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ORIGINAL ARTICLE

Evaluation of current survival and prognostic factors in multiple myeloma: Staging ISS or R-ISS?

Gökhan Pektaş[1] **Ferhat Yılmaz**[2] **Şeyma Öncü**[3]
Merve Becit Kızılkaya[4] **Gökhan Sadi**[5]
Mehmet Bilgehan Pektaş[3]

[1] Division of Hematology, Faculty of Medicine, Muğla Sıtkı Koçman University. Muğla / Türkiye
[2] Division of Internal Medicine, Faculty of Medicine, Muğla Sıtkı Koçman University. Muğla / Türkiye
[3] Department of Medical Pharmacology, Faculty of Medicine, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
4 Department of Toxicology, Faculty of Pharmacy, Afyonkarahisar Health Sciences University. Afyonkarahisar / Türkiye
[5] Department of Biology, Kamil Özdağ Science Faculty, Karamanoğlu Mehmetbey University. Karaman / Türkiye

Abstract

Multiple myeloma (MM) is a complex hematological malignancy, and understanding the factors influencing prognosis and survival is crucial for improving patient outcomes. This study aims to evaluate the factors influencing the prognosis and survival of MM patients by comparing the International Staging System (ISS) with the Revised ISS (R-ISS). MM patients treated and followed up between 2015 and 2023 were retrospectively analyzed. According to ISS staging, 21.4% of patients were categorized as Stage 1, 30% as Stage 2, and 48.6% as Stage 3. Similarly, the R-ISS system revealed 14.3% as Stage 1, while 42.9% were Stage 2, and 42.9% were Stage 3. These findings indicate that the two systems provide differing stage distributions, which could impact prognosis evaluation. Mortality occurred in 58.6% of patients during the follow-up period, highlighting the severity of the disease in later stages. Further analysis revealed that higher levels of red cell distribution width (RDW), phosphorus content, lactate dehydrogenase (LDH), and beta-2 microglobulin levels were significantly associated with mortality, emphasizing their potential as markers of poor prognosis. In particular, ISS Stage II and III, R-ISS Stage III, along with elevated RDW, total protein, phosphorus, and LDH, were identified as independent prognostic factors. These results suggest that while both staging systems offer valuable insights, specific biomarkers play a crucial role in refining prognostic accuracy. In conclusion, while the ISS system appears to provide more meaningful staging information in this cohort compared to R-ISS, integrating additional biomarkers like RDW and LDH could enhance the prediction of patient outcomes.

Keywords: Multiple myeloma, ISS, R-ISS, LDH, RDW

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Corresponding Author:
Mehmet Bilgehan Pektaş
Email: bilgehan.pektas@afsu.edu.tr

Introduction

Multiple myeloma (MM) is a complex hematological malignancy characterized by the clonal proliferation of abnormal plasma cells within the bone marrow, leading to a variety of clinical manifestations. It is marked by distinct genetic features, including chromosomal translocations involving oncogenes and mutations in key tumor suppressor genes. These genetic alterations contribute to the pathogenesis of MM by promoting uncontrolled cellular proliferation and survival, which in turn can lead to significant complications such as osteolytic bone lesions, renal impairment, anemia, and hypercalcemia [1]. Globally, MM is diagnosed in approximately 2% of all cancer cases, accounting for 13% of all hematological malignancies [2,3]especially in the US, Australia, and Western Europe. In the US, MM accounts for almost 2% of cancer diagnoses and over 2% of cancer deaths (more than double the global proportion. In Türkiye, the burden of this disease is substantial, with an estimated annual incidence of 7,500 new cases and around 3,000 fatalities attributable to MM each year [4]. The increasing prevalence underscores the need for enhanced awareness, early diagnosis, and the development of effective therapeutic strategies to improve patient outcomes.

The incidence and mortality rates of MM remain high, despite the promising results of the markers presently employed for the diagnosis and follow-up of the disease. Results from randomized clinical trials indicate that the median survival in MM is approximately 6 years [5]. However, predicting survival is challenging and requires consideration of multiple factors. Commonly used biomarkers for assessing survival include evaluations of tumor burden and disease risk classification in patients diagnosed with MM. The development of effective, sensitive, and specific prognostic biomarkers is crucial for detecting the disease in its early stages and combating malignancy more effectively [6].

Studies on prognostic factors in the diagnosis and follow-up of MM have increased in recent years. The *Durie-Salmon* Staging System (DSS), first introduced in 1975, is still used today due to its applicability in diagnosing MM [7]. However, advancements in genetic research have highlighted the role of genetics in the etiology of MM, creating a need for new classifications. It has also been observed that a standardized international system is required for MM staging. Currently, patients are classified into high-risk and low-risk genetic groups based on simple cytogenetic and fluorescence *in situ* hybridization analyses. To address this, the International Staging System (ISS) was developed in 2005 [8]. Although the ISS was widely used at first, it required revision as it did not consistently predict clinical outcomes. This led to the development of the Revised-International Staging System (R-ISS) in 2015, followed by the Second Revision of the International Staging System (R2-ISS) in 2022 [9,10]. Despite these updates, the biomarkers used to determine prognosis in MM follow-up remain unclear and are not always helpful in guiding treatment decisions. As a result, these staging systems are continually updated, while studies investigating the impact of other biomarkers, such as immunological markers, socioeconomic status, and genetic factors, on MM prognosis are ongoing [11-13].

A review of the literature highlights the need for further research to better understand the prognosis of MM, assess the effectiveness of the ISS and R-ISS staging systems, and identify biomarkers that can predict outcomes using routine laboratory tests. In response to these gaps, this study aimed to evaluate the relationship between key factors including demographic characteristics (age and gender), diagnostic groups (immunoglobulin types), and ISS/R-ISS stages and survival in patients diagnosed with MM. By exploring these relationships, we hope to contribute valuable insights that can improve prognostic accuracy and guide more personalized treatment approaches in MM management.

Materials and Methods

Study Population and the Data Collection

This descriptive, cross-sectional study analyzed data from 70 patients aged 18 and older, diagnosed with MM and treated at the Division of Hematology between 2015 and 2023. Patients

who were pregnant or lactating, were excluded from the study. Age, gender, ISS and R-ISS stages, diagnostic group, date of diagnosis, survival time, laboratory findings (complete blood count and biochemistry), and prognosis (with or without mortality) data were recorded and analyzed. In accordance with regulations on processing and protecting personal health data, and the principles set out in the Declaration of Helsinki, all patient identities were anonymized. Myeloma-defining events include the presence of clonal plasma cells exceeding 60% in the bone marrow, a free light chain ratio above 100, and the presence of more than one focal lesion measuring 5 mm or larger on whole-body magnetic resonance imaging. In addition, hypercalcemia, renal failure, anemia, and bone disease serve as key indicators of malignancy. This study included the data from patients diagnosed with MM within the specified date range. Declaration of Helsinki, all identity information of the patients was anonymized, and approval was received for the study from the Medical Ethics Committee of Aydın Adnan Menderes University (2023/230).

IgG, IgA, IgM, ISS and R-ISS System

The patients' immunoglobulin (Ig) levels, including IgG, IgA, and IgM, as well as beta-2 microglobulin (B2M) levels, were measured using a nephelometric system. For quantitative and qualitative assessments, serum immunofixation electrophoresis and protein electrophoresis were employed as standard procedures in the follow-up of all patients. Kappa and lambda light chain levels were determined using electrophoresis. Serum lactate dehydrogenase (LDH) activity and albumin levels were analyzed using the chemiluminescence method and measured spectrophotometrically. The response criteria established by the International Myeloma Working Group served as the basis for evaluating patient responses [14].

Statistical Analysis

Descriptive statistics were presented as numbers (n), percentages (%), medians (interquartile ranges, IQR), means (± standard deviation), and minimum-maximum values. The suitability of the data for normal distribution was assessed using the *Shapiro-Wilk* test. The Chi-square test was applied to identify factors affecting prognosis. Variables found to be significant in binary analyses, as well as those identified in the literature, were included in the model for Cox regression analysis. Additionally, age and variables significant in binary analyses (phosphorus, RDW, and LDH) were categorized into two groups based on the median. Beta-2 microglobulin levels were divided into three groups according to the values used in the ISS and R-ISS systems (3.5-5.5 mg/L). Survival analyses were conducted using *Kaplan-Meier* analysis. The Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) was utilized for the analysis, and a *p*-value of less than 0.05 was considered statistically significant.

Results

Data from a total of 70 patients were evaluated, with a mean age of 70.69 ± 10.6 years (minimum: 42, maximum: 87). Among the patients, 52.9% (n=37) were aged 73 or younger, and 41.4% (n=29) were women. The mean follow-up period was 1149.74 ± 781.01 days (minimum: 11, maximum: 2571). According to the ISS staging, 21.4% (n=15) of patients were classified as Stage 1, 30% (n=21) as Stage 2, and 48.6% (n=34) as Stage 3. In terms of the R-ISS staging, 14.3% (n=10) were Stage 1, 42.9% (n=30) were Stage 2, and 42.9% (n=30) were Stage 3. Mortality occurred in 58.6% (n=41) of the patients during the follow-up period (Table 1).

When evaluating factors affecting prognosis, the mortality rate was found to be higher in patients over 73 years of age, in males, and in those with high R-ISS stages; however, these findings were not statistically significant. Similarly, mortality increased significantly with higher ISS stages (Linear trend, Table 2).

In examining laboratory values, RDW, phosphate, LDH, and B2M levels were significantly higher in patients who experienced mortality ($p<0.005$) (Table 3).

According to the results of the *Kaplan-Meier* survival analysis, the median survival time was 1104 days for patients aged ≤ 73 years and 709 days for those aged > 73 years; 1482 days for females and 708 days for males; 961 days for ISS Stage 2 and 600 days for Stage 3; 1449 days

for R-ISS Stage 2 and 583 days for Stage 3; 737 days for IGA diagnosis; and 925 days for IGG diagnosis (Figure 1).

Regarding laboratory results, median survival times were calculated as 634 days for RDW (>15.55), 665 days for phosphate levels (>3.6 mg/dL), 586 days for LDH (>187.5 U/L), and 605 days for B2M (≥5.5 mg/L) (Figure 1). In the Cox regression analysis, ISS Stage II and III, R-ISS Stage III, RDW, total protein, phosphate, and LDH were identified as independent variables influencing prognosis. Specifically, ISS Stage II was associated with a 4.02-fold increase in mortality, Stage III was linked to a 4.6-fold increase, and R-ISS Stage III was associated with a 3.02-fold increase in mortality risk (Table 4).

Discussion

The current study examined the effects of age and gender on mortality, as well as the staging systems used for the prognosis in patients diagnosed with MM. In MM, as age increases, the ISS stage also rises, leading to decreased survival times. A large multicenter study (n=10,549) found that advanced age is a significant risk factor for early mortality [15]. The mean age of mortality in MM was 75 years, with approximately 80% of deaths occurring in individuals over the age of 65 [16]. Similarly, a retrospective study identified a significant relationship between age and mortality rates [17]. In a recently published retrospective cohort study, survival times were reported to decrease significantly with increasing age [18]. In our study, although the mortality rate increased with age, the result was not statistically significant. This may be due to the smaller sample size of our study compared to others.

The literature indicates that MM is more commonly diagnosed in men than in women [19]. However, a single-center retrospective study found no significant difference in survival time between male and female patients diagnosed with MM [20]. Similarly, a retrospective cohort study focused on patients with extramedullary MM, a rare subtype, also reported no significant association between gender and survival outcomes [21]. In our study, while the mortality rate was higher among men, we did not observe a statistically significant difference, aligning with these previous findings.

The ISS, an international staging system that is easy to apply in clinical practice, is cost-effective and has been used for nearly 20 years to predict the course of the disease. Serum albumin and B2M were identified as independent prognostic markers, leading to the creation of three subgroups, with Stage 3 being associated with the worst survival outcomes [22]. A retrospective study also found that early mortality was linked to advanced disease stage [23]. Similarly, a single-center study reported that survival rates

Table 1. The demographic and clinical features of the study group.

Age	**Median (IQR)**	**73 (63-79)**
Gender, n (%)	Female	29 (41.4)
	Male	41 (58.6)
ISS, n (%)	Stage 1	15 (21.4)
	Stage 2	21 (30)
	Stage 3	34 (48.6)
R-ISS, n (%)	Stage 1	10 (14.3)
	Stage 2	30 (42.9)
	Stage 3	30 (42.9)
Ig content, n (%)	IGA kappa	13 (18.6)
	IGA lambda	5 (7.1)
	IGG kappa	23 (32.9)
	IGG lambda	28 (40)
	Kappa light chain	1 (1.4)
Follow-up period (day)	Median (IQR)	943 (468-1870)
Prognosis, n (%)	Alive	29 (41.4)
	Mortality	41 (58.6)

decreased as the ISS stage increased [24]. In our study, ISS stage was found to be an independent risk factor for mortality. Compared to Stage 1, mortality was 4 times higher in Stage 2 and 4.6 times higher in Stage 3. The relatively high proportion of patients at ISS Stage 3 in our cohort

Table 2. Evaluation of factors affecting prognosis in patients diagnosed with MM.

	Factors	***Mortality (-) n (%)***	***Mortality (+) n (%)***	***p****
Age	*≤ 73 years*	17 (45.9)	20 (54.1)	**0.417**
	>73 years	12 (36.4)	21 (63.6)	
Gender	*Female*	14 (48.3)	15 (51.7)	0.328
	Male	15 (36.6)	26 (63.4)	
ISS, n (%)	*Stage 1*	11 (73.3)	4 (26.7)	**0.017****
	Stage 2	7 (33.3)	14 (66.7)	
	Stage 3	11 (32.4)	23 (67.6)	
R-ISS, n (%)	*Stage 1*	6 (60)	4 (40)	0.185
	Stage 2	14 (46.7)	16 (53.3)	
	Stage 3	9 (30)	21 (70)	
IG content	*IGA*	8 (44.4)	10 (55.6)	0.698
	IGG	20 (39.2)	31 (60.8)	

*: Chi-square test.

**: Linear trend

Table 3. Comparison of laboratory findings and prognosis.

Laboratory Parameters	***Mortality (-) (n=29) Mean (SD)***	***Mortality (+) (n=41) Mean (SD)***	****P values Mortality (-) vs Mortality (+)***
Hemoglobin (g/dL)	10.57 (2.21)	9.71 (2.08)	0.074
RBC (x10^6/µL)	3.6 (0.83)	3.33 (0.89)	0.068
WBC (µL)	6436.2 (2157.32)	5497.07 (2126.83)	0.055
MNS (µL)	3831.37 (1776.37)	3157.8 (1585.6)	0.156
MLS (µL)	1694.19 (840.37)	1585.12 (758.16)	0.482
RDW-CV (%)	**14.70 (1.46)**	**16.92 (2.54)**	**<0.001**
Total Protein (g/L)	87.79 (20.96)	79.82 (18.82)	0.109
Albumin (g/L)	35.96 (6.55)	35.85 (7.08)	0.680
Calcium (mg/dL)	9.34 (1.01)	9.82 (1.85)	0.579
Phosphate (mg/dL)	3.44 (0.71)	3.96 (1.04)	0.030
ALP (U/L)	78.17 (34.24)	76.02 (24.92)	0.981
Creatinine (mg/dL)	1.66 (1.86)	1.41 (1.05)	0.531
Uric acid (mg/dL)	6.23 (1.87)	6.7 (2.86)	0.919
Urea (mg/dL)	56.72 (46.8)	52.15 (27.93)	0.612
LDH (U/L)	**184 (56.54)**	**273.9 (170.94)**	**0.002**
B2M (mg/L)	**6 (5.75)**	**10.06 (11.63)**	**0.025**
Sedimentation (mm/h)	87.1 (36.49)	79.85 (44.85)	0.515
CRP (mg/L)	22.64 (46.67)	19.86 (36.75)	0.314
Ferritin (ng/mL)	211.53 (198.73)	382.95 (468.09)	0.109

*: *Mann Whitney U* test. SD: standard deviation.

may explain the significantly higher mortality rate.

The R-ISS was developed by adding two additional prognostic factors to the original ISS staging system for MM. These include genetic risk that is assessed by fluorescence in situ hybridization, and LDH levels [9]. In an international clinical study (n=3,060), five-year survival rates were reported as 82% for R-ISS Stage 1, 62% for Stage 2, and 40% for Stage 3 [25]. Another study found three-year survival rates of 88% for R-ISS Stage 1, 75% for Stage 2, and

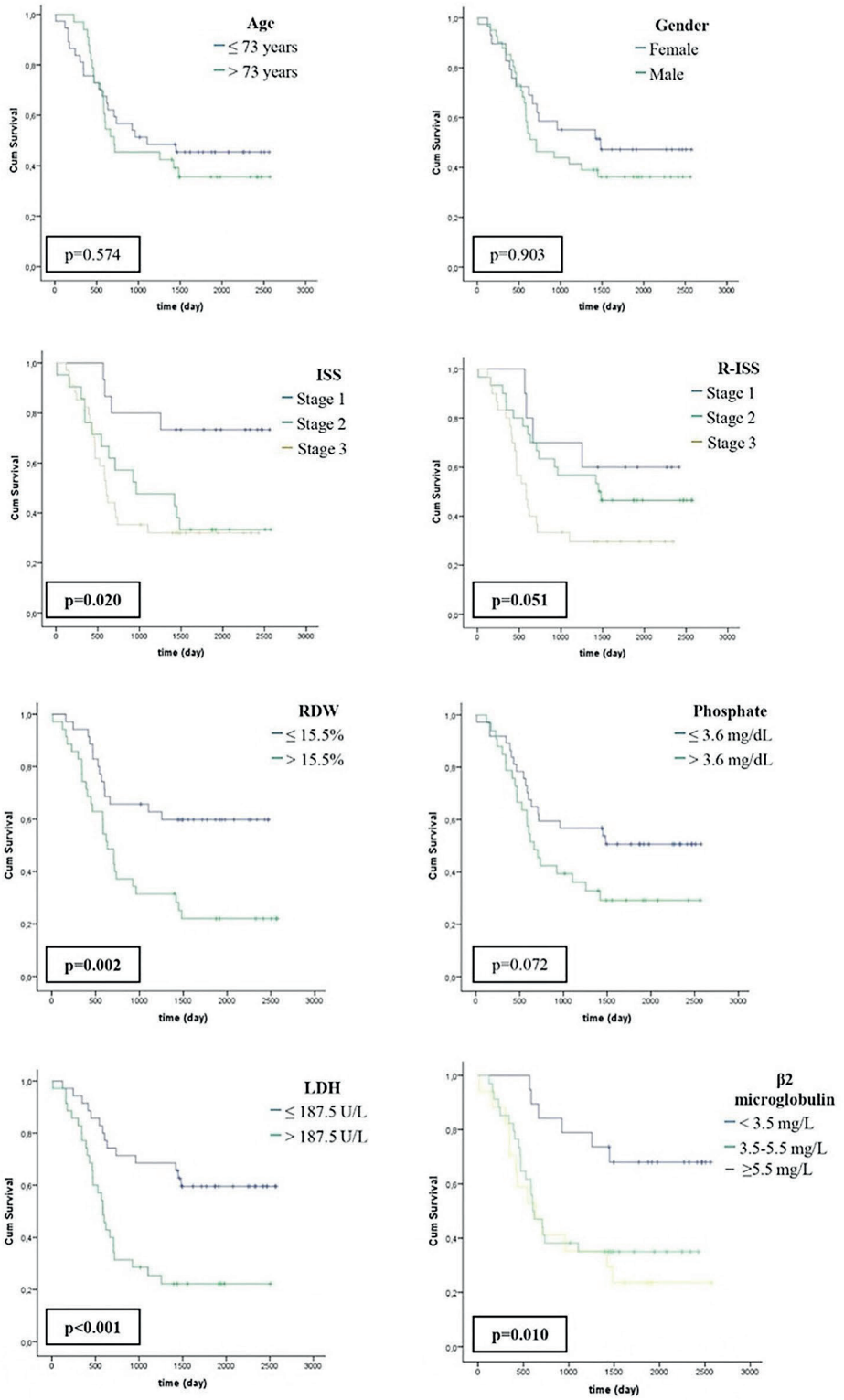

Figure 1. *Kaplan-Meier* survival graphics for different prognostic factors.

56% for Stage 3 [26]. In the present study, these rates were lower, with survival rates of 60%, 47%, and 30%, respectively. In a retrospective cohort study, R-ISS Stage 3 was identified as one of the strongest predictors of early mortality in patients aged 70 and older [27]. Similarly, in a smaller-scale study (n=102), R-ISS was found to be a more useful prognostic tool than ISS for risk stratification in MM patients who were not suitable for transplantation [28]. However, in a study using data from three clinical trials, no significant difference in prognosis was found between the ISS and R-ISS systems for newly diagnosed MM patients [29]. In the current study, while R-ISS did not show a significant difference in prognosis in binary analysis, it became significant in regression analysis, with Stage 3 increasing mortality threefold compared to Stage 1.

It has recently been reported that RDW may serve as an inflammatory biomarker in cardiovascular diseases [30]. However, its significance has rarely been explored in MM patients. In a study conducted in Korea, it was found that patients with higher RDW levels had shorter survival times during the follow-up period [31]. Similarly, a retrospective study showed that RDW levels decreased in patients in complete remission and increased as the disease progressed. Furthermore, the study reported that patients with high RDW values before treatment had shorter survival times [32]. In our study, RDW was also identified as an independent risk factor for mortality. Based on these findings, RDW may be a simple and easily accessible biomarker for both monitoring and predicting prognosis in MM patients. An increased RDW not only has a high negative predictive value for diagnosing various disorders but also provides crucial information regarding short- and long-term prognosis. In our study, phosphate levels, like RDW, were also found to be a significant risk factor in predicting mortality and were higher in patients who did not survive. Kidney and parathyroid diseases, which frequently cause phosphate metabolism disorders, have been reported as complications associated with MM [33,34]. However, the low creatinine levels observed in MM patients who developed mortality complicates the association between renal dysfunction and elevated phosphate levels. Additionally, the lack of a significant difference in calcium levels between groups does not support a clear relationship with parathyroid dysfunction. Therefore, it is hypothesized that a different mechanism may exist between MM pathogenesis and phosphate metabolism.

Lactate dehydrogenase has long been recognized as a critical biomarker in various cancers, and its role in MM prognosis is no exception. In our study, LDH levels were significantly higher in patients who did not survive and were identified as an independent risk factor for prognosis. Similarly, a retrospective study found that elevated LDH levels are a marker of poor prognosis in MM patients [35]. Another study reported that high LDH levels were an independent risk factor for shorter survival times, particularly in elderly MM patients [36]. The results of our study align with these findings in the literature, further confirming the importance of LDH as a prognostic indicator in MM.

Beta-2 microglobulin has long been recognized as an important biomarker in the assessment of disease burden and prognosis in MM [37]. While this protein is produced at a constant rate under normal physiological conditions, elevated serum concentrations are observed in various autoimmune, renal, and hematological diseases. In MM, increased B2M levels have been associated with poor prognosis and treatment resistance [38]. B2M is one of the criteria included in the ISS and R-ISS staging systems, where serum levels above 5.5 mg/L classify the disease as Stage 3. A retrospective study found that patients with high B2M levels had lower overall survival rates [39]. Similarly, another study reported that elevated B2M was a negative prognostic factor, reducing remission rates [40]. In our study, while a significant increase in LDH was detected in patients who developed mortality, B2M lost its significance in multiple analyses and was no longer identified as an independent risk factor.

Conclusion

In conclusion, the current study provides valuable insights into the prognostic factors influencing mortality in patients diagnosed with MM, with a particular focus on age, gender, and various staging systems. Key findings indicate

that ISS and R-ISS are commonly used to predict patient prognosis, with the ISS demonstrating greater effectiveness in assessing mortality risk. As patients age, their ISS stage tends to increase, correlating with decreased survival rates. Gender differences in MM prognosis remain ambiguous, as this study, along with previous research, found no significant difference in survival times between male and female patients, despite higher mortality rates observed in men. The ISS, which incorporates serum albumin and B2M as independent prognostic markers, was associated with increased mortality in advanced stages. The R-ISS was developed to enhance the prognostic capabilities of the ISS by including additional factors such as genetic risk and LDH levels. However, this study reported lower survival rates across R-ISS stages compared to previous findings. Additionally, this study examined RDW and phosphate levels as emerging prognostic markers, both of which were associated with an increased risk of mortality. LDH levels were confirmed as significant prognostic indicators, consistent with existing literature, whereas B2M, despite its established relevance, lost statistical significance in multiple analyses in this study.

The limitations of our study include its single-center design, small sample size, and the lack of evaluation of treatment and other factors that could influence prognosis. However, the strengths of this study lie in its eight-year follow-up period, providing up-to-date data from the Mediterranean region, and the assessment of staging systems whose clinical relevance is still under debate. Additionally, the scarcity of similar studies in literature further underscores the importance of this research.

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Conflict of interest

The authors declare no competing interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon a reasonable request.

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