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Could ratio of hemoglobin to red cell distribution width and ratio of absolute lymphocyte count to absolute monocyte count be a prognostic tool in newly diagnosed multiple myeloma patients?

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Abstract

Introduction: Hemoglobin/red cell distribution width (RDW) ratio (HRR) and lymphocyte-to-monocyte ratio (LMR) are two novel biomarkers associated with overall survival (OS) and prognosis in several types of cancers. The aim of this study is to investigate the value of HRR and LMR in newly diagnosed multiple myeloma (MM) patients. Methods: A total of 180 patients were included in this study. Patients diagnosed with MM between May 2013 and May 2019 at a single center were evaluated. HRR was calculated by dividing hemoglobin to RDW, both measured from the same sample. LMR was calculated by dividing absolute lymphocyte count (ALC) to absolute monocyte count (AMC). Results: The cutoff value for HRR was taken as 0.61, and the cutoff value for LMR was taken as 3.28. Patients were divided into low HRR, high HRR, low LMR, and high LMR groups. OS of the patients with low HRR was found lower compared with high HRR (36.7 months for low HRR and 53.2 months for high HRR, $p < 0.001$). Also, OS was found lower in the low LMR group (39.4 months for low LMR and 51.7 months for high LMR, $p = 0.016$). On multivariate analysis, low HRR and low LMR were predictive factors of OS (hazard ratio (HR) 2.08, 95% confidence intervals (CI) 1.31–3.03, and $p = 0.002$ for low HRR; HR 1.47, 95% CI 0.92–2.29, and $p = 0.010$ for low LMR). Conclusion: Combining both HRR and LMR could be a prognostic biomarker and it reflects the status of the immune system in newly diagnosed MM patients.

Keywords:
multiple myeloma, hemoglobin, red cell distribution width, lymphocyte–monocyte ratio, prognostic

Introduction

Multiple myeloma (MM) is described as a clonal proliferation of malignant plasma cells secreting monoclonal immunoglobulin with heavy or light chains. This incurable disease is accounted for 1–2% of all cancers and 15% of hematological malignancies [1, 2]. Usual presentation and end-organ diseases of MM include anemia, hypercalcemia, lytic bone lesions, and renal disease.

Anemia itself is accepted as myeloma defining event and is associated with involvement of bone marrow of malignant plasma cells [3]. As a surrogate of red blood cell size and variability, red cell distribution width (RDW) is investigated in several cancer types and associated with stage, grade, activity, and prognosis in certain types of cancers [4, 5]. Likewise, RDW is demonstrated to be correlated with inflammatory states and chronic conditions [6, 7]. Although erythropoiesis can be affected by any chronic condition, the variability of RDW, the inclusion of hemoglobin levels, and inflammatory markers to the equation might bring insight to the pathogenesis of how erythropoiesis is affected and the role of bone marrow microenvironment (BME) in MM [8]. Besides, RDW itself was proposed as a prognostic factor in symptomatic MM patients [9].

As mentioned earlier, BME holds an essential role in the pathogenesis of MM. The interactions between BME and malign plasma cells are demonstrated to be related to prognosis [10, 11]. These interactions cause an immune system to escape due to tumor-associated macrophages [12]. The immunosuppressive microenvironment and the effect of stromal cell–myeloma cell interferences stimulate the expansion of malign plasma cell clone. These immune escape and tumor growth are generated by myeloid-derived suppressor cells [13]. Peripheral absolute lymphocyte count (ALC) and absolute monocyte count (AMC) could preview the balance between the immune system and malignancy-associated immune escape. Monocyte count could be regarded as myeloid-derived suppressor cells, and therefore the ratio of ALC/AMC (LMR) may implicate the effect of the impaired immune system on MM [14]. There are studies regarding the effect of LMR on overall survival (OS), but combining hemoglobin/RDW ratio (HRR) with LMR may reveal the effects of immune dysregulation on plasma cell disease [15, 16, 17]. Besides, there is insufficient data on the effect of HRR in MM, especially in the era of novel agents. Therefore, in this study, we aimed to evaluate the possible impact of HRR and LMR on newly diagnosed MM patients treated with novel agents as the first line.

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Patients and methods

This retrospective study included 180 patients diagnosed with MM according to International Myeloma Working Group (IMWG) definitions between May 2013 and May 2019 in Trakya University Hematology Department. Baseline demographic features, including age and sex, and disease-related data, including heavy and light chain types of immunoglobulin, International staging system (ISS), whole blood count (WBC), results of the bone marrow sample analysis and treatments, were recorded from patient files. WBC was performed with Beckman Coulter DXH 800 device, and fresh blood samples were obtained after 8 h of fasting and before treatment.

Cytogenetic analysis was performed from bone marrow samples obtained at the time of diagnosis and included high-risk determinants of MM, such as ISS and revised ISS (R-ISS), according to the definitions of IMWG [18, 19]. The ratio of hemoglobin (g/dl) to RDW (%) was calculated by the formula hemoglobin/RDW, and LMR was calculated by the formula ALC/AMC. Overall survival (OS) was accepted as time from date of treatment to date of last follow-up or death from any cause.

This study was conducted according to the principles of the Helsinki declaration and was approved by the local ethical committee (TUTF-BAEK 2019-248).

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS) version 20 was used for statistical analysis. Kolmogorov-Smirnov test was performed to assess the distribution of the parameters. Descriptive statistics were used to evaluate the characteristics of patients. The correlation of HRR and LMR with different variables was assessed with Pearson's chi-squared test or Fisher's exact test for categorical variables and with Mann-Whitney U test for continuous variables. The OS is defined as the time from the diagnosis of MM to death from any cause. Kaplan-Meier OS estimates were conducted for survival analysis. Log-rank test and Cox regression analysis were performed to evaluate the estimate hazard ratios (HRs) and 95% confidence intervals (CI). A *p*-value <0.05 was considered to be statistically significant. Receiver operating characteristic (ROC) curves and area under the curve (AUC) are constructed to define best cutoff values for HRR and LMR.

Results

A total of 180 newly diagnosed MM patients were included in this study. The mean age of the patients was 66.77 years. Eighty-seven patients were male and 93 patients were female. Sixty-eight patients were classified as ISS-1, 51 patients were classified as ISS-2, and 61 patients were classified as ISS-3. Fifty-seven patients (31.6%) evaluated were R-ISS-1, 41 (22.8%) patients evaluated were R-ISS-2, and 82 (45.6%) patients evaluated were R-ISS-3. Thirty-six (20%) patients were regarded as high risk according to the analysis. Moreover, in autologous hematopoietic stem cell transplant (ASCT) eligible patients, ASCT was performed after 4–6 cycles of induction chemotherapy containing bortezomib. Ninety-seven (53.9%) patients received bortezomib cyclophosphamide dexamethasone, 8 patients (4.4%) received bortezomib thalidomide dexamethasone, 33 patients (18.3%) received bortezomib dexamethasone, and 15 patients received VTD-PACE (bortezomib, thalidomide, dexamethasone, cyclophosphamide, doxorubicin, cisplatin, and etoposide). The demographic characteristics of the patients were summarized in table I.

The cutoff point for HRR was selected as 0.61 according to ROC analysis with an AUC value of 0.64 (95% CI 0.561–0.724). The most discriminative value of LMR was also calculated with ROC analysis and found to be 3.28 with an AUC value of 0.62 (95% CI 0.538–0.703). Patients were categorized as low LMR < 3.28, high LMR > 3.28, low HRR < 0.61, and high HRR > 0.61. Patients with low LMR had a lower OS compared with patients with high LMR (*p* = 0.018, HR 1.67, 95% CI 1.09–2.57), and patients with low HRR had a lower OS compared with high HRR (*p* = 0.001, HR 2.046, 95% CI 1.33–3.13) (Kaplan-Meier OS analysis for HRR and LMR was shown in figures 1 and 2, respectively). Univariate analysis and characteristics of the patients according to LMR and HRR were given in tables II and III.

Table I. Demographic and clinical characteristics data of the patients

Characteristics	
Age	66.77 ± 11.16 (28–93)
Gender	
Male	87 (48.3%)
Female	93 (51.7%)
Laboratory parameters	
Hemoglobin (g/dl)	11.01 (6.1–15.7)
Creatinine (mg/dl)	1.36 (0.42–6.90)
Calcium (mg/dl)	9.6 (7.1–18.4)
Albumin (g/dl)	3.6 (1.8–4.7)
LDH (U/L)	229.3 (92–662)
Beta-2 microglobulin (ng/ml)	5,687.3 (1,301–20,000)
CRP (mg/dl)	1.62 (0.1–17.9)
ISS	
1	68 (37.8%)
2	51 (28.3%)
3	61 (31.9%)
Revised ISS	
1	57 (31.7%)
2	41 (22.8%)
3	82 (45.6%)
Cytogenetic risk	
High risk	36 (20%)
Standard risk	144 (80%)
Frontline treatment	
Bortezomib cyclophosphamide dexametasone	97 (53.9%)
Bortezomib thalidomide dexametasone	8 (4.4%)
Bortezomib dexametasone	33 (18.3%)
VTD-PACE	15 (8.3%)
Others (melphalan-prednisolone, etc)	27 (15.1%)
Upfront ASCT	
Yes	61 (33.9%)
No	119 (66.1%)
Immunoglobulin type	
IgG	96 (53.3%)
IgA	43 (23.9%)
Light chain	38 (21.1%)
Non-secretory	2 (1.1%)
IgM	1 (0.6%)
Lytic lesion on presentation	
Yes	156 (86.7%)
No	24 (13.3%)

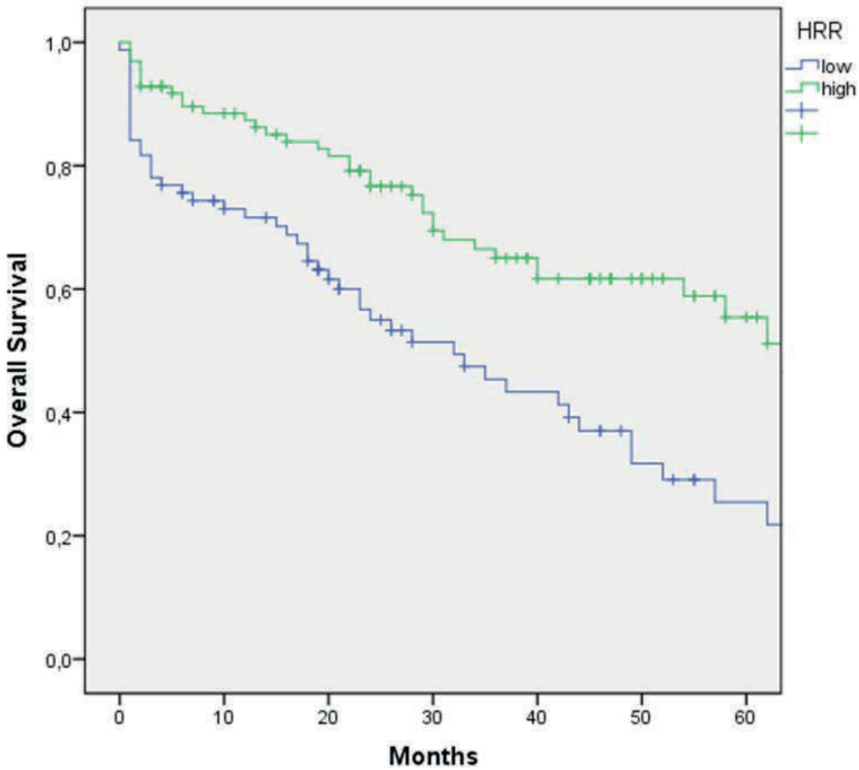

Fig. 1. Kaplan-Meier curve for overall survival of low HRR and high HRR

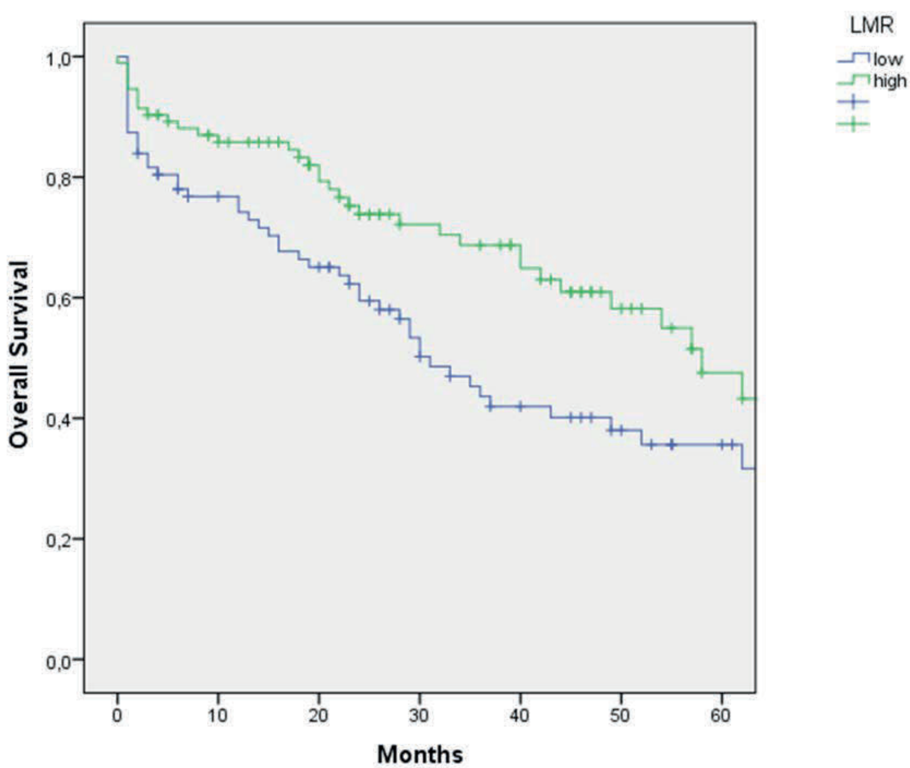

Fig. 2. Kaplan-Meier curve for overall survival of low LMR and high LMR

Table II. Characteristics of the multiple myeloma patients according to LMR

	Low LMR <3.28 (n:87)	High LMR >3.28 (n:93)	*p*-value
Age			
>65 years old	55 (63%)	45 (48%)	0.072
<65 years old	32 (36%)	48 (52%)	
Gender			
Male	45 (52%)	42 (45%)	0.456
Female	42 (48%)	51 (55%)	
Cytogenetic risk			
High risk	19 (22%)	17 (18%)	0.580
Standard risk	68 (78%)	76 (82%)	
ISS			
1	26 (29%)	42 (45%)	0.069
2	25 (28%)	26 (28%)	
3	36 (43%)	25 (27%)	
Revised ISS			
1	21 (25%)	36 (39%)	0.082
2	20 (22%)	21 (22%)	
3	46 (53%)	36 (29%)	
Immunoglobulin type			
IgG	41 (47%)	55 (59%)	0.125
IgA	19 (22%)	24 (26%)	
Light chain	25 (29%)	13 (14%)	
Non-secretory	1 (1%)	1 (1%)	
IgM	1 (1%)	0	
Laboratory parameters			
Hemoglobin (g/dl)	10.8	11.1	0.27
Creatinine (mg/dl)	1.51	1.19	**0.014**
Calcium (mg/dl)	9.54	9.87	0.176
Albumin (g/dl)	3.61	3.76	0.087
LDH (U/L)	234	224	0.527
Beta-2 microglobulin (ng/ml)	6,702	4,737	**0.004**
CRP (mg/dl)	1.90	1.35	0.18
Frontline treatment			
Bortezomib cyclophosphamide dexametasone	46 (53%)	51 (55%)	0.833
Bortezomib thalidomide dexametasone	4 (4%)	4 (4%)	
Bortezomib dexametasone	17 (19%)	16 (17%)	
VTD-PACE	6 (7%)	9 (10%)	
Others (melphalan-prednisolone, etc)	14 (16%)	13 (14%)	
Upfront ASCT			
Yes	22 (22%)	39 (41%)	**0.027**
No	65 (78%)	54 (58%)	
Overall survival months	39.44 ± 3.72	51.79 ± 3.68	**0.016**

Univariate analysis for low LMR, HR: 1.67 (95% CI 1.09–2.57)

On multivariate analysis, low HRR and low LMR are associated with lower OS (HR for HRR 2.08, 95% CI 1.31–3.03, $p = 0.002$; and HR for low LMR 1.47, 95% CI 0.92–2.29, $p = 0.010$). Also ASCT, high-risk MM, and ISS-3 were associated with lower OS on multivariate analysis (details of the multivariate cox-regression analysis was given in table. IV). Furthermore, we have stratified our patients into four groups: low LMR and low HRR, low LMR and high HRR, high LMR and low HRR, and high LMR and high HRR. The OS of these four groups was 34.6, 44.8, 40.5, and 56.1 months, respectively. OS was lower in the low LMR and low HRR groups, which was higher in high LMR and high HRR groups.

Discussion

MM is an incurable disease with complex biological heterogeneity. The underlying complex biology plays a unique role in the clinical course and prognosis of the disease. In this study, baseline WBC parameters were analyzed for their probable role in the OS of MM patients. These findings underline that no matter how complicated diseases and treatments become in the real world, simple laboratory tests such as complete blood count will always be valuable. In this regard, both HRR and LMR have been associated with prognosis in several types of cancers [4, 20]. In two recent analyses, HRR is suggested as a prognostic factor for survival in both non-small cell lung cancer and head and neck cancer [21, 22].

Anemia itself is a common phenomenon in cancer patients and is caused by several mechanisms. An association with anemia and prognosis is demonstrated in several types of solid and hematological malignancies [23, 24]. Development of anemia in MM is caused by the infiltration of malign plasma cells in the bone marrow, which results in suppressing erythropoiesis and dysregulated apoptosis of plasma cells [3, 25]. However, stromal and endothelial cells in

Table III. Characteristics of the multiple myeloma patients according to HRR

	Low HRR <0.61 (n:82)	High HRR >0.61 (n:98)	*p*-value
Age >65 years old <65 years old	 31 (38%) 51 (62%)	 49 (50%) 49 (50%)	 0.132
Gender Male Female	 40 (49%) 42 (51%)	 47 (48%) 51 (52%)	 0.516
Cytogenetic risk High risk Standard risk	 20 (24%) 62 (76%)	 16 (16%) 82 (84%)	 0.195
ISS 1 2 3	 18 (22%) 30 (36%) 34 (42%)	 50 (51%) 21 (21%) 27 (28%)	 **0.001**
Revised ISS 1 2 3	 12 (14.6%) 17 (20.7%) 53 (64.6%)	 45 (45.9%) 24 (24.5%) 29 (29.6%)	 **0.001**
Immunoglobulin type IgG IgA Light chain Non-secretory IgM	 41 (50%) 26 (31.7%) 13 (15.9%) 1 (1.2%) 1 (1.2%)	 55 (56.1%) 17 (17.3%) 25 (25.5%) 1 (1.0%) 0	 0.118
Laboratory parameters Hemoglobin (g/dl) Creatinine (mg/dl) Calcium (mg/dl) Albumin (g/dl) LDH (U/L) Beta-2 microglobulin (ng/ml) CRP (mg/dl)	 9.7 1.60 9.6 3.4 237 7,429 2.19	 12.0 1.16 9.7 3.9 222 4,229 1.11	 **0.000** **0.014** 0.883 0.000 0.338 **0.000** **0.011**
Frontline treatment Bortezomib cyclophosphamide dexametasone Bortezomib thalidomide dexametasone Bortezomib dexametasone VTD-PACE Others (melphalan-prednisolone, etc)	 38 (46.3%) 5 (6.1%) 17 (20.7%) 9 (11.0%) 13 (15.7%)	 59 (60.2%) 3 (3.1%) 16 (16.3%) 6 (6.1%) 14 (14.2%)	 0.168
Upfront ASCT Yes No	 23 (28%) 59 (72%)	 38 (39%) 60 (61%)	 0.155
Overall survival months	36.70 ± 3.77	53.32 ± 3.54	**0.001**

Univariate analysis for low HRR, HR; 2.046 (95% CI 1.33–3.13)

Table IV. Multivariate analysis for overall survival

Multivariate analysis			
	Hazard ratio (HR)	**95% CI**	***p*-value**
LMR < 3.28	1.47	0.92–2.29	**0.010**
HRR < 0.61	2.08	1.31–3.03	**0.002**
Gender	0.74	0.47–1.14	0.178
Age	0.99	0.97–1.02	0.782
No ASCT versus ASCT	0.14	0.07–0.27	**0.000**
High risk MM	0.35	0.21–0.59	**0.000**
ISS	1.89	1.09–3.30	**0.023**
Revised ISS	0.79	0.35–1.19	**0.008**

bone marrow contribute to the development of anemia by producing specific cytokines, particularly interleukin 6 (IL-6) [8]. Likewise, renal insufficiency also contributes to the development of anemia in MM patients via erythropoietin deficiency [26]. Furthermore, the interaction of plasma cells with the tumor microenvironment might play a role in the progression of the disease and the worsening of anemia [11].

Indeed, RDW itself is a reliable marker of red cell size variability. Several relations with RDW and age-related clonal hematopoiesis were reported. Even high RDW was associated with the risk of acute myeloid leukemia development in healthy individuals [27]. Besides, there was an association of increased RDW with worse OS in myelodysplastic syndrome (MDS) patients, especially in patients with refractory anemia [28]. This observation might be regarded as the effects of dysregulated erythropoiesis on RDW in MDS [28]. RDW is also associated with several types of solid and hematological malignancies [4, 29]. For example, in a recent analysis, high RDW was associated with lower progression-free survival and OS in MM [30]. A retrospective analysis including 161 patients with diffuse large B cell lymphoma evaluated the relationship of RDW with OS [31]. The authors reported that high RDW was associated with lower progression-free survival and OS [31]. Considering the high incidence of anemia in solid and hematological cancers, it is noteworthy that high RDW was associated with lower survival in several hematological malignancies. Therefore, HRR is thought to be a logical and surrogate prognostic marker. However, data including HRR in hematological malignancies are scarce. Several studies including data of real-world patients are needed in hematological cancers, especially in MM. Although hemoglobin or RDW alone has been shown to have an impact on prognosis in MM patients, we have shown that HRR may affect OS and prognosis alone. Considering that both low hemoglobin and high RDW have an impact on prognosis, it will not be difficult and surprising to predict that HRR may also affect prognosis. However, multivariate analysis showed that HRR is associated with poor prognosis compared with high HRR. A second important issue is that both hemoglobin and RDW might be affected by nutritional deficiencies besides the effect of MM infiltration and cytokines. In this case, HRR can be suggested as a more powerful and reliable marker.

The BME holds a critical role, especially in the progress of MM [10]. The interactions in malign plasma cells with BME cause an immunosuppressive state and may result in an immune escape causing myeloma cell growth [11, 13]. These interplays stimulate several regulatory or inhibitory cells. Various suggestions have been made to measure and show the contribution of immunosuppression induced by tumor microenvironment [13, 32]. It has been shown that both ALC and AMC could be an indirect indicator of immune surveillance. Thus, LMR, which is obtained by dividing ALC by AMC, could also be an additional determiner [12, 16]. Several studies investigated the effect of LMR in MM. The prognostic value of ALC, AMC, and LMR was analyzed in 189 MM patients retrospectively [17]. In multivariate analysis, low LMR was an independent poor prognostic factor. Low LMR is reported to be <2.9 in this study. In another retrospective analysis, the authors stated that peripheral blood monocyte count could be correlated with tumor-associated macrophages, thus reflecting immune status [16]. This study included 372 newly diagnosed MM patients and cutoff value for LMR was determined as 3.6. Low LMR is associated with lower progression-free survival and OS on multivariate analysis [16]. Another study questioned the value of LMR evaluated in 285 MM patients [33]. In this study, the cutoff for LMR was 4.2, and low LMR is found to be an independent factor for OS [33]. These studies indicated the value of LMR in MM patients. In our study, fewer patients in the low LMR group proceeded to the ASCT, which may be the explanation for lower OS in the low LMR group. As we mentioned earlier, the search for a basic and reliable marker for immune regulation and prognosis is mandatory. The main limitation of the studies involving LMR is that lymphocyte and monocyte counts can be affected by a variety of reasons that do not affect the disease, mainly infections. In addition, different cutoff values are taken for LMR in different studies. This situation is also a confounding factor. Therefore, we consider that the combination of LMR and HRR might partially overcome these limitations.

Although medicine is becoming more and more complicated every day, simple, easily accessible, and useful markers are required to predict the prognosis of malignant diseases, especially in developing countries. In this study, we found that two complete blood count parameters that can be easily obtained, such as HRR and LMR, might be independent factors in predicting prognosis in MM patients.

Authors' contributions

EU – reviewed the data and the manuscript. HOK – data acquisition, data interpretation, reviewed the manuscript. SB – statistical analysis, reviewed the manuscript, data analysis. AMD – edited the data, reviewed the statistical analysis, reviewed the manuscript ana critical review. MB – collected the data, wrote the manuscript, statistical analysis. UD – collected the data, literature search. VB – collected and edited the data. SKG – data acquisaiton and interpretation, reviewed the manuscript.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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