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Survival in patients with multiple myeloma: evaluation of possible associations with bone marrow fibrosis and investigation of factors independently associated with survival

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Abstract

Background: Multiple myeloma (MM) is characterized by infiltration of neoplastic plasma cells in the bone marrow. Although many novel agents have been developed in the last decade, MM remains a non-curable disease. The association between bone marrow fibrosis (BMF) and MM survival is unknown, and the considerable changes in patient survival during the last few decades necessitates new studies to examine survival and associated factors in patients with MM.

Results: A total of 72 patients with MM, 39 (54.17%) males and 33 (45.83%) females, were included in this retrospective study. Fifteen patients did not have BMF, 55 had BMF (grades 1–4); there were no significant differences between these groups in terms of any of the parameters examined. The 5-year overall survival (OS) rate was 56.5 ± 7.4%. Mean OS was 81.54 ± 7.01 months, mean progression-free survival (PFS) after first-line treatment was 14.07 ± 2.54 months, and mean PFS after autologous stem cell transplantation (ASCT) was 25.92 ± 3.66 months. Survival times or mortality risk were not found to be associated with BMF in any of the analyses (HR 1.208, [95% CI 0.408–3.578], $p = 0.733$). Mortality risk was increased by 8.163-fold in patients with hypercalcemia (HR 8.163, 95% CI 2.413–27.617, $p = 0.001$), while it was decreased by 0.243-fold in patients with favourable response to first-line treatment (HR 0.243, 95% CI 0.078–0.756, $p = 0.015$). Younger patients (< 60 years) had a 1.981-fold greater risk of progression after first-line treatment (HR 1.981, 95% CI 1.111–3.532, $p = 0.021$), while those with hypercalcemia had a 3.160-fold greater risk of progression after ASCT (HR 3.160, 95% CI 1.103–9.052, $p = 0.032$). Low haemoglobin levels were also associated with increased mortality risk ($p = 0.024$).

Conclusion: Although hypercalcemia, unfavourable treatment response, young age and a low haemoglobin level were found to be indicators of poor prognosis in patients with MM, no relationship was found between BMF and survival.

Keywords: Multiple myeloma, Bone marrow fibrosis, Survival, Prognostic factors, Survival analysis

Background

Multiple myeloma (MM) is a monoclonal plasma cell disease characterized by lytic bone lesions, anaemia, hypercalcemia and renal failure (Rajkumar 2011). MM accounts for 1% of all malignancies and approximately 10% of haematological malignancies and is the second

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most frequently diagnosed haematologic malignancy (Rajkumar 2019; Siegel et al. 2015). It has been reported that the age of onset of MM is about 66 years and it is mostly seen in males (Kyle et al. 2003).

Prolonging the time to disease progression in patients with newly diagnosed MM is currently the primary treatment goal (Fonseca et al. 2017). The treatment steps of MM consist of important stages such as initial (first-line) treatment, stem cell transplantation if appropriate, consolidation / maintenance treatment, and treatment for relapse (Rajkumar and Kyle 2005). Treatment paradigms and outcomes for patients with MM have changed dramatically, with more effective and less toxic therapeutic agents recently introduced (Kumar et al. 2014). One of the most important parameters that change positively in this process is the survival time of patients with MM (Pulte et al. 2015).

Although the average survival time in MM is approximately 5–7 years, large differences in survival may occur depending on various factors (Rajkumar and Kumar 2016). The stage of the disease, cytogenetic abnormalities and response to treatment are some of the factors that affect survival. In patients with MM, increased bone marrow fibrosis (BMF) has also been reported as one of the factors that reduce the survival time (Subramanian et al. 2007). Patients with MM with BMF (especially those with extensive BMF) have a worse prognosis even when treated with immunomodulatory agents and proteasome inhibitors (Paul et al. 2020). Understanding the changes in the bone marrow microenvironment and the prognostic implications of these changes is of great importance to further improve the efficacy of myeloma treatment and outcomes for patients with MM. However, few studies have evaluated the relationship between BMF and disease prognosis and survival in patients with MM (Rajkumar 2016; S Vincent Rajkumar et al. 2014a, b).

Herein, our aims were to report the incidence and grade of BMF among patients with MM and to investigate whether presence or degree of BMF was associated with survival duration. In addition, we sought to describe the demographic, clinical and laboratory characteristics of patients with MM and to determine factors independently associated with survival times and survival rates.

Methods

Study plan and data collection

Our study was carried out with a pre-specified plan to include all eligible patients who were followed up with a diagnosis of MM in University of Health Sciences Prof. Dr. Cemil Taşçıoğlu City Hospital and Ege University Medical Faculty Hospital. The study was approved by the Ethics Committee of the Okmeydani Training and Research Hospital (No: 1389, Date: 06/08/2019). Informed consent was obtained from all individual participants included in the study.

Within the scope of the study, the medical records of patients who were diagnosed with MM between 2008 and 2019 in two institutions were evaluated retrospectively. Data of patients aged over 18 years who met the diagnostic criteria for MM and were evaluated for BMF in bone marrow biopsies, were included in the study. Patients diagnosed as having advanced heart failure, decompensated liver cirrhosis and advanced lung disease were not included in the study group.

Data on demographic characteristics, myeloma type, myeloma stage, treatment protocols, date of diagnosis, genetic mutation status, presence of hypercalcemia, anaemia or lytic lesion at diagnosis, serum lactate dehydrogenase (LDH) and creatinine levels, concomitant diseases, presence of concomitant plasmacytoma, autologous transplant status were recorded from the patients' medical records retrospectively.

Outcome measures

The primary outcomes of this study were to assess the incidence and grade of BMF and to determine whether BMF was associated with survival in patients with MM. Secondary outcomes included the assessment of demographic, clinical and laboratory characteristics of patients with MM, and to determine factors independently associated with survival times and survival rates.

Diagnosis and staging of multiple myeloma

The Updated International Myeloma Study Group MM diagnostic criteria were used to diagnose MM. Accordingly, a bone marrow clonal plasma cell ratio of $\geq 10\%$ or the presence of biopsy-proven plasmacytoma together with one or more myeloma-defining events is required for the diagnosis of MM in bone marrow evaluation. Myeloma defining events consist of hypercalcemia, renal failure, anaemia, lytic bone lesions (CRAB findings) and three specific biomarkers [clonal bone marrow plasma cells $\geq 60\%$, serum free light chain ratio ≥ 100, multiple focal lesions on magnetic resonance imaging (MRI). In the absence of myeloma-defining events, at least one of the SLiM criteria is required (S: bone marrow clonal plasma cell ratio $\geq 60\%$, Li: affected/unaffected serum free light chain ratio ≥ 100, M: Presence of multiple focal lesions of 5 mm or larger on whole-body MRI) (Rajkumar 2016; S. V. Rajkumar et al. 2014a, b).

The Durie-Salmon staging system was used for the staging of MM. In this staging system developed by Durie and Salmon in 1975, disease stage is determined by evaluating factors such as haemoglobin, calcium and lytic bone lesions (Durie et al. 2015).

Treatments, response and prognosis

The chemotherapy regimens used in the majority of patients with MM were Vincristine-Adriamycin-Dexamethasone (VAD), Bortezomib-Cyclophosphamide-Dexamethasone (VCD), Bortezomib-Melphalan-Dexamethasone (VMP), Bortezomib-Dexamethasone (BD), Revlimid-Dexamethasone (RD), Lenalidomide-Cyclophosphamide-Dexamethasone (LCD) and Velcade-Lenalidomide-Dexamethasone (VRD).

Responses to treatments and allogeneic stem cell transplantation in patients with MM were grouped as progressive disease (PD), stable disease (SD), partial response (PR), very good partial response (VGPR) and complete response (CR), as defined by the International Myeloma Working Group (IMWG).

Prognosis was assessed as duration (months) of overall survival (OS), progression-free survival (PFS), and the percentage of patients who were alive at 5 years (5-year OS) and at the end of the study.

Evaluation of bone marrow fibrosis

The presence of fibrosis in the bone marrow was evaluated in four groups (Grade 0: No reticulin fibres visible, Grade 1: Occasional fine individual fibres and fine mesh foci, Grade 2: Fine fibre network throughout most of the section; no coarse fibres, Grade 3: Messy fibre network with scattered thick coarse fibres but no mature collagen, Grade 4: Wide, thick fibre network with areas of collagenisation) (Bain et al. 2019). During the analyses, two groups were formed among the patients in terms of BMF, Grade 0 and Grades 1–2-3–4, and comparisons were performed.

Statistical analysis

All analyses were performed using the SPSS v21 statistical software package (SPSS Inc., Chicago, IL, USA). Prior to the analysis we assessed the distribution of key variables for normality. According to the normality of the distribution, continuous data are given as mean ± standard deviation or median (minimum–maximum). Categorical data is summarized with frequency and relative percentage. Between-group comparisons of the continuous variables were performed with the independent samples t-test or the Mann–Whitney *U* test depending on normality of distribution. Between-group comparisons of categorical variables were performed with appropriate chi-square tests or the Fisher's exact test. Survival times were calculated using the Kaplan–Meier method. Comparisons of survival times between groups were performed using the log-rank test. Cox regression analysis (forward conditional method) was utilized to identify factors independently associated with prognosis. Statistical significance value was accepted as $p < 0.05$.

Results

Demographic and clinical characteristics

A total of 72 patients with MM were included in our study, 39 (54.17%) were male and 33 (45.83%) were female. The mean age of the patients was 62.43 ± 13.41 (range 34–87) years. The most common comorbidity in the patients was hypertension, the most common type of MM was immunoglobulin (Ig)-G kappa and the most common stage was stage-III (A/B). Genetic mutation evaluation was performed in 38.89% ($n = 28$) of the patients and the most common genetic mutation was found to be del 17p (10.71%). ASCT had been performed in 49.3% ($n = 35$) of the patients. Mortality rate was found to be 33.33% ($n = 24$) (Table 1).

Bone marrow fibrosis

Any-grade BMF was present in 55 (78.57%) patients, while 15 (21.43%) patients did not have fibrosis. When reported according to grades, Grade 1 fibrosis was identified in 31 (44.29%), Grade 2 was identified in 15 (21.43%), Grade 3 was identified in 8 (11.43%), and Grade 4 was identified in 1 (1.43%) patient(s). The comparison of patients without BMF (Grade 0) and those with any degree of fibrosis (Grades 1–2–3–4) did not reveal any significant differences between the groups, including disease staging, clinical characteristics, treatment(s), treatment response(s), progression after therapy, and survival rates (1–5 years and study duration).

Overall survival

Five-year OS rate was determined to be 56.5 ± 7.4% and mean OS was 81.54 ± 7.01 (95.% CI: 67.80–95.29) months. No significant associations were found between OS duration and age, sex, comorbidity, MM type, lytic lesion, plasmacytoma and BMF grade (Table 2). The OS of patients in stage III (A/B) (62.21 ± 7.53 [95% CI 47.46–76.96]) was lower than in other stages (117.77 ± 6.95 [95% CI 104.15–131.39], $p = 0.003$). The OS of patients with hypercalcemia (32.94 ± 7.90 [95% CI 17.46–48.43], $p = 0.023$) and high creatinine level (39.07 ± 7.18 [95% CI 25.00–53.13], $p = 0.012$) was found to be significantly lower than those without. The 5-year OS rates of patients with VGPR or CR to first-line therapy (78.5 ± 8.8, $p = 0.003$) and those with ASCT (73.6 ± 8.8, $p = 0.007$) were significantly higher than others. BMF was not associated with OS (HR 1.208, [95% CI 0.408–3.578], $p = 0.733$) (Table 2, Fig. 1).

Cox regression analysis was performed and hypercalcemia and low haemoglobin level were found as poor prognostic factors, while having VGPR or CR after

Table 1 Distribution of patients in the study group in terms of characteristics

	Total (*n* = 72)	**Bone marrow fibrosis grade**		
		0 (*n* = 15)	**1–4 (*n* = 55)**	***p***
Age (*n* = 72)	62.43 ± 13.41	63.87 ± 14.28	62.11 ± 13.45	0.659
< 60	28 (38.89%)	5 (33.33%)	22 (40.00%)	0.864
≥ 60	44 (61.11%)	10 (66.67%)	33 (60.00%)	
Sex (*n* = 72)				
Male	39 (54.17%)	7 (46.67%)	32 (58.18%)	0.615
Female	33 (45.83%)	8 (53.33%)	23 (41.82%)	
Concomitant malignancy (*n* = 72)	2 (2.78%)	1 (6.67%)	1 (1.82%)	0.385
Comorbidity (*n* = 72)	46 (63.89%)	12 (80.00%)	34 (61.82%)	0.313
Diabetes mellitus	7 (9.72%)	1 (6.67%)	6 (10.91%)	1.000
Hypertension	23 (31.94%)	5 (33.33%)	18 (32.73%)	1.000
Heart disease	10 (13.89%)	3 (20.00%)	7 (12.73%)	0.437
Kidney disease	9 (12.50%)	2 (13.33%)	7 (12.73%)	1.000
Pulmonary disease	7 (9.72%)	1 (6.67%)	6 (10.91%)	1.000
Thyroid disease	4 (5.56%)	1 (6.67%)	3 (5.45%)	1.000
Others	17 (23.61%)	6 (40.00%)	11 (20.00%)	0.171
Type (*n* = 72)				
IgG kappa	27 (37.50%)	6 (40.00%)	20 (36.36%)	0.343
IgG lambda	16 (22.22%)	2 (13.33%)	13 (23.64%)	
IgA kappa	7 (9.72%)	1 (6.67%)	6 (10.91%)	
IgA lambda	8 (11.11%)	1 (6.67%)	7 (12.73%)	
Light chain kappa	9 (12.50%)	2 (13.33%)	7 (12.73%)	
Light chain lambda	5 (6.94%)	3 (20.00%)	2 (3.64%)	
Stage (*n* = 66)				
Silent	2 (3.03%)	1 (7.69%)	1 (1.96%)	0.079
Stage I (A)	11 (16.67%)	5 (38.46%)	6 (11.76%)	
Stage II (A/B)	6 (9.09%)	1 (7.69%)	5 (9.80%)	
Stage III (A/B)	47 (71.21%)	6 (46.15%)	39 (76.47%)	
Haemoglobin (*n* = 71)	10.32 ± 2.23	10.06 ± 2.44	10.40 ± 2.16	0.604
Lytic lesion (*n* = 52)	33 (63.46%)	4 (40.00%)	28 (70.00%)	0.138
Plasmacytoma (*n* = 70)	22 (31.43%)	6 (42.86%)	16 (29.63%)	0.356
Calcium (*n* = 49)	9.29 (8.02–14.42)	9.30 (8.02–11.02)	9.30 (8.18–14.42)	0.533
Hypercalcemia (*n* = 68)	9 (13.24%)	1 (7.69%)	8 (15.09%)	0.675
High creatinine (> 2) (*n* = 71)	18 (25.35%)	2 (13.33%)	16 (29.63%)	0.321
LDH (*n* = 62)	201 (63–541)	211.5 (137–350)	201 (63–541)	0.737
Genetic mutation (*n* = 28)	6 (21.43%)	0 (0.00%)	6 (27.27%)	0.555
del 17p (*n* = 28)	3 (10.71%)	0 (0.00%)	3 (13.64%)	1.000
t (4;14) (*n* = 27)	1 (3.70%)	0 (0.00%)	1 (4.76%)	1.000
t (14;16) (*n* = 25)	1 (4.00%)	0 (0.00%)	1 (5.00%)	1.000
t (14;20) (*n* = 14)	1 (7.14%)	0 (0.00%)	1 (10.00%)	1.000
Treatment (*n* = 72)	68 (94.44%)	14 (93.33%)	52 (94.55%)	1.000
Treatment (first-line) (*n* = 68)				
VAD	28 (41.18%)	4 (28.57%)	22 (42.31%)	0.410
VCD	16 (23.53%)	2 (14.29%)	14 (26.92%)	
VAD + VCD	2 (2.94%)	1 (7.14%)	1 (1.92%)	
VD	8 (11.76%)	3 (21.43%)	5 (9.62%)	
Others	14 (20.59%)	4 (28.57%)	10 (19.23%)	
Treatment response (first-line) (*n* = 58)				
PD	7 (12.07%)	1 (7.69%)	6 (13.95%)	0.932

Table 1 (continued)

	Total ($n=72$)	Bone marrow fibrosis grade		
		0 ($n=15$)	1–4 ($n=55$)	*p*
SD	3 (5.17%)	1 (7.69%)	2 (4.65%)	
PR	15 (25.86%)	3 (23.08%)	10 (23.26%)	
VGPR	11 (18.97%)	2 (15.38%)	9 (20.93%)	
CR	22 (37.93%)	6 (46.15%)	16 (37.21%)	
Progression after treatment (first-line) ($n=59$)	53 (89.83%)	12 (85.71%)	40 (90.91%)	0.624
Autologous stem cell transplantation (ASCT) ($n=71$)	35 (49.30%)	6 (40.00%)	27 (50.00%)	0.694
ASCT response ($n=28$)				
SD	1 (3.57%)	0 (0.00%)	0 (0.00%)	0.552
PR	1 (3.57%)	0 (0.00%)	1 (5.00%)	
VGPR	8 (28.57%)	1 (16.67%)	7 (35.00%)	
CR	18 (64.29%)	5 (83.33%)	12 (60.00%)	
Progression after ASCT ($n=32$)	30 (93.75%)	6 (100.00%)	23 (92.00%)	1.000
Number of treatment lines ($n=72$)				
0	4 (5.56%)	1 (6.67%)	3 (5.45%)	0.370
1	18 (25.0%)	6 (40.00%)	12 (21.82%)	
2	25 (34.72%)	5 (33.33%)	20 (36.36%)	
3	15 (20.83%)	1 (6.67%)	13 (23.64%)	
4	5 (6.94%)	2 (13.33%)	3 (5.45%)	
5	5 (6.94%)	0 (0.00%)	4 (7.27%)	
Response after last-line therapy ($n=55$)				
Relapse after CR	3 (5.45%)	1 (7.69%)	2 (5.00%)	0.365
PD	17 (30.91%)	3 (23.08%)	13 (32.50%)	
SD	2 (3.64%)	0 (0.00%)	2 (5.00%)	
PR	6 (10.91%)	3 (23.08%)	3 (7.50%)	
VGPR	7 (12.73%)	0 (0.00%)	6 (15.00%)	
CR	20 (36.36%)	6 (46.15%)	14 (35.00%)	
Follow-up time (months) ($n=72$)	31 (2–125)	27 (4–113)	31 (2–125)	0.864
One-year survival	58 (80.56%)	14 (93.33%)	42 (76.36%)	0.273
Two-year survival	46 (63.89%)	11 (73.33%)	34 (61.82%)	0.602
Three-year survival	33 (45.83%)	6 (40.00%)	26 (47.27%)	0.835
Four-year survival	23 (31.94%)	4 (26.67%)	18 (32.73%)	0.761
Five-year survival	13 (18.06%)	3 (20.00%)	10 (18.18%)	1.000
Final status ($n=72$)				
Alive	47 (65.28%)	11 (73.33%)	36 (65.45%)	0.771
Exitus	24 (33.33%)	4 (26.67%)	18 (32.73%)	
Died during follow-up	1 (1.39%)	0 (0.00%)	1 (1.82%)	

Data are given as mean ± standard deviation or median (minimum–maximum) for continuous variables and frequency (percent) for categorical variables, according to the normality of the distribution

first-line treatment were found as good prognostic factors. Patients with hypercalcemia had a mortality risk 8.163 times higher than other patients (HR 8.163, 95% CI 2.413–27.617, $p=0.001$). Patients whose response to first-line treatment was VGPR or CR had a 0.243-fold lower mortality risk than other patients (HR 0.243, 95% CI 0.078–0.756, $p=0.015$). In addition, a low haemoglobin level was found to be associated with an increased risk of mortality ($p=0.024$). BMF was not found to be independently associated with mortality (Table 3, Figs. 2, 3).

Progression-free survival

The mean PFS in the study group after first-line treatment was 14.07 ± 2.54 months. No association was found between post-treatment PFS and sex, presence of comorbidity, presence of lytic lesion, presence of plasmacytoma, hypercalcemia, high creatinine and BMF level.

Table 2 Comparison of Survival times (months) calculated using Kaplan–Meier analysis and the groups with the Log-rank test

	n	Exitus	Mean ± Standard Error (95% Confidence Interval)	5-year survival (%)	p
Overall survival	72	24	81.54 ± 7.01 (67.80–95.29)	56.5 ± 7.4	N/A
Age					
< 60	28	7	58.30 ± 5.45 (47.63–68.98)	56.4 ± 14.2	0.295
≥ 60	44	17	77.69 ± 8.80 (60.45–94.93)	55.1 ± 8.6	
Sex					
Male	39	13	83.22 ± 9.17 (65.25–101.19)	59.0 ± 9.2	0.878
Female	33	11	75.77 ± 10.42 (55.34–96.19)	52.0 ± 12.2	
Comorbidity					
No	26	7	83.75 ± 12.80 (58.67–108.84)	54.2 ± 15.5	0.374
Yes	46	17	71.59 ± 7.70 (56.49–86.69)	55.1 ± 8.5	
Type					
Heavy chain	58	23	75.08 ± 7.72 (59.94–90.21)	50.4 ± 7.9	0.051
Light chain	14	1	70.36 ± 4.47 (61.59–79.13)	92.9 ± 6.9	
Stage					
Others	19	1	117.77 ± 6.95 (104.15–131.39)	92.3 ± 7.4	**0.003**
Stage III (A/B)	47	22	62.21 ± 7.53 (47.46–76.96)	42.6 ± 8.8	
Lytic lesion					
No	19	7	49.68 ± 7.80 (34.39–64.97)	58.3 ± 12.6	0.861
Yes	33	16	52.19 ± 6.24 (39.96–64.42)	41.3 ± 10.2	
Plasmacytoma					
No	48	16	79.97 ± 8.91 (62.50–97.44)	56.7 ± 8.9	0.683
Yes	22	8	75.75 ± 10.32 (55.53–95.98)	53.8 ± 13.5	
Hypercalcemia					
No	59	17	86.87 ± 7.65 (71.88–101.86)	62.3 ± 8.0	**0.023**
Yes	9	6	32.94 ± 7.90 (17.46–48.43)	19.4 ± 16.2	
High creatinine (> 2)					
No	53	14	89.86 ± 7.89 (74.39–105.33)	64.4 ± 8.5	**0.012**
Yes	18	10	39.07 ± 7.18 (25.00–53.13)	28.7 ± 14.5	
Bone marrow fibrosis level					
0	15	4	85.27 ± 11.77 (62.20–108.34)	70.9 ± 12.4	0.730
1–4	55	18	82.66 ± 7.96 (67.07–98.26)	58.0 ± 8.3	
Response to treatment (primary line)					
Others	25	12	48.45 ± 7.64 (33.47–63.43)	34.7 ± 13.6	**0.003**
VGPR & CR	33	5	105.31 ± 7.92 (89.79–120.82)	78.5 ± 8.8	
Autologous stem cell transplantation					
No	36	16	48.98 ± 6.90 (35.45–62.51)	42.2 ± 11.1	**0.007**
Yes	35	7	99.64 ± 8.35 (83.28–116.01)	73.6 ± 8.8	

p values marked with bold indicate statistically significant differences between the groups

The duration of PFS was significantly shorter in those younger than 60 years (7.34 ± 2.13 [95% CI 3.17–11.52], $p = 0.011$), those who had heavy chain type (9.89 ± 1.99 [95% CI 6.00–13.78], $p = 0.007$) and those in stage III (A/B) (8.82 ± 2.55 [95% CI 3.82–13.82], $p = 0.024$). BMF was not associated with PFS (Table 4, Fig. 4).

In Cox regression analysis, younger patients (< 60 years) were found to have a 1.981-fold greater risk of progression after first-line treatment than older patients (HR 1.981, 95 CI%: 1.111–3.532, $p = 0.021$) (Table 5, Fig. 5).

When PFS values after ASCT were assessed, we found that mean PFS was 25.92 ± 3.66 months after ASCT in patients with MM. In the presence of hypercalcemia, the mean PFS was found to be significantly shorter after ASCT ($p = 0.021$) (Table 6, Fig. 6). Patients with hypercalcemia had a 3.160-fold greater risk of progression after

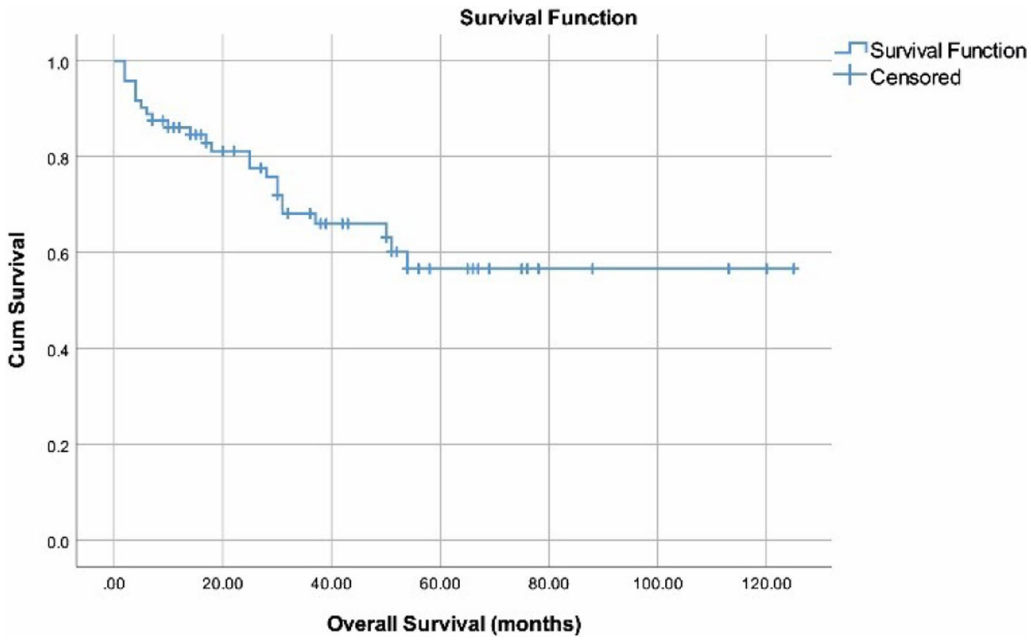

Fig. 1 Overall survival

Table 3 Factors affecting mortality, Cox regression analysis

	β Coefficient	Std Error	p	Exp (β)	95% CI Exp(β)	
					Lower limit	Upper limit
Hypercalcemia	2.100	0.622	0.001	8.163	2.413	27.617
VGPR & CR	− 1.413	0.578	0.015	0.243	0.078	0.756
Haemoglobin	− 0.333	0.147	0.024	0.717	0.537	0.956

CI, confidence Interval

ASCT compared to those without hypercalcemia (HR 3.160, 95% CI 1.103–9.052, $p = 0.032$) (Table 7, Fig. 7).

Discussion

New therapeutic agents and treatment modalities in MM have achieved significantly longer OS in the last two decades (Landgren and Rajkumar 2016). Despite these advances, MM is not a curable disease and it is assumed that the disease will relapse in every patient. The OS in patients with MM was reported as 33 months before the 2000s, whereas today the average survival is 5–7 years (Paul et al. 2020; Rajkumar and Kumar 2016).

In our study, any-grade BMF was found to be present in 78.57% of our patients. The presence or absence of BMF and its grade were not associated with any of the parameters examined. The mean OS in patients with MM was 81.54 ± 7.01 months, similar to the range reported in the literature. In addition, the mean PFS was 14.07 ± 2.54 months after first-line therapy and 25.92 ± 3.66 months after ASCT. Survival duration and survival rates were not found to be associated with BMF presence or degree. Cox regression with mortality as the dependent variable revealed that mortality risk was significantly increased in the presence of hypercalcemia (8.163-fold) and significantly decreased in patients with VGPR or CR to first-line therapy (0.243-fold). Low haemoglobin was also independently associated with higher risk of mortality. PFS was independently associated with age, with patients younger than 60 years of age demonstrating shorter time until progression. When patients with ASCT were examined, hypercalcemia was again found to be associated with shorter PFS and higher likelihood of progression (3.160-fold).

Estimates of survival in patients with MM may vary depending on the source of the data and can be affected by the age of the patients, along with many other factors (Rajkumar 2020). In previous studies, younger patients

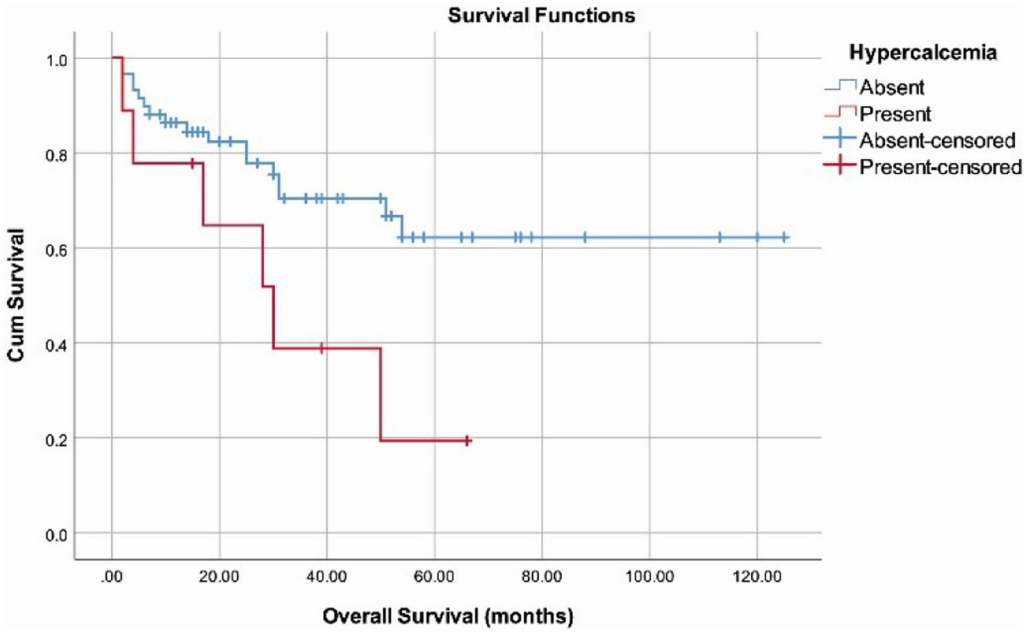

Fig. 2 Overall survival by hypercalcemia

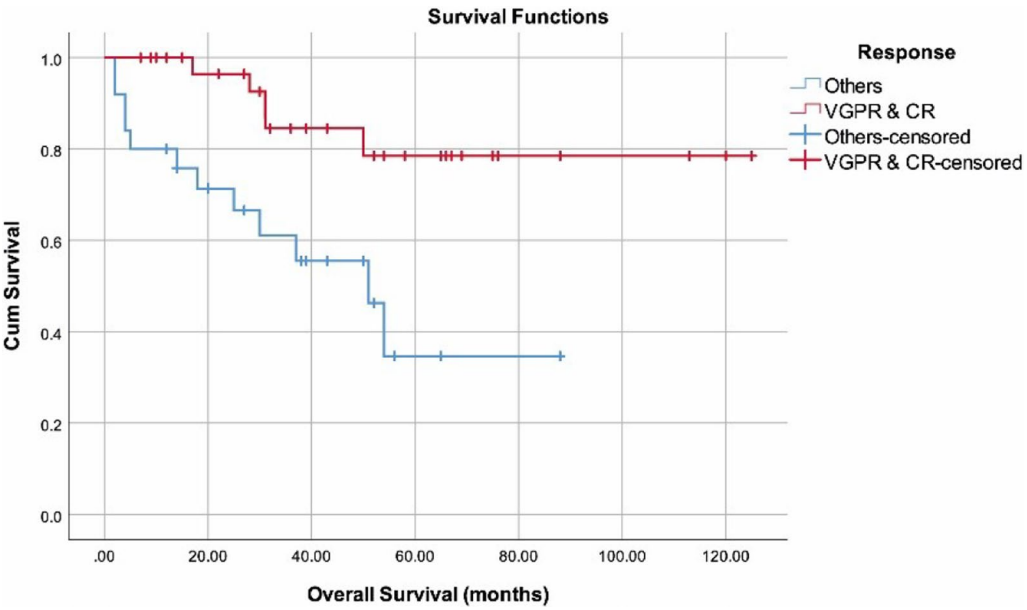

Fig. 3 Overall survival by first-line treatment response

were reported to have better OS (Durie et al. 2015; Kaya et al. 2012; Yusuf et al. 2016) and it was reported that a 1-year increase in age increased the risk of mortality 1.03 times (Paul et al. 2020). In this study, we found that OS did not differ according to age groups, while PFS was shorter in younger patients. The characteristics of the patients in the study group in terms of comorbidity and performance may have caused this result.

As expected survival in MM is affected by the response to treatment (Rajkumar 2020) and CR to treatment was reported to be an independent predictive factor for increased OS and PFS times (Babarović et al. 2012; Gay

Table 4 Comparison of Progression-free survival times (months) after the first treatment calculated using Kaplan–Meier analysis and groups with Log-rank test

	n	Progression	Mean ± Standard Error (95% CI)	*p*
Progression-free survival	59	53	14.07 ± 2.54 (9.09–19.05)	N/A
Age				
< 60	25	23	7.34 ± 2.13 (3.17–11.52)	**0.011**
≥ 60	34	30	18.52 ± 3.75 (11.16–25.87)	
Sex				
Male	34	30	16.03 ± 3.66 (8.86–23.21)	0.364
Female	25	23	11.51 ± 3.27 (5.09–17.92)	
Comorbidity				
No	21	20	10.91 ± 3.48 (4.08–17.73)	0.203
Yes	38	33	15.78 ± 3.46 (9.00–22.55)	
Type				
Heavy chain	47	44	9.89 ± 1.99 (6.00–13.78)	**0.007**
Light chain	12	9	30.22 ± 8.44 (13.68–46.77)	
Stage				
Others	16	14	21.98 ± 5.18 (11.82–32.14)	**0.024**
Stage III (A/B)	38	37	8.82 ± 2.55 (3.82–13.82)	
Lytic lesion				
No	15	15	5.67 ± 1.52 (2.69–8.64)	0.692
Yes	26	26	6.65 ± 2.78 (1.20–12.10)	
Plasmacytoma				
No	36	32	11.11 ± 2.67 (5.88–16.35)	0.247
Yes	21	20	17.55 ± 4.73 (8.27–26.83)	
Hypercalcemia				
No	47	42	13.11 ± 2.78 (7.66–18.57)	0.396
Yes	8	7	21.63 ± 9.23 (3.53–39.72)	
High creatinine (> 2)				
No	46	42	13.75 ± 2.68 (8.50–19.01)	0.971
Yes	13	11	13.69 ± 5.81 (2.31–25.08)	
Bone marrow fibrosis level				
0	14	12	20.55 ± 6.59 (7.64–33.47)	0.220
1–4	44	40	12.61 ± 2.73 (7.26–17.95)	

p values marked with bold indicate statistically significant differences between the groups

et al. 2011). Similarly, in our study, mortality was found to be lower in patients with at least a VGPR response to treatment. This relationship we found between treatment response and survival may be a guide for new treatment strategies. Obtaining a deep response with strong treatments in the early step will contribute to OS.

In patients with myeloma bone disease, together with the lack of bone formation, excessive calcium release occurs as a result of excessive bone resorption, leading to hypercalcemia (Walker et al. 2014) and hypercalcemia is one of the defining symptoms of MM (Rajkumar 2016). The prevalence of hypercalcemia has been reported as 9–19.5% in different studies (Yusuf et al. 2016; Zagouri et al. 2017) and has been associated with increased mortality risk and shorter survival time (Bao et al. 2020; Kastritis et al. 2011). In our study group, hypercalcemia was detected in 13.24% of patients with MM. Hypercalcemia was found to increase the risk of mortality ($p = 0.023$) and progression after ASCT ($p = 0.032$).

Anaemia, which is associated with poor quality of life, decreased performance, hypoxia and ischaemic complications in patients with MM, has been reported to be one of the poor prognostic factors (Caro et al. 2001; Mittelman 2003). These effects become even more important given that most patients with MM are older (Mittelman 2003). We found that low haemoglobin levels increased the risk of mortality, consistent with the literature.

It has been reported that the bone marrow microenvironment, consisting of extracellular matrix proteins, cytokines/chemokines, bone marrow stromal cells,

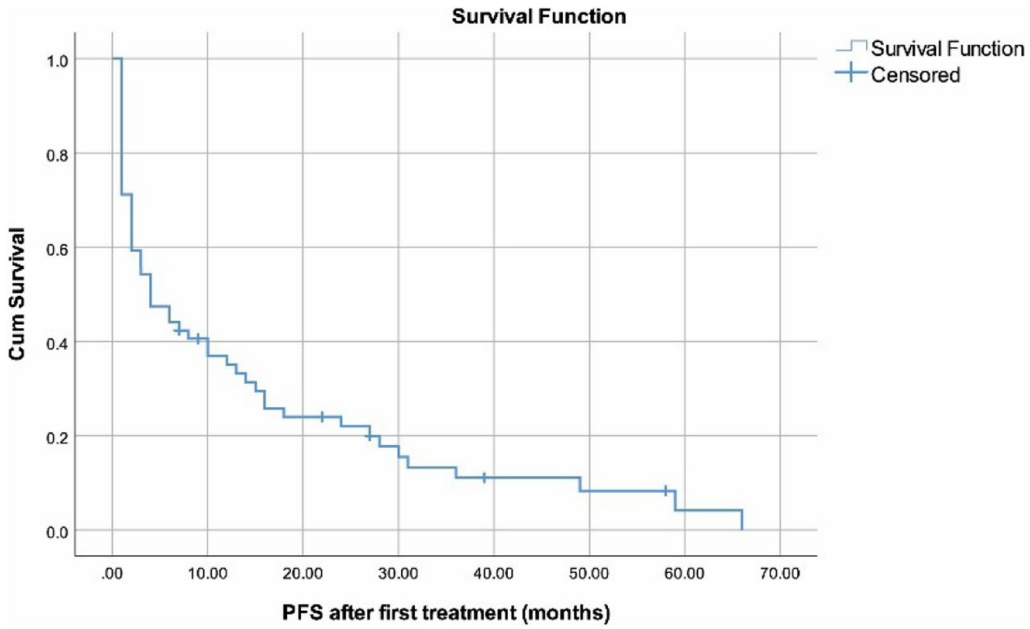

Fig. 4 Progression-free survival after first-line therapy

Table 5 Factors affecting progression after the first treatment, Cox regression analysis

	β Coefficient	Std Error	*p*	Exp (β)	95.0% CI for Exp(β)	
					Lower limit	Upper limit
Age (< 60)	0.683	0.295	0.021	1.981	1.111	3.532

CI, confidence interval

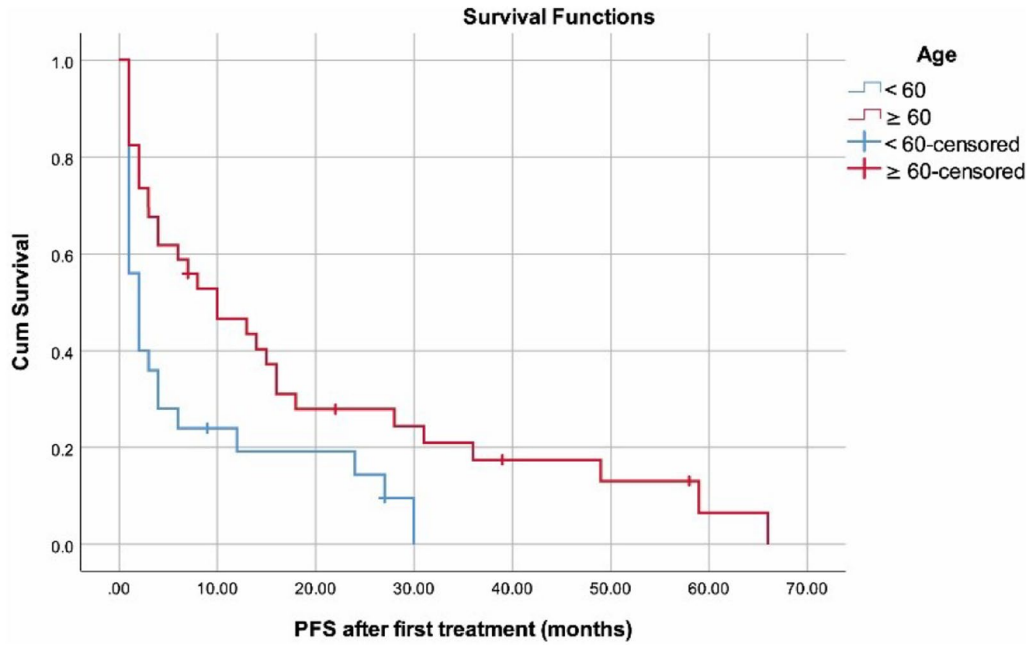

Fig. 5 Progression-free survival after first-line therapy by age

Table 6 Comparison of progression-free survival (months) after autologous stem cell transplantation calculated using Kaplan–Meier analysis and the groups with the log-rank test

	n	Progression	Mean ± Standard Error (95% CI)	*p*
Progression-free survival times	32	30	25.92 ± 3.66 (18.75–33.08)	N/A
Age				
< 60	20	18	28.87 ± 5.02 (19.04–38.70)	0.238
≥ 60	12	12	21.08 ± 5.09 (11.11–31.06)	
Sex				
Male	18	18	21.83 ± 4.79 (12.45–31.22)	0.202
Female	14	12	31.35 ± 5.68 (20.22–42.48)	
Comorbidity				
No	16	16	24.13 ± 4.60 (15.11–33.14)	0.401
Yes	16	14	28.18 ± 5.91 (16.60–39.76)	
Type				
Heavy chain	24	23	25.31 ± 4.71 (16.07–34.55)	0.815
Light chain	8	7	26.29 ± 2.71 (20.98–31.59)	
Stage				
Others	10	10	29.00 ± 6.08 (17.08–40.92)	0.642
Stage III (A/B)	21	19	25.53 ± 4.71 (16.30–34.76)	
Lytic lesion				
No	5	5	36.60 ± 10.91 (15.21–57.99)	0.190
Yes	16	15	23.75 ± 5.44 (13.09–34.42)	
Plasmacytoma				
No	18	16	29.85 ± 5.35 (19.37–40.33)	0.169
Yes	14	14	21.00 ± 4.78 (11.63–30.38)	
Hypercalcemia				
No	24	22	29.58 ± 4.54 (20.69–38.47)	**0.021**
Yes	5	5	11.40 ± 4.80 (1.99–20.81)	
High creatinine (> 2)				
No	23	22	27.04 ± 4.14 (18.93–35.16)	0.772
Yes	9	8	22.83 ± 8.07 (7.01–38.66)	
Bone marrow fibrosis level				
0	6	6	22.17 ± 3.58 (15.15–29.19)	0.479
1–4	25	23	26.32 ± 4.60 (17.31–35.33)	

p values marked with bold indicate statistically significant differences between the groups

CI, confidence interval

mesenchymal stem cells, osteoblasts and osteoclasts, inflammatory cells, megakaryocytes and microvessels, plays an important role in the survival, clonal evolution of myeloma cells, and the development of drug resistance (Paul et al. 2020). Reticulin is a normal component of the bone marrow microenvironment and can be increased in many malignant and non-malignant diseases. BMF occurs with the deposition of reticulin or collagen in the bone marrow stromal environment (Paul et al. 2020). Although the frequency of BMF has been reported as 30%–38% in previous studies (Hallgrimsdottir et al. 2013; Singhal et al. 2004), in our patient group, the rate was quite high (78.57%) compared with other studies. The reason for this is that patients who were evaluated for BMF were included in the study. In addition, the staging systems and the treatment regimens used in the studies were not similar, which may have caused the differences between the results. In the study of Paul et al., it was reported that patients with BMF had significantly shorter OS and PFS. In their univariate analysis, it was reported that BMF was significantly associated with both survival times in patients with MM, but this effect was not preserved in the multivariate analysis (Paul et al. 2020). On the other hand, there are also studies reporting that no relationship was found between BMF and OS and PFS in patients with MM. In our study group, no association was found between the level of BMF and OS and PFS of patients with MM.

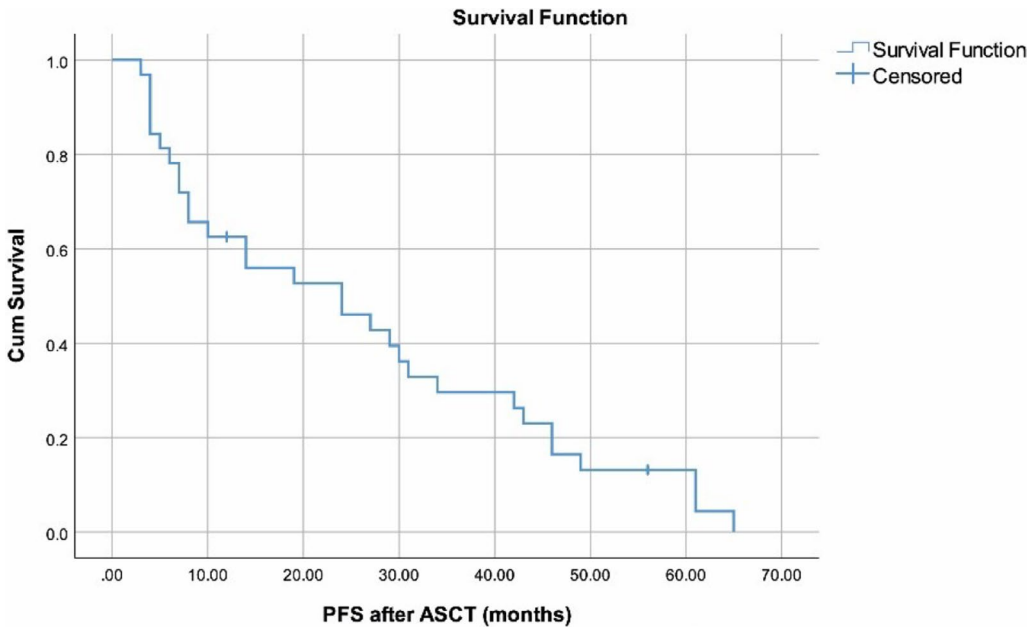

Fig. 6 Progression-free survival after autologous stem cell transplantation

Table 7 Important factors of progression after autologous stem cell transplantation, Cox regression analysis

	β Coefficient	Standard Error	p	Exp(β)	95% CI Exp(β)	
					Lower limit	Upper limit
Hypercalcemia	1.150	0.537	0.032	3.160	1.103	9.052

CI, confidence interval

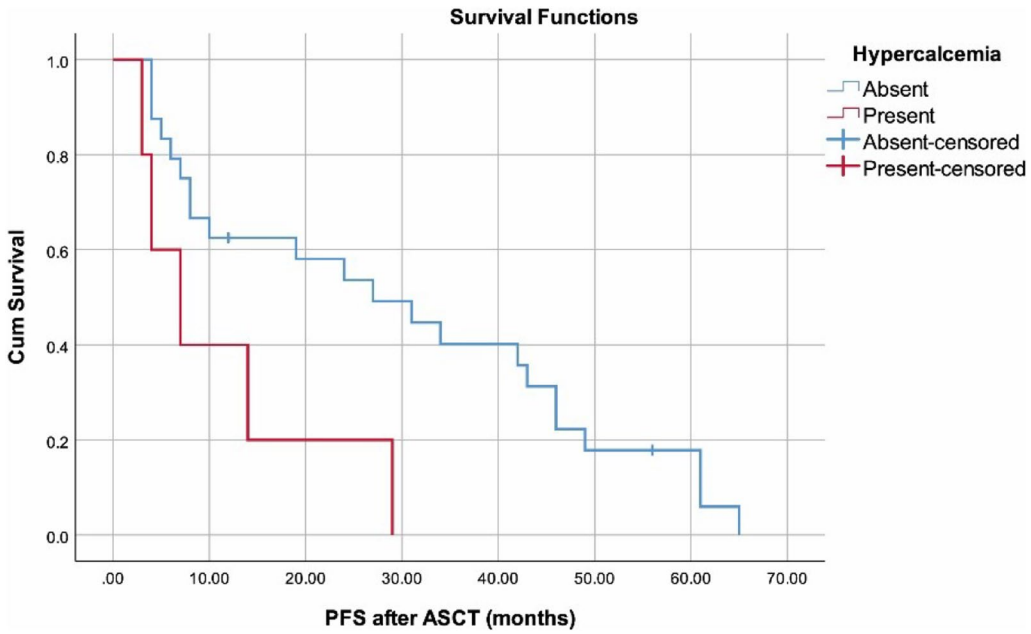

Fig. 7 Progression-free survival after autologous stem cell transplantation by hypercalcemia

Limitations

The most important limitation of the study is its retrospective design. Data from patients with MM who were not examined for BMF could have yielded different results. However, this factor can only be controlled in a prospective study. Another limitation of our study is that we did not use a more up-to-date staging system than the Durie-Salmon system for staging MM. The reason for this was the inclusion of patients from the past. The Durie-Salmon staging system was used because this is the only classification system that can be used for both old and new patients. Despite these limitations, our study is valuable in that it includes detailed analyses of patient data from two major centres over a 12-year period and also shares the results of BMF evaluated by limited studies.

Conclusions

As a result of the analyses, BMF was found to be common among patients with MM (78.57%), but its presence or degree was not associated with survival. The mean OS in patients with MM was 81.54 ± 7.01 months, the mean PFS was 14.07 ± 2.54 months after first-line therapy and 25.92 ± 3.66 months after ASCT. It was determined that hypercalcemia and low haemoglobin levels increased the risk of mortality and favourable treatment response decreased the risk of mortality. Being younger (< 60 years) was to be associated with increased risk of progression after first-line therapy. Hypercalcemia presence increased the risk of progression after ASCT. Patients with MM should be closely monitored in terms of hypercalcemia, low haemoglobin and poor treatment response, which adversely affect survival. Prospective studies that determine the effect of BMF on survival and prognosis in patients with MM will be beneficial.

Abbreviations

MM: Multiple myeloma; BMF: Bone marrow fibrosis; LDH: Lactate dehydrogenase; CRAB: Consist of hypercalcemia, renal failure, anaemia, lytic bone lesions; MRI: Magnetic resonance imaging; VAD: Vincristine-Adriamycin-Dexamethasone; VMP: Bortezomib-Melphalan-Dexamethasone; BD: Bortezomib-Dexamethasone; RD: Revlimid-Dexamethasone; LCD: Lenalidomide-Cyclophosphamide-Dexamethasone; VRD: Velcade-Lenalidomide-Dexamethasone; PD: Progressive disease; SD: Stable disease; PR: Partial response; VGPR: Very good partial response; CR: Complete response; IMWG: International Myeloma Working Group.

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Author contributions

EED contributed to design, data collection, data analyses, results, discussion, literature review and writing—editing; AA contributed to data collection, data analyses; ND contributed to data collection, data analyses, results; DA contributed to data collection, data analyses, results; IM contributed to data collection, discussion and writing—editing; SA contributed to data collection, data analyses, results; FKK contributed to data analyses; RE contributed to design, data collection, discussion and literature review; GS contributed to design and data analyses. All authors read and approved the final manuscript for submission. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Okmeydani Training and Research Hospital (No: 1389, Date: 06/08/2019). Informed consent was obtained from all individual participants included in this study.

Consent for publication

Not applicable.

Competing interests

No competing interest within authors.

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References

Babarović E, Valković T, Štifter S, Budisavljević I, Seili-Bekafigo I, Duletić-Načinović A, Lučin K, Jonjić N (2012) Assessment of bone marrow fibrosis and angiogenesis in monitoring patients with multiple myeloma. Am J Clin Pathol 137(6):870–878

Bain BJ, Clark DM, Wilkins BS (2019) Bone marrow pathology. Wiley, Oxford

Bao L, Wang Y, Lu M, Chu B, Shi L, Gao S, Fang L, Xiang Q (2020) Hypercalcemia caused by humoral effects and bone damage indicate poor outcomes in newly diagnosed multiple myeloma patients. Cancer Med 9(23):8962–8969

Caro JJ, Salas M, Ward A, Goss G (2001) Anemia as an independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. Cancer 91(12):2214–2221

Durie B, Hoering A, Rajkumar SV, Abidi MH, Epstein J, Kahanic SP, Thakuri MC, Reu FJ, Reynolds CM, Sexton R (2015) Bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): results of the randomized phase III trial SWOG S0777. Blood 126(23):25

Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, Richardson P (2017) Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia 31(9):1915–1921

Gay F, Larocca A, Wijermans P, Cavallo F, Rossi D, Schaafsma R, Genuardi M, Romano A, Liberati AM, Siniscalchi A (2011) Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. Blood 117(11):3025–3031

Hallgrimsdottir T, Porwit A, Björkholm M, Rossmann E, Steingrimsdottir H, Lund SH, Kristinsson SY (2013) Bone marrow fibrosis in patients with multiple myeloma: a new prognostic factor for survival? Blood 122(21):1946

Kastritis E, Katodritou E, Pouli A, Hatzimichael E, Delimpasi S, Michalis E, Zomas A, Kartasis Z, Parcharidou A, Gika D (2011) Frequency and prognostic

significance of hypercalcemia in patients with multiple myeloma: an analysis of the database of the Greek Myeloma Study Group. Blood 118(21):5083
Kaya H, Peressini B, Jawed I, Martincic D, Elaimy AL, Lamoreaux WT, Fairbanks RK, Weeks KA, Lee CM (2012) Impact of age, race and decade of treatment on overall survival in a critical population analysis of 40,000 multiple myeloma patients. Int J Hematol 95(1):64–70
Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 28(5):1122–1128
Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR (2003) Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78(1):21–33
Landgren O, Rajkumar SV (2016) New developments in diagnosis, prognosis, and assessment of response in multiple myeloma. Clin Cancer Res 22(22):5428–5433
Mittelman M (2003) The implications of anemia in multiple myeloma. Clin Lymphoma 4:S23–S29
Paul B, Zhao Y, Loitsch G, Feinberg D, Mathews P, Barak I, Dupuis M, Li Z, Rein L, Wang E (2020) The impact of bone marrow fibrosis and JAK2 expression on clinical outcomes in patients with newly diagnosed multiple myeloma treated with immunomodulatory agents and/or proteasome inhibitors. Cancer Med 9(16):5869–5880
Pulte D, Jansen L, Castro FA, Emrich K, Katalinic A, Holleczek B, Brenner H, Group GCSW (2015) Trends in survival of multiple myeloma patients in Germany and the United States in the first decade of the 21st century. Br J Haematol 171(2):189–196
Rajkumar SV (2011) Treatment of multiple myeloma. Nat Rev Clin Oncol 8(8):479–491
Rajkumar SV (2016) Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 91(7):719–734
Rajkumar SV (2019) Multiple myeloma: Every year a new standard? Hematol Oncol 37:62–65
Rajkumar SV (2020) Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 95(5):548–567
Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, Kumar S, Hillengass J, Kastritis E, Richardson P (2014a) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15(12):e538-548
Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O, Paiva B, Dispenzieri A, Weiss B, LeLeu X, Zweegman S, Lonial S, Rosinol L, Zamagni E, Jagannath S, Sezer O, Kristinsson SY, Caers J, Usmani SZ, Lahuerta JJ, Johnsen HE, Beksac M, Cavo M, Goldschmidt H, Terpos E, Kyle RA, Anderson KC, Durie BG, Miguel JF (2014b) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15(12):e538-548
Rajkumar SV, Kumar S (2016) Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 91(1):101–119
Rajkumar SV, Kyle RA (2005) Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 80(10):1371–1382
Siegel RL, Miller KD, Jemal A (2015) (2015) Cancer statistics. CA Cancer J Clin 65(1):5–29
Singhal N, Singh T, Singh ZN, Shome D, Gaiha M (2004) Histomorphology of multiple myeloma on bone marrow biopsy. Indian J Pathol Microbiol 47(3):359–363
Subramanian R, Basu D, Dutta TK (2007) Significance of bone marrow fibrosis in multiple myeloma. Pathology 39(5):512–515
Walker RE, Lawson MA, Buckle CH, Snowden JA, Chantry AD (2014) Myeloma bone disease: pathogenesis, current treatments and future targets. Br Med Bull 111(1):117–138
Yusuf AA, Natwick T, Werther W, Felici D, Mahue M, Bridges KR, Peng Y (2016) A retrospective analysis to examine factors associated with mortality in Medicare beneficiaries newly diagnosed with multiple myeloma. Curr Med Res Opin 32(12):1989–1996
Zagouri F, Kastritis E, Zomas A, Terpos E, Katodritou E, Symeonidis A, Delimpasi S, Pouli A, Vassilakopoulos TP, Michalis E (2017) Hypercalcemia remains an adverse prognostic factor for newly diagnosed multiple myeloma patients in the era of novel antimyeloma therapies. Eur J Haematol 99(5):409–414

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