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Clinical and Laboratory Predictors of Mortality in Multiple Myeloma

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Research Article

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Abstract

Background

Multiple myeloma (MM) is a plasma cell malignancy characterized by bone marrow infiltration and organ dysfunction. Despite advances in treatment, the disease exhibits heterogeneous clinical outcomes, necessitating reliable prognostic markers. The prognostic significance of bone marrow plasma cell (PC) percentage and reticulin fibrosis in predicting mortality remains unclear and controversial in the literature.

Methods

We conducted a retrospective analysis of 97 patients diagnosed with multiple myeloma. Bone marrow PC percentage and reticulin fibrosis grade were assessed alongside comprehensive clinical, hematological, and biochemical parameters. Cox proportional hazards regression analysis was employed to identify independent predictors of mortality. Median follow-up and survival outcomes were calculated using Kaplan-Meier methodology.

Results

The median overall survival was 44.5 months. Higher bone marrow PC percentages correlated with increased reticulin fibrosis grade; however, neither parameter independently predicted mortality in multivariate analysis. Advanced age (> 68.5 years) and low platelet count (< 190.5×10³/μL) emerged as significant independent predictors of mortality. Additionally, elevated β2-microglobulin levels, renal dysfunction, elevated lactate dehydrogenase (LDH), and advanced International Staging System (ISS) stage were independently associated with increased mortality risk.

Conclusion

Age, platelet count, and established biochemical markers (β2-microglobulin, LDH, renal function) are reliable predictors of mortality in multiple myeloma, whereas bone marrow PC percentage and reticulin fibrosis grade do not independently predict survival outcomes. These findings support the prioritization of readily available clinical and laboratory parameters over bone marrow histological features for prognostication in MM. Further prospective multicenter studies are warranted to validate these findings and refine risk stratification strategies.

Introduction

Multiple myeloma (MM) is a malignancy of clonal plasma cells (PCs) characterized by the production of monoclonal immunoglobulins and infiltration of the bone marrow, which leads to end-organ damage

such as anemia, renal failure, hypercalcemia, and osteolytic bone disease [1–3]. MM is typically preceded by precursor conditions, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM [4, 5]. Despite significant advances in therapy, MM remains incurable and displays a heterogeneous clinical course. The considerable variability in survival outcomes highlights the need for reliable prognostic markers that reflect tumor burden, disease biology, and host factors [6].

MM is a malignancy in which interactions between tumor cells and the bone marrow microenvironment play a critical role, not only in disease progression but also in treatment planning. A PCs percentage of ≥ 10% in the bone marrow is a key diagnostic criterion for MM. Higher PC percentages are associated with greater bone marrow infiltration and more pronounced systemic manifestations [7–9]. However, the prognostic significance of PCs burden for survival remains controversial. Some studies have reported that patients with a PCs percentage > 50% have significantly lower overall survival (OS) and progression-free survival (PFS) compared to those with ≤ 50% [9].

Bone marrow fibrosis (BMF), resulting from cytokine-mediated activation of fibroblasts, is another pathological feature observed in a subset of MM patients [10]. BMF is characterized by the accumulation of reticulin or collagen fibers in the bone marrow stroma. However, reticulin is a normal component of the bone marrow and may increase in both benign and malignant diseases. Some studies have found no association between the presence of BMF and OS or PFS [10], whereas others have reported that BMF is common in newly diagnosed multiple myeloma (NDMM) and is associated with higher ISS stage and poorer survival [11].

The International Staging System (ISS) and impaired renal function are established prognostic factors in MM [12]. Additionally, anemia, renal dysfunction, hypercalcemia, and advanced age have all been associated with poor prognosis in MM patients [13–16].

This study aimed to evaluate the relationship between hematological and biochemical parameters, bone marrow PC percentage, reticulin fibrosis grade, and mortality risk in patients diagnosed with MM.

Materials and Methods

Study Design and Patient Population:

Study design : Retrospective cross-sectional study desing

This retrospective cross-sectional, observational study included 97 patients diagnosed with MM according to the International Myeloma Working Group (IMWG) 2014 criteria and followed up between January 2017 and December 2025 at Afyon Health Sciences University [17]. Demographic data, laboratory findings, bone marrow clonal PC percentage, and fibrosis grades from biopsy specimens at diagnosis were obtained from patient records. The percentages of PCs were obtained from bone marrow biopsy reports. The fibrosis stage was examined by a pathologist and defined as reticulin fibrosis, scored

according to the European Consensus for bone marrow fibrosis grading and cellularity assessment, where grade 1 indicates mild reticulin fibrosis, and grades 2–3 indicate moderate to severe fibrosis [18].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Normality was assessed with the Kolmogorov–Smirnov test. Non-parametric methods were applied when appropriate. Cox proportional hazards regression analysis was used to identify independent predictors of mortality. The Hazard Ratio (HR), 95% confidence intervals (CI), and *p*-values were calculated for all variables. The level of statistical significance was set at $p < 0.05$.

Ethical Approval

The study was approved by the Afyon Health Sciences University Ethics Committee (approval date: 5 December 2025, approval number: 2025/827). The study was conducted in accordance with the Declaration of Helsinki.

Results

The mean age of patients diagnosed with MM was 67.15 ± 9.52 years, and 60.8% were male. The median PC percentage ranged from 10% to 95%, with a mean of 60.56% ± 26.11. The proportion of patients with reticulin fibrosis grade 2 was 23.4%, grade 3 was 19.1%, and grade 1 was 57.4%. ISS stage 3 was observed in 58.1% of patients. The rate of IgG-positive patients was 57.7%, and IgA-positive patients was 26.8%. The rates of kappa and lambda light chain positivity were 60.8% and 40.2%, respectively. CD138 was detected in all patients, while CD56 positivity was observed in 66% (Table 1).

Table 1. Baseline demographic, laboratory, and disease characteristics.

Variable	Mean ± SD / *n* (%)	Min–Max
Demographic and Clinical		
Age (years)	67.15 ± 9.52	41–80
Gender		
Female	39 (39.2)	—
Male	58 (60.8)	—
Hematological Parameters		
Hemoglobin (g/dL)	10.28 ± 2.12	4.5–16.04
Leukocyte count (×10³/μL)	6.76 ± 2.77	1.37–15.83
Neutrophil count (×10³/μL)	7.71 ± 15.07	0.71–75.2
Lymphocyte count (×10³/μL)	1.41 ± 0.69	0.09–3.55
Monocyte count (×10³/μL)	1.05 ± 2.4	0.09–15.3
Hematocrit (%)	32.33 ± 5.62	21.9–46.3
Platelet count (×10³/μL)	189.62 ± 88.84	2.49–483
Red blood cell count (×10⁶/μL)	3.42 ± 0.78	2.16–6.13
Platelet-to-RBC ratio	55.68 ± 27.32	1–137.1
Biochemical Parameters		
β2-microglobulin (mg/L)	7.98 ± 6.95	1.4–31
Total protein (g/dL)	8.31 ± 4.03	3.4–39
Albumin (g/dL)	3.61 ± 1.06	1.74–7.51
Globulin (g/dL)	4.27 ± 2.12	1.1–9.36
Urea (mg/dL)	56.2 ± 34.36	16.5–161.1
Creatinine (mg/dL)	1.66 ± 1.55	0.31–7.18
ESR (mm/h)	80.56 ± 36.47	12–141
LDH (U/L)	268.91 ± 163.53	103–1058
Bone Marrow Characteristics		
Plasma cell percentage (%)	60.56 ± 26.11	10–95
Reticulin fibrosis grade		

Grade 1	54 (57.4)	—
Grade 2	22 (23.4)	—
Grade 3	18 (19.1)	—
ISS stage		
Stage 1	5 (11.6)	—
Stage 2	13 (30.2)	—
Stage 3	25 (58.1)	—
Immunoglobulin Type		
IgG positive	57 (57.7)	—
IgM positive	1 (1.0)	—
IgA positive	26 (26.8)	—
IgD positive	2 (2.1)	—
Light Chain Type		
Kappa	59 (60.8)	—
Lambda	39 (40.2)	—
Immunophenotype		
CD138 expression	97 (100)	—
CD56 expression	64 (66.0)	—

On average, patients received 2.26 ± 1.5 different treatment regimens. At the time of evaluation, 40% of patients had stable disease, 16.8% were in remission, 26.3% had refractory disease, and 16.8% had progressive disease. An ECOG performance score of 3 was observed in 42.7% of patients (Table 2).

Table 2. Treatment response and ECOG performance status.

Variable	Mean ± SD / *n* (%)	Min–Max
Number of treatments	2.26 ± 1.5	1–8
Response status		
Stable disease	38 (40.0)	—
Remission	16 (16.8)	—
Refractory disease	25 (26.3)	—
Disease progression	16 (16.8)	—
ECOG performance score		
ECOG score 1	18 (18.8)	—
ECOG score 2	23 (24.0)	—
ECOG score 3	41 (42.7)	—
ECOG score 4	14 (14.6)	—

Correlation Between Plasma Cell Percentage and Other Parameters

As the plasma cell percentage increased, the erythrocyte sedimentation rate (ESR) increased significantly, while hemoglobin (HGB), lymphocyte count, platelet count (PLT), red blood cell count (RBC), and albumin levels decreased significantly (Table 3).

Table 3. Correlation analysis between Plasma Cell percentage and other parameters.

		Plazma Hücre Oranı
Hemoglobin (HGB)	r	**-0,533****
	p	**<0,001**
Leukocyte count	r	-0,196
	p	0,115
Neutrophil count	r	-0,334
	p	0,175
Lymphocyte count	r	**-0,279***
	p	**0,045**
Monocyte count	r	0,011
	p	0,937
HTC	r	-0,21
	p	0,387
Platelet (PLT) count	r	**-0,268***
	p	**0,031**
Red blood cell (RBC) count	r	**-0,430****
	p	**0,002**
PLT/RBC	r	0,056
	p	0,703
B2mg	r	0,109
	p	0,411
Total Protein	r	0,048
	p	0,709
Albumin	r	**-0,374****
	p	**0,002**
Globulin	r	0,119
	p	0,38
ÜRE	r	-0,033
	p	0,81

Creatinine	r	0,01
	p	0,937
ESR (Sedim, mm/h)	r	**0,273***
	p	**0,029**
CRAB	r	0,136
	p	0,342
LDH	r	0,116
	p	0,36

Spearman's Rho Correlation Analysis *Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

The mean plasma cell percentage was significantly higher in patients with moderate to severe bone marrow fibrosis (grades 2–3) compared to those with mild fibrosis (grade 1) ($p < 0.001$) (Table 4).

Table 4. Plasma cell percentage according to reticulin fibrosis grade.

Fibrosis Grade	Mean PC % ± SD	*p*-Value
Grade 1 (mild)	51.66 ± 24.47	<0.001
Grades 2–3 (moderate–severe)	75.58 ± 22.26	

Cox proportional hazards regression analysis identified several independent predictors of mortality. Advanced age (>68.5 years) was the strongest predictor (HR = 2.85, 95% CI: 1.52–5.35, $p = 0.001$). Low platelet count (<190.5×10³/μL) was also significantly associated with increased mortality (HR = 2.12, 95% CI: 1.18–3.81, $p = 0.012$). Elevated β2-microglobulin, high creatinine, elevated urea, high LDH, and advanced ISS stage (stage 3) were also independent predictors of poor survival. Notably, neither bone marrow plasma cell percentage nor reticulin fibrosis grade independently predicted mortality (Table 5).

Table 5. Cox regression analysis of mortality predictors.

Variable	Hazard Ratio (HR)	95% CI	*p*-Value
Age > 68.5 years	2.85	1.52–5.35	0.001
Platelet count < 190.5×10³/μL	2.12	1.18–3.81	0.012
β2-microglobulin (per mg/L increase)	1.08	1.03–1.13	0.002
Creatinine (per mg/dL increase)	1.24	1.08–1.43	0.003
Urea (per mg/dL increase)	1.01	1.00–1.02	0.018
LDH (per U/L increase)	1.002	1.001–1.004	0.008
ISS stage 3	2.45	1.25–4.80	0.009
Hemoglobin (per g/dL increase)	0.88	0.78–0.99	0.035
Plasma cell percentage	1.01	0.99–1.02	0.456
Reticulin fibrosis grade 2–3	1.32	0.74–2.35	0.347

The median overall survival was 44.5 months (95% CI: 38.2–50.8 months). Kaplan–Meier survival analysis demonstrated significantly shorter survival in patients with age >68.5 years, platelet count <190.5×10³/μL, elevated β2-microglobulin, renal dysfunction, and ISS stage 3 disease. However, survival did not differ significantly based on plasma cell percentage or reticulin fibrosis grade.

Discussion

This retrospective cross-sectional study of MM patients evaluated the prognostic significance of clinical, laboratory, and bone marrow histological parameters. Our findings demonstrate that age, platelet count, β2-microglobulin, renal function markers, LDH, and ISS stage are independent predictors of mortality, while bone marrow PCs and reticulin fibrosis grade do not independently predict survival outcomes.

Advanced age has been consistently identified as an adverse prognostic factor in MM. Older patients often have reduced tolerance to intensive chemotherapy, higher comorbidity burden, and poorer functional status, all of which contribute to inferior outcomes [13,14]. Some studies have reported that patients over 65 years have significantly shorter overall survival compared to younger patients [13,14]. In contrast, one report found that OS did not differ by age group, although PFS was shorter in younger patients [10]. In our study, consistent with most of the literature, advanced age (>68.5 years) was associated with worse outcomes, with these patients experiencing shorter survival.

The incidence of BMF in MM patients is reported to be approximately 8–57% in the literature. The presence of BMF has been related to the magnitude of PC infiltration and was associated with poorer prognosis [11,19]. Higher frequency and degree of fibrosis and higher PC percentage have been reported to be associated with a poorer response to treatment [20]. In our study, the rate of grade 2–3 fibrosis in

patients was 42.5%. Consistent with the literature, PC percentage was significantly higher in patients who had moderate to severe BMF compared to those with mild fibrosis ($p < 0.001$).

Furthermore, one study found that patients with a bone marrow PCs percentage above 60% had shorter PFS and OS, and these differences remained significant in multivariate analysis [21]. Another study reported that anemia, renal failure, and hypercalcemia, in addition to high bone marrow PCs percentages, were associated with lower survival rates [22]. In our study, the mean PCs percentage was 60.56% ± 26.11. As the PCs percentage increased, ESR increased significantly, while hemoglobin, lymphocyte, and platelet counts decreased significantly. However, in multivariate Cox regression analysis, neither PCs percentage nor reticulin fibrosis grade independently predicted mortality, suggesting that these histological parameters reflect disease burden but do not add independent prognostic value beyond established clinical and laboratory markers.

Hypercalcemia, kidney failure, anemia, and bone disease are referred to as CRAB findings and indicate active disease. There are studies examining the relationship between CRAB findings and prognosis; one of them showed that anemia and hypercalcemia did not affect survival [23]. In another analysis, the presence of osteolytic bone disease and hypercalcemia were related to poor prognosis [24]. A study of MM patients showed that hemoglobin levels >8 g/dL, lower bone marrow PC count (<20%), and normal creatinine and calcium levels positively impacted survival [25].

Hemoglobin and platelet counts were also significant predictors in our study, reflecting bone marrow failure and extensive disease involvement. Anemia in MM is multifactorial, resulting from PC infiltration of the bone marrow, reduced erythropoietin production due to renal impairment, and chronic inflammation with cytokine-mediated suppression of erythropoiesis. One study found that moderate to severe thrombocytopenia ($<100\times10^3/\mu L$) was associated with shorter survival, suggesting that platelet count can serve as an accessible prognostic biomarker and indicator of the tumor microenvironment [26]. In our study, both anemia and thrombocytopenia were associated with higher mortality rates, consistent with the majority of the literature. ROC analysis showed that a platelet count above $190.5\times10^3/\mu L$ was associated with a higher mean survival time, highlighting its clinical utility as a simple prognostic marker.

Severe renal impairment is associated with high mortality and morbidity rates and poor outcomes [27,28]. Renal dysfunction, characterized by elevated urea and creatinine levels, is a frequent complication of MM, occurring in approximately 50% of patients at diagnosis and is associated with increased mortality [29]. Additionally, elevated β2-microglobulin indicates high tumor burden and poor prognosis [29]. In our study, elevated urea and creatinine levels confirmed their importance as significant predictors of mortality and their continued role in guiding treatment plans, as reflected in the CRAB criteria and ISS staging system.

Our findings have important clinical implications. While bone marrow biopsy remains essential for diagnosis, our results suggest that readily available clinical and laboratory parameters; particularly age, platelet count, renal function markers, and β2-microglobulin provide sufficient prognostic information for

risk stratification and treatment planning. This is particularly relevant in resource-limited settings where repeated bone marrow biopsies may not be feasible. The identification of platelet count as an independent predictor is particularly noteworthy, as it is a simple, inexpensive, and routinely available parameter that can be easily monitored during follow-up.

Limitations

This study has several limitations. First, its retrospective design may introduce selection bias. Second, the relatively small sample size of patients may limit the generalizability of our findings. Third, we did not include cytogenetics-based risk classification (Revised ISS scoring), which is an important prognostic factor in MM. Fourth, treatment regimens varied among patients, which may have influenced survival outcomes. Despite these limitations, our study provides comprehensive evaluation of clinical and laboratory data, PC percentages, and the degree of reticulin fibrosis obtained from biopsy samples, and identifies platelet count as a simple, accessible prognostic marker.

Conclusion

Clinical and laboratory markers such as age, hematological parameters (particularly platelet count), renal function markers (urea and creatinine), β2-microglobulin, and ISS stage remain the most reliable predictors of mortality in MM, with age being the most important independent predictor. While bone marrow PC percentage and reticulin fibrosis grade reflect disease burden and bone marrow dysfunction, their prognostic roles do not add independent value beyond established clinical markers. These findings support the use of readily available clinical and laboratory parameters over bone marrow histology for prognostication. Prospective studies involving larger patient cohorts and incorporating genetic risk factors (such as Revised ISS scoring with cytogenetics) are needed to better define the integrated role of these parameters in predicting treatment responses and outcomes in MM.

Declarations

Ethical Approval and Consent to Participate

This retrospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Afyon Health Sciences University. Due to the retrospective nature of the study design and the fact that a portion of the patients had deceased during the study period, individual informed consent was not obtained. The patient consent form is not among the documents required by our hospital's ethics committee for retrospective studies.

Publication Permission

All authors have reviewed and approved the final manuscript for publication. The manuscript has not been published previously elsewhere. All authors consent to the publication of this work in its current

form.

Data Availability Statement:

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient privacy restrictions.

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Conflicts of Interest:

The authors declare no conflicts of interest.

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Authors' Contributions:

Nermin Keni Begendi: Conceptualization, methodology, data collection, formal analysis, writing – original draft, writing – review and editing, supervision, project administration.

Mustafa Duran: Data collection, formal analysis, writing – review and editing, validation.

Çiğdem Özdemir: Histopathological assessment, bone marrow evaluation, reticulin fibrosis grading, writing – review and editing, validation.

All authors have read and approved the final manuscript.

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