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?

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 = 0.010 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 malignant 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 malignant 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.
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 | Median (IQR) |
|-----------------|--------------|
| 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 dexamethasone | 97 (53.9%) |
| Bortezomib thalidomide dexamethasone | 8 (4.4%) |
| Bortezomib dexamethasone | 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                  | 11 (1%)              | 11 (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)                    | 1.30                 | 1.35                  | 0.18    |
| Frontline treatment            |                      |                       |         |
| Bortezomib cyclophosphamide dexametasone | 46 (53%) | 51 (55%) | 0.833 |
| Bortezomib thalidomide dexametasone | 4 (4%)    | 4 (4%)                |         |
| Bortezomib dexametaseone       | 17 (19%)             | 16 (17%)              |         |
| VTD-PACE                       | 6 (7%)               | 9 (10%)               |         |
| Others (melphalan-prednisolone, etc) | 14 (16%) | 13 (14%) |         |
| Overall survival months        | 39.44 ± 3.72         | 51.79 ± 3.68          | 0.016   |

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

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

|                      | 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 erythropoetin 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].

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 acquisition 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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