.913-3.084)	0.096
ISS stage (I-II vs III)	1.889 (1.167–3.056)	**0.01**	1.610 (0.985-2.632)	0.058	1.483 (0.901-2.442)	0.122	1.455 (0.885-2.392)	0.139
BMPC% (<35.25 vs ≥35.25)	1.589 (0.913–2.768)	0.102						
HGB (g/L, < 81.5 vs ≥81.5)	1.354 (0.803–2.282)	0.256						
Ca^{2+} (mmol/L, < 2.505 vs ≥2.505)	1.555 (0.966–2.503)	0.069						
β_2-MG (mg/L, < 4.78 vs ≥4.78)	1.067 (0.662–1.72)	0.789						
Scr (mmol/L, < 137.5 vs ≥137.5)	1.806 (1.107–2.948)	**0.018**	1.470 (0.873–2.476)	0.148	1.574 (0.936–2.646)	0.087	1.452 (0.843–2.501)	0.178
LDH (U/L, < 151.5 vs ≥151.5)	1.076 (0.659–1.757)	0.771						
ALB (g/L, < 27.45 vs ≥27.45)	1.206 (0.680–2.141)	0.521						
CRP (mg/L, < 5.845 vs ≥5.845)	1.406 (0.870–2.272)	0.165						
Bone disease (Yes vs No)	1.112 (0.64–1.931)	0.706						
Cytogenetic abnormalities (Standard risk vs High risk)	3.078 (1.893–5.004)	**<0.001**	2.606 (1.573–4.317)	**<0.001**	2.088 (1.239–3.519)	**0.006**	2.362 (1.413–3.948)	**0.001**
First-line induction chemotherapy								
Conventional chemotherapy vs PIs or/and IMiDs based chemotherapy	1.642 (0.977–2.76)	0.061						
Treatment after progression								
Conventional chemotherapy vs PIs or/and IMiDs based chemotherapy	0.377 (0.197–0.724)	**0.003**						
Conventional chemotherapy vs ASCT	0.349 (0.216–0.565)	**<0.001**						
PIs or/and IMiDs based chemotherapy vs ASCT	0.379 (0.198–0.727)	**0.003**						
Conventional chemotherapy or PI or/and IMiD based chemotherapy vs ASCT	0.328 (0.175–0.615)	**0.001**	0.322 (0.164–0.630)	**0.001**	0.208 (0.104–0.417)	**<0.001**	0.283 (0.145–0.555)	**<0.001**
Treatment response (CR vs VGPR)	1.193 (0.733–1.941)	0.477						
TTP after VGPR/CR								
≤ 6 months vs >6 months	0.129 (0.056–0.294)	**<0.001**	0.236 (0.098–0.568)	**0.001**				
≤ 12 months vs >12 months	0.209 (0.121–0.361)	**<0.001**			0.177 (0.092–0.340)	**<0.001**		
≤ 24 months vs >24 months	0.404 (0.246–0.665)	**<0.001**					0.493 (0.285–0.856)	**0.012**

ALB: albumin, ASCT: autologous hematopoietic stem cell transplantation, BMPC: bone marrow plasmacyte, β_2-MG: β_2-microglobulin, Ca^{2+}: calcium, CI: confidence interval, CR: complete remission, CRP: C-reactive protein, ECOG: eastern cooperative oncology group, HGB: hemoglobin, IMiDs: immunomodulatory drugs, ISS: international staging system, LDH: lactate dehydrogenase, PIs: proteasome inhibitors, TTP: time to progression, VGPR: very good partial remission.

Table 3. Univariable and multivariable analysis of risk factors for MM progression within 24 months after VGPR/CR.

	Univariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (< 68 vs ≥68)	1.431 (0.943–2.1736)	0.092		
ECOG (≤1 vs ≥2)	0.581 (0.389–0.870)	**0.008**	1.589 (1.057–2.388)	**0.026**
ISS stage (I-II vs III)	1.780 (1.190–2.662)	**0.005**	1.559 (1.029–2.362)	**0.036**
BMPC% (<35.25 vs ≥35.25)	1.199 (0.750–1.916)	0.449		
HGB (g/L, < 81.5 vs ≥81.5)	0.947 (0.626–1.434)	0.798		
Ca^{2+} (mmol/L, < 2.505 vs ≥2.505)	1.092 (0.731–1.632)	0.667		
β_2-MG (mg/L, < 4.78 vs ≥4.78)	0.923 (0.619–1.374)	0.692		
Scr (mmol/L, < 137.5 vs ≥137.5)	0.975 (0.622–1.529)	0.913		
LDH (U/L, < 151.5 vs ≥151.5)	0.895 (0.597–1.341)	0.589		
ALB (g/L, < 27.45 vs ≥27.45)	1.028 (0.644–1.641)	0.909		
CRP (mg/L, < 5.845 vs ≥5.845)	2.247 (1.499–3.367)	**<0.001**	2.365 (1.574–3.554)	**<0.001**
Bone disease (Yes vs No)	1.241 (0.759–2.030)	0.389		
Cytogenetic abnormalities (Standard risk vs High risk)	1.627 (1.088–2.432)	**0.018**	1.471 (0.980–2.209)	0.063
First-line induction chemotherapy				
Conventional chemotherapy vs PIs or/and IMiDs based chemotherapy	0.536 (0.355–0.811)	**0.003**	0.574 (0.377–0.876)	**0.010**
Treatment response (CR vs VGPR)	1.264 (0.841–1.901)	0.260		

ALB: albumin, BMPC: bone marrow plasmacyte, β_2-MG: β_2-microglobulin, Ca^{2+}: calcium, CI: confidence interval, CR: complete remission, CRP: C-reactive protein, ECOG: eastern cooperative oncology group, HGB: hemoglobin, IMiDs: immunomodulatory drugs, ISS: international staging system, LDH: lactate dehydrogenase, OR: odds ratio, PIs: proteasome inhibitors, Scr: serum creatinine, VGPR: very good partial remission.

Discussion

MM is a complex disease that exhibits diverse clinical outcomes, varying for each individual patient based on their unique disease progression characteristics [12–14]. It is critical to identify important predictors for the prognosis of patients with MM so as to conduct risk-adapted treatment approaches. Several validated risk stratification systems, such as IMWG, Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), ISS, and Revised-ISS (R-ISS) criteria, are commonly used for risk assessment at the time of MM diagnosis [15–18]. However, prognostic indicators at diagnosis alone may not fully capture the dynamic nature of MM management [19–21]. This research mainly aims to study the impact of TTP after VGPR or CR on outcome of MM patients and highlight the informative value of TTP in formulating treatment strategies.

This study investigated the TTP in 209 patients with MM who achieved VGPR or CR after first-line chemotherapy, and analyzed its correlation with survival outcomes. Considering the important influence of ASCT consolidation therapy on the survival of patients with MM, this study excluded 25 patients with ASCT consolidation therapy to reduce the study cohort heterogeneity. The clinical characteristics of 209 patients with MM illustrated that patients with advanced age, high ECOG scores, ISS stage III, high CRP level, and first-line conventional induction chemotherapy had a higher risk of MM progression within 12 months after VGPR/CR. Therefore, patients with MM with these high risk characteristics at diagnosis should pay more attention to the follow-up and consolidation treatment after VGPR or CR.

In this study, although there was no significant difference in OS between the ≤ 6 months group and the ≤ 12 months group, the OS of patients in the ≤ 6 months group was shorter than that in the 6–12 months group. Consequently, patients who experienced MM progression within 6 months after VGPR/CR had the worst median OS of 33.63 months, followed by those who progressed within 6–12 months with a median OS of 79.6 months, while the best outcomes were observed in patients who progressed beyond 12 months. Taking the influence of survival time before MM progression on OS into consideration, we further analyzed OS-1 which started from the occurrence time of MM progression. The significant differences of OS-1 between different TTP groups were largely similar to those of OS except for that between ≤ 24 months and > 24 months groups. Durie et al. were the first to report that TTP is an important predictive factor for survival in the era of conventional agents [22]. Majithia et al. demonstrated that patients who relapsed within 12 months of initiating therapy with novel agents, regardless of transplant status, had a markedly poor prognosis, with a median OS of 21.0 months compared to not realized (NR) ($P < 0.001$) [5]. Another cohort study involving 297 newly diagnosed patients with MM receiving first-line ASCT found that 14.5% of patients relapsed within 1 year of ASCT and had dismal outcomes, with a median post-ASCT survival of 18 months compared to >6 years ($P < 0.001$) in late relapsing patients [23]. These studies were conducted in different first-line treatment contexts, whereas our study included patients with MM with first-line conventional or PIs and/or IMiDs based chemotherapy. Additionally, we divided the 209 patients with MM into specific

subgroups based on progression within 6 months, 6–12 months, or 12–24 months after VGPR/CR, which were less studied in previous researches. Survival comparisons in this study revealed that patients who experienced earlier progression after VGPR/CR had poorer OS and OS-1, except for the patients who progressed within 12–24 months compared to those who progressed more than 24 months after VGPR/CR. A study by Sidana et al. evaluated 351 patients who achieved CR with first-line therapy and found that patients with a sustained duration of CR $\geq$ 24 months had better OS [7]. Our results also showed that the median OS of patients with progression within 24 months after VGPR/CR was poorer compared to that more than 24 months, which is consistent with the findings of Sidana et al. However, when comparing the OS of patients with TTP > 24 months to those with 12 months < TTP $\leq$ 24 months, we observed that the OS difference between patients with TTP $\leq$ 12 months and TTP > 24 months accounted for the significant OS difference between patients with TTP $\leq$ 24 months and TTP > 24 months after VGPR/CR. Meanwhile, we found no significant difference in OS-1 between $\leq$ 24 months and > 24 months groups, which suggested that MM patients with TTP $\leq$ 24 months and TTP > 24 months had parallel survival time starting from myeloma progression.

Patients with MM who experience disease progression within 12 or 24 months after VGPR/CR have poor survival outcomes. It is crucial to understand the impact of treatment options before and after progression on OS. Our results indicate that patients receiving first-line induction chemotherapy with a three-drug combination of PIs and/or IMiDs exhibit a survival advantage over those treated with a two-drug combination of PIs and/or IMiDs, particularly in those who experience disease progression within 24 months after achieving VGPR/CR. According to the IMWG recommendations, treatment for relapsed MM includes sensitive chemotherapy, novel agent-based chemotherapy, and ASCT [24]. Similarly, in our cohort, post-progression treatments mainly consisted of conventional chemotherapy, PIs and/or IMiDs based chemotherapy, and ASCT. Our study revealed that patients with MM treated with novel agent chemotherapy after progression had better OS compared to those treated with conventional chemotherapy. Furthermore, the results of OS and OS-2 analysis both revealed that ASCT provided the greatest survival benefit for patients who progressed within 12 or 24 months after VGPR/CR, compared to conventional chemotherapy and PIs and/or IMiDs-based chemotherapy. Several studies have supported the use of ASCT as a treatment option for patients with MM after disease recurrence, regardless of whether they received ASCT as part of their initial treatment [24–26]. In this study, patients underwent ASCT for the first time after MM progression. Previous clinical trials have shown that late ASCT remains a viable treatment option for patients experiencing their first recurrence of MM who did not receive ASCT as part of their initial therapy [27]. Two additional randomized clinical trials investigated the effect of second ASCT versus subsequent chemotherapy on PFS and OS for patients experiencing their first relapse, both showing that second ASCT was a safe and effective therapy associated with superior PFS and OS compared to chemotherapy alone [28,29]. Besides, our data indicated that even patients with MM progression within 12 or 24 months after VGPR/CR had favorable outcomes with subsequent ASCT. However, Majithia et al's study reported that the survival disadvantage of patients with MM who relapsed within 12 months of initial therapy persisted even when considering just patients who conducted subsequent therapies [5]. This difference may be attributed to the fact that subsequent treatments used for early relapsed patients were similar to those utilized as front-line treatments in Majithia et al.'s study. Therefore, ASCT remains a superior treatment option that can improve the prognosis of patients with MM with early progression.

Our study has several limitations due to its retrospective design and lack of a standardized protocol for patients' baseline characteristics, follow-up frequency, tests for progression, and different therapies before and after progression. However, many of these factors, including patients' baseline characteristics and therapies before and after progression, were adjusted in our multivariable analysis. We identified TTP after VGPR/CR as an independent predictive factor for OS, with shorter TTP ($\leq$6 months, $\leq$12 months, and $\leq$24 months) being associated with poorer OS. In addition, we found that ECOG performance status, ISS stage, CRP levels at diagnosis and first-line induction chemotherapy were independent predictors of MM progression within 24 months after VGPR/CR. Previous studies also reported that high CRP levels were present and related to poor outcomes in patients with MM [30,31]. This suggests that clinicians should consider the physical condition, inflammatory markers, disease staging and treatment of patients with MM when assessing the risk of progression. Even after adjusting for characteristics in multivariable models, it is critical to clearly acknowledge that patients who receive second line ASCT are different by default from those who don't. This confounding by indication is inevitable in this study. Additionally, it is also important to note that our cohort excluded patients receiving immunotherapy after MM progression due to the small number of cases. The findings from this study are expected to be validated in prospective large-scale clinical studies.

Conclusions

The TTP after VGPR/CR remains a significant independent prognostic factor for patients with MM. Our study highlights that patients with TTP $\leq$ 6 months have worse outcomes compared to those with 6 months < TTP $\leq$ 12 months, and patients with 6 months < TTP $\leq$ 12 months have poorer outcomes than those with TTP > 12 months. Additionally, patients with 12 months < TTP $\leq$ 24 months exhibit similar outcomes to those with a TTP > 24 months. Thus, patients with MM who experience earlier disease progression within 12 months after achieving VGPR/CR have significantly worse survival outcomes. This observation underscores the aggressive nature of myeloma biology and active proliferation of myeloma cells in cases of early progression. Furthermore, our findings demonstrate the potential benefits of ASCT as a treatment option for patients with MM with disease progression within 12 or 24 months after VGPR/CR. Therefore, early progression status of patients with MM should alert providers to the high-risk nature of this population, and these patients should be considered for aggressive second-line treatments such as ASCT or available clinical trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

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