Original article

Prognostic Value of Hemoglobin to Red Cell Distribution Width Ratio for Patients with Multiple Myeloma

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Abstract

Aim: Multiple myeloma (MM) is a malignant hematological disorder characterized by clonal plasma cell proliferation and is often associated with renal impairment, anemia, and increased mortality. This study aims to determine whether the hemoglobin-to-red cell distribution width ratio (HRR) at the time of diagnosis acts as an independent prognostic factor for overall survival (OS).

Subjects and methods: This study included patients diagnosed with MM between 2017 and 2023 at the University Hospital Center Osijek. Data were obtained from medical records, and statistical analysis was conducted using SPSS 23 and MedCalc Statistical Software version 22.018 with significance set at $\alpha = 0.05$.

Results: A total of 56 patients with MM were included in the study, consisting of 29 (52%) males and 27 (48%) females. Male patients demonstrated significantly higher HRR values (P = 0.04), with notable variations related to the International Staging System (ISS). Patients with elevated HRR (HR = 0.63) had significantly longer survival rates. The cut-off HRR value for predicting mortality was ≤ 5.09. Receiver operating characteristic (ROC) analysis revealed that 42 patients (75%) had HRR values above 5.09, while 14 (25%) had values ≤ 5.09. Patients with HRR values above 5.09 demonstrated significantly better survival outcomes.

Conclusion: There is a statistically significant difference in HRR values based on sex, ISS, and outcome, in male patients, patients in ISS stage I and survivors exhibiting higher HRR levels. Reduced HRR is associated with poorer outcomes and OS in MM patients, establishing HRR as a straightforward and valuable prognostic indicator for long-term survival in MM.

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Introduction

Multiple myeloma (MM) is a malignant hematopoietic disorder characterized by the clonal proliferation of plasma cells within the bone marrow, resulting in the overproduction of monoclonal immunoglobulins or their light chains. This neoplastic process leads to severe complications, including osteolytic bone lesions, renal insufficiency, anemia, and hypercalcemia, all of which profoundly affect the morbidity and mortality of patients (1). Although MM remains an incurable malignancy, advancements in therapeutic modalities have significantly improved overall survival and quality of life (2). Prognosis in MM is influenced by a range of clinical and laboratory parameters. The hemoglobin-to-red cell distribution width ratio (HRR) has recently been identified as a novel prognostic biomarker. Anemia, commonly observed in MM, is reflected by decreased hemoglobin levels, while elevated red cell distribution width (RDW) is often indicative of anisocytosis, inflammation, and oxidative stress, all of which are associated with advanced disease (3–8). Emerging evidence suggests that HRR, as a readily available and cost-effective biomarker, holds potential in predicting patient outcomes. The focus of this study was to examine the prognostic value of HRR in patients with MM, with an emphasis on its association with disease progression and OS. Furthermore, the integration of HRR with other prognostic markers such as the International Staging System (ISS), may enhance risk stratification and guide individualized therapeutic strategies for MM patients.

Patients and methods

This retrospective study included 56 patients diagnosed with MM over a six-year period (December 2017 to November 2023) at the Department of Hematology, University Hospital Center Osijek. Basic patient data, including sex, disease outcome and laboratory results such as hemoglobin, RDW, albumin and beta-2-microglobulin were collected from medical records. The HRR ratio was calculated, and the ISS score was determined based on the beta-2-microglobulin to albumin value.

Statistical methods

Categorical data were presented as absolute and relative frequencies, while the normality of numerical variables was tested using the Shapiro–Wilk test. Continuous data were described using the median and interquartile range (IQR). Differences between two groups were tested with the Mann–Whitney U test (including the Hodges-Lehmann difference and a 95% confidence interval), while differences across three or more independent groups were assessed using the Kruskal–Wallis test (with post hoc Conover analysis). Cox regression analysis was used to assess the prognostic value of the HRR on survival, which was visualized with Kaplan–Meier curves. The diagnostic value of HRR for OS was evaluated using Receiver operating characteristic (ROC) analysis based on sensitivity and specificity. All P-values were two-sided, with the significance level set at $\alpha = 0.05$. Data analysis was performed using MedCalc® Statistical Software version 22.018 (MedCalc Software Ltd, Ostend, Belgium) and SPSS 23 (IBM Corp, Armonk, NY, 2015).

Results

This study included 56 patients diagnosed with MM, with 29 (52%) being male and 27 (48%) female. According to the ISS, 27 patients (48%) were classified as stage III, 18 patients (32%) as stage II, and 11 patients (20%) as stage I. Moreover, 37 patients (66%) had a positive treatment outcome (survived), while 19 patients (34%) did not survive. The median follow-up time for patients was 24.5 months, with a maximum of 76 months and a minimum of 2 months. The two-year OS rate was calculated on a sample of 29 patients who met the criteria, as the remaining 27 patients had not reached the two-year follow-up mark. Of these, 20 patients (69%) survived for two years post-diagnosis, while 9 patients (31%) passed away within two years of their MM diagnosis. Male patients exhibited significantly higher HRR values compared to females (Mann–Whitney U test, P = 0.04).

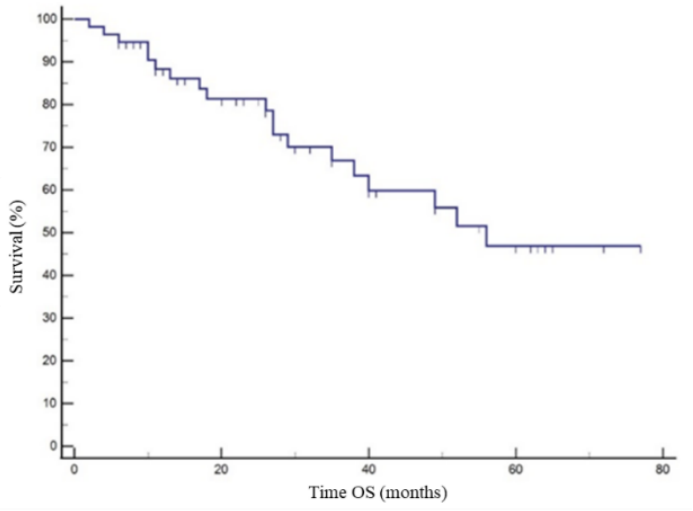

Figure 1. Kaplan-Meier`s overall survival curve

Overall survival (OS) is shown by Kaplan Meier curve (Figure 1).

Additionally, patients classified as ISS stage I had the highest HRR values, while those in stage III showed the lowest values (Kruskal–Wallis test, P < 0.001). Furthermore, patients with a negative treatment outcome (death) had significantly lower HRR values than those who survived (Mann–Whitney U test, P = 0.01) (Table 1).

Cox regression analysis confirmed that a higher HRR is associated with better overall survival (OS) (HR = 0.63) (Table 2).

Table 1. The differences in the hemoglobin/RDW ratio concerning sex and clinical characteristics

	Median (interquartile range) Hemoglobin/RDW ratio	§Difference (95 % confidence interval)	*P*
Gender			
Male	7,23 (5,29 – 9,26)	-1,29 (-2,74 to -0,08)	**0,04***
Female	6,12 (4,36 – 7,20)		
International Staging System			
I	10,32 (8,51 – 10,94)		**<0,001†‡**
II	7,16 (5,14 – 8,50)		
III	5,32 (4,30 – 6,67)		
Outcome			
Survived	7,13 (5,42 – 9,26)	-1,67 (-2,99 to -0,36)	**0,01***
Died	5,28 (4,26 – 7,30)		

IQR – interquartile range; *Mann–Whitney U test; §Hodges-Lehmann median difference
†Kruskal–Wallis test (post-hoc Conover);
‡at the level of P < 0,05 there are significant differences between all values

Table 2. Overall survival estimate for HRR ratio values (Cox regression)

	ß	*P*	HR (95% Confidence interval)
Overall survival			
hemoglobin/RDW ratio (HRR)	-0,457	**0,004**	0,63 (0,47 to 0,86)

ß – regression coefficient, HRR – hemoglobin/red cell distribution width, RDW – red blood cell distribution width, HR – hazard ratio

The diagnostic value of HRR was assessed using a ROC curve, which evaluated sensitivity and specificity, adjusting the cut-off points to differentiate between survival and death outcomes. The cut-off value for predicting death was determined to be ≤ 5.09 (Table 3, Figure 2).

Table 3. Values of the ROC analysis of the HRR ratio in the assessment of OS outcomes

Factor	AUC	95 % CI	Sensitivity	Specificity	*cut- off*	Youden index	*P*
HRR ratio	0,708	0,572 – 0,822	47	86	≤ 5,09	0,339	**0,004**

AUC – area under the curve; CI – confidence interval; HRR – hemoglobin/red cell distribution width; ROC – receiver operating characteristics; OS – overall survival

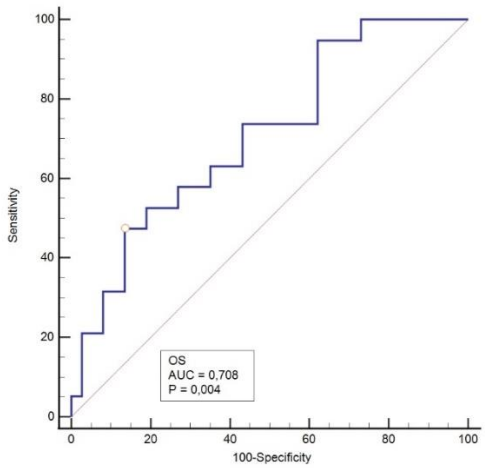

Figure 2. Hemoglobin to red cell distribution width ratio as diagnostic indicator of overall survival (ROC-analysis)

Based on this threshold (derived from the ROC analysis), 42 (75%) patients had an HRR value greater than 5.09, while 14 (25%) had values ≤ 5.09. The two-year OS rate varied based on HRR values. Among patients with an HRR values ≤ 5.09, the two-year OS rate was 50%, whereas for patients with an HRR above 5.09, the two-year OS rate was 72%. Patients with HRR values above 5.09 demonstrated significantly longer survival (Figure 3, Table 4).

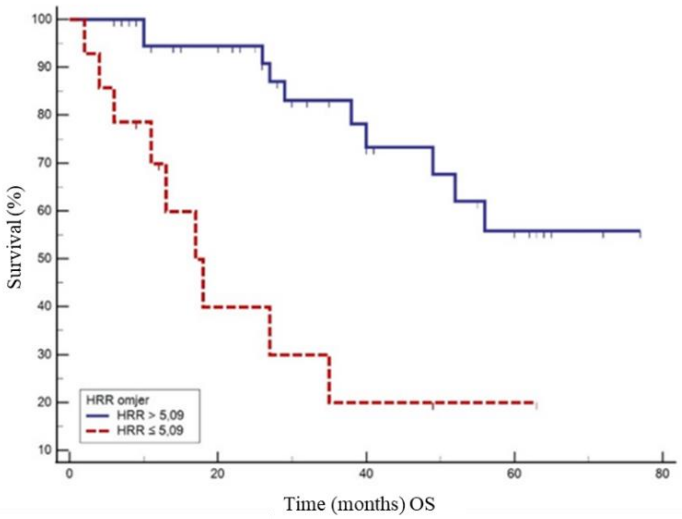

Figure 3. Kaplan-Meier curves of overall survival (OS) versus hemoglobin to red cell distribution width ratio (HRR)

Table 4. Overall survival (OS) in terms of HRR ratio

HRR ratio	Outcome		Arithmetic mean (months)	95 % Confidence interval	Median	95 % Median confidence interval	P value (Log rank test)
	Died	Alive					
> 5,09	10	32	59,6	51,0 do 68,2	-	-	**<0,001**
≤ 5,09	9	5	25,4	13,0 do 37,7	17	6 do 35	

HRR – hemoglobin/red cell distribution width

Discussion

The distribution of participants in this study aligns with epidemiological data showing a higher prevalence of male cases (9). HRR values were significantly higher in men compared to women, which is consistent with previous research on esophageal carcinoma (3). This difference may be attributed to higher baseline hemoglobin levels in men, likely influenced by factors such as body composition, testosterone levels, and hormonal regulation (10). One of the key findings of this study is the association between lower HRR values and more advanced stages of disease according to the ISS. Patients classified as ISS stage III had the lowest HRR values, while those in stage I had the highest. This relationship between lower HRR values and higher disease stages has been reported in other studies, further supporting the relevance of HRR as a prognostic indicator in MM (11). Understanding this association is crucial for assessing prognosis and informing treatment decisions. Patients with lower HRR values and higher ISS scores likely represent a subset of individuals with a more aggressive disease course and an increased risk of mortality. Integrating HRR with established prognostic markers such as ISS may enhance risk stratification, enabling more personalized therapeutic approaches and potentially improving patient outcomes (12 – 14). This study's findings demonstrate that HRR is an independent prognostic marker for OS and disease outcome, with lower HRR values indicating worse prognosis and higher mortality risk. Previous research on other malignancies, including cancers of the esophagus, head and neck, lung, and hematological malignancies, has shown similar associations between lower HRR values and advanced disease stages, highlighting the potential of HRR as a reliable prognostic marker (3,11,15 – 18). Despite these promising results, it is important to acknowledge the limitations of this study. The small sample size and single-center design may limit the generalizability of the findings, and the retrospective nature of the study introduces the possibility of bias. Larger, prospective studies are needed to validate the prognostic significance of HRR in MM and to explore its potential role in guiding clinical management. Nevertheless, these results suggest that HRR holds promise as a valuable marker for understanding disease progression and personalizing treatment strategies in MM.

Conclusion

The results of this study confirm the utility of HRR as a simple and routinely accessible prognostic marker that could be integrated into standard diagnostic and monitoring protocols for MM patients.

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Disclosure

Funding. No specific funding was received for this study.
Competing interests. None to declare.

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Analysis and interpretation of data: NM, VP, JSP
Conception and design: NM, VP, JSP
Critical revision of the article for important intellectual content: NM, VP, JSP
Drafting of the article: NM, VP, JSP
Final approval of the article: NM, VP, JSP
Guarantor of the study: NM, VP, JSP

Prognostička vrijednost omjera vrijednosti hemoglobina i širine distribucije eritrocita u bolesnika s multiplim mijelomom

Sažetak

Cilj: Multipli mijelom (MM) je zloćudni hematološki poremećaj karakteriziran klonalnom proliferacijom plazma stanica i često je povezan s bubrežnim oštećenjem, anemijom i povećanom smrtnošću. Ova studija ima za cilj utvrditi djeluje li omjer hemoglobina i širine distribucije eritrocita (HRR) u trenutku postavljanja dijagnoze kao neovisni prognostički faktor za ukupno preživljenje (OS).

Ispitanici i metode: Studija je uključila pacijente kojima je dijagnosticiran MM između 2017. i 2023. godine u Kliničkom bolničkom centru Osijek. Podaci su prikupljeni iz medicinske dokumentacije, a statistička analiza provedena je pomoću SPSS-a 23 i MedCalc statističkog softvera verzije 22.018, uz razinu značajnosti postavljenu na α =0,05.

Rezultati: U studiju je bilo uključeno ukupno 56 pacijenata s MM-om, od kojih je 29 (52%) bilo muškaraca, a 27 (48%) žena. Muški pacijenti pokazali su značajno više vrijednosti HRR-a (P = 0,04), s primjetnim razlikama vezanim uz Međunarodni sustav stadija (ISS). Pacijenti s povišenim HRR-om (HR = 0,63) imali su značajno dulje stope preživljenja. Granična vrijednost HRR-a za predviđanje smrtnosti iznosila je ≤ 5,09. Analiza krivulje radne karakteristike primatelja (ROC) otkrila je da je 42 pacijenta (75%) imalo HRR vrijednosti iznad 5,09, dok je 14 (25%) imalo vrijednosti ≤ 5,09. Pacijenti s HRR vrijednostima iznad 5,09 pokazali su značajno bolje ishode preživljenja.

Zaključak: Postoji statistički značajna razlika u vrijednostima HRR-a s obzirom na spol, ISS i ishod, pri čemu muški pacijenti, pacijenti u ISS stadiju I te preživjeli imaju više razine HRR-a. Smanjeni HRR povezan je s lošijim ishodima i ukupnim preživljenjem kod pacijenata s MM-om, što HRR čini jednostavnim i vrijednim prognostičkim pokazateljem za dugoročno preživljenje kod MM-a.