# The Predictive Role of the Neutrophil/Lymphocyte Ratio in Survival with Multiple Myeloma: A Single Center Experience

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*Background:* Recent studies have shown a positive correlation between tumor-related immune response markers and the poor outcome in solid tumors. In this study, we aimed to investigate the neutrophil/lymphocyte ratio (NLR) in multiple myeloma. To the best of our knowledge, this would be the second report concerning this topic. *Methods:* We retrospectively reviewed the data for 52 multiple myeloma patients. The patients were grouped using the baseline NLR as NLR $\leq$ 1.72 and NLR > 1.72 using receiver operating characteristic analysis to determine a cut off. We compared the two groups in terms of both the known prognostic factors of the myeloma and the overall survival (OS). *Results:* Our study showed that NLR is associated with C-reactive protein and β2 microglobulin ($P = 0.02$ and $P = 0.001$, respectively). The patients with NLR > 1.72 had significantly worse stages, performance status, and kidney functions. The whole group's OS was estimated as 35.1 months while the patients with lower NLR had better OS when compared with those with NLR > 1.72 (42.75 and 26.14 months, respectively, *P*: 0.04). *Conclusion:* Neutrophil/lymphocyte ratio, which is associated with stage, performance status, and kidney functions, can be used in daily practice as a predictor for survival in multiple myeloma. Simply adding NLR to the routine charts may enrich our data for larger studies. J. Clin. Lab. Anal. 0:1–8, 2016. © 2016 Wiley Periodicals, Inc.

**Key words:** multiple myeloma; neutrophil/lymphocyte ratio; prognosis; treatment outcome

## INTRODUCTION

Multiple myeloma (MM) is a malign disease of plasma cells and according to the International Myeloma Working Group (IMWG) criteria, symptomatic MM diagnosis is made in cases of bone marrow clonal plasma cells >10% or related organ impairment accompanied by clonal plasmacytoma (1). Traditionally, the prognosis in MM is described as the stage at the time of diagnosis, but clinical progress of myeloma patients and their survival apparently vary. The factors that influence the risk and prognosis in myeloma are classified into three groups: tumor biology, tumor burden, and patient-related factors (2). The varieties of markers which can be used for prognosis increase are associated with a better understanding of tumor biology.

In light of new data, it is accepted that inflammation is a significant component of the neoplastic process. Aside from the fact that many cancers arise from the sites of chronic infection or inflammation, it is believed that the tumor microenvironment, which is largely orchestrated by the inflammatory cells and signaling molecules of the immune system, is an indispensable participant in the process of the proliferation of the tumor cells, survival, invasion, and migration (3). An increasing number of studies point to a positive

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correlation between angiogenesis, carcinoma-associated fibroblasts, and inflammatory infiltrating cells and poor outcome (4), inflammatory markers, such as the sedimentation rate, the C-reactive protein (CRP; 5), and various scores derived from the proportions of inflammatory cells, are found to be related to the prognosis in various solid tumors in addition to the absolute number of inflammatory cells (6–8). The neutrophil/lymphocyte ratio (NLR) obtained by the absolute neutrophil count divided by the absolute lymphocyte count, which is one of these, is also associated with prognosis in hematological malignancies, such as Hodgkin lymphoma, and diffuse large B-cell lymphoma in new clinical studies (9, 10). To the best of our knowledge, the relationship of NLR to the prognosis in myeloma patients has been examined in only one study, which suggested that NLR can be used as a simple prognostic factor that is associated with both the overall survival (OS), and event-free survival (EFS; 11). Taking this as a basis, in our study, we aimed to find out the relationship of NLR to other proven prognostic factors in MM patients and its effect on OS in the patients followed at our center.

## MATERIALS AND METHODS

The data related to 80 MM patients diagnosed at the Department of Hematology, the Dıskapı Training and Research Hospital, between 2009 and 2014 were examined. We scanned the patients for comorbidities according to the Charlson Comorbidity index. We investigated for pulmonary, cardiac, renal, hepatic, rheumatic diseases, solid tumors, infections, cerebrovascular diseases, peptic ulcer, and diabetes mellitus. We excluded 12 patients with chronic obstructive pulmonary disease or dyspnea, six patients with coronary or congestive heart disease, one patient with diabetes mellitus, and nine patients presented with infectious events in order to eliminate the possibility of affecting the systemic inflammatory response. We did not exclude patients with impaired renal functions if it was associated with myeloma. We examined the recorded medications of the patients. None of the remaining patients was taking medications, such as steroids, anabolic hormones, or beta two agonists, which could affect the NLR. The study was performed with informed consent obtained from the patients in order to use their medical records in retrospective research. Fifty-two patients who fulfilled the International Myeloma Working Group criteria were included. The data collected retrospectively included age, gender, M protein type, International Staging System (ISS) and Durie-Salmon stages, Eastern Cooperative Oncology Group (ECOG) performance status, erythrocyte sedimentation rate (ESR), CRP, lactate dehydrogenase (LDH), total protein, albumin, creatinine, calcium, and β2 microglobulin levels at diagnosis. All the patients were diagnosed with MM for the first time, and samples were taken from an antecubital vein before treatment. A complete blood count (CBC) was determined by the electrical impedance method in an automatic blood counter device (Counter LH 780) from the EDTA containing the blood. The type of M protein was determined by both serum and urine immunofixation electrophoresis. Cytogenetic abnormalities were not routinely analyzed at the time of the diagnosis for most of the patients, so the data for the cytogenetic risk factors was not available.

The NLR was calculated as an absolute neutrophil count divided by an absolute lymphocyte count using the data obtained from the CBC. The NLR showed an AUC of 0.60 (95% CI, 0.413–0.770) with a cut-off value of 1.72 by ROC analysis. Using this cut-off value, the sensitivity and specificity were calculated as 76% and 52%, respectively. The patients were grouped as NLR $\leq$ 1.72 (*n*: 22) and NLR > 1.72 (*n*: 30).

Due to the lack of data related to the progression in most of the patients, the event-free survival could not be calculated. The overall survival (OS) was defined as the time from diagnosis to death as a result of any cause. The significant differences between the groups were determined by the Kruskal–Wallis and Mann–Whitney tests. A value of $P < 0.05$ was considered statistically significant. The overall survival was estimated using the Kaplan–Meier method and the log-rank test was used for the comparison of the outcomes. A Cox regression model was used to analyze the independent prognostic risk factors. A *P*-value <0.05 was considered statistically significant. The statistical analyses were performed using SPSS software version 15 (SPSS for Windows, Version 15.0, Chicago, IL).

## RESULTS

The patients were grouped as NLR $\leq$ 1.72 (*n*: 22) and NLR > 1.72 (*n*: 30) using the ROC analysis as described in the materials and method. The characteristic features of the patients are shown in Table 1. The patient group composed of 28 males (53.8%) and 24 (46.2%) females, and there was no significant difference between the NLR groups in terms of gender distribution. The ages of the patients were between 34 and 88, and the median age of the patients was 65.5. The low-NLR group's median age was 63.2, while the high-NLR group's was 66.2, but the difference was not statistically significant (*P*: 0.26). The M component was the IgG type in 48.1% of the patients, and light chain and IgA followed this. While similarly IgG was

the most common M component type in the low-NLR group, it was a low chain type in most of the patients in the high-NLR group (43.3%). This distribution was statistically significant ($P = 0.03$). The median β2-microglobulin was 6.11 and 12.34, respectively, in the low- and high-NLR groups ($P$: 0.001), while the albumin was not any different between the two groups ($P$: 0.57).

The ISS staging was distributed differently, and was most probably related to the β2 microglobulin difference between the groups. While 54% of the patients in the low-NLR group were ISS stage II, 73.3% of the patients in the high-NLR group were ISS stage III ($P = 0.001$, Table 1). While the high Durie–Salmon Stage was more commonly observed in the high-NLR group, this difference was not statistically significant ($P = 0.067$). When the ECOG performance status was grouped as good (0–2) and worse (3–4), it was noted that the higher NLR group mostly consisted of patients with a worse ECOG status ($P$:

**TABLE 1. Patients' Characteristics According to the Neutrophil/Lymphocyte Ratio (NLR) at Diagnosis**

| | All cases ($n = 52$) | NLR ≤ 1.72 ($n = 22$) | NLR > 1.72 ($n = 30$) | $P$ ([a]) |
|---|---|---|---|---|
| Age (median. range) | 65.5 (34–88) | 59 (49–77) | 67 (34–88) | 0.26 |
| Gender *n* (%) | | | | |
| Male | 28 (53.8%) | 9 (40.9%) | 19 (63.3%) | 0.16 |
| Female | 24 (46.2%) | 13 (59.1%) | 11 (36.7%) | |
| M component *n* (%) | | | | |
| Light chain | 16 (30.8%) | 3 (13.6%) | 13 (43.3%) | 0.03 |
| IgG | 25 (48.1%) | 15 (68.2%) | 10 (33.3%) | |
| IgA | 11 (21.2%) | 4 (18.2%) | 7 (23.3%) | |
| β2 Microglobulin (mg/l) | 6.6 (2.1–52) | 4.8 (2.2–23.7) | 8.9 (2.1–52.0) | 0.001 |
| ISS Stage *n* (%) | | | | |
| I | 7 (13.5%) | 5 (22.7%) | 2 (6.7%) | 0.001 |
| II | 18 (34.6%) | 12 (54.5%) | 6 (20%) | |
| III | 27(51.9%) | 5 (22.7%) | 22 (73.3%) | |
| Durie–Salmon Stage *n* (%) | | | | |
| I | 20 (38.5%) | 10 (45.5%) | 10 (33.3) | 0.067 |
| II | 16 (30.8%) | 9 (40.9%) | 7 (23.3%) | |
| III | 16 (30.8%) | 3 (13.6%) | 13 (43.3%) | |
| ECOG *n* (%) | | | | |
| 0–2 | 28 (53.8%) | 16 (72.7%) | 12 (40%) | 0.026 |
| 3–4 | 24 (46.2%) | 6 (27.3%) | 18 (60%) | |
| Treatment *n* (%) | | | | |
| VAD[b] | 31 (59.6%) | 14 (63.6%) | 17 (56.7%) | 0.86 |
| Bortezomib [c] | 18 (34.6%) | 7 (31.8%) | 11 (36.7%) | |
| Other[d] | 3 (5.8%) | 1 (4.5%) | 2 (6.7%) | |
| Treatment response *n* (%) | | | | |
| CR | 11 (21.15%) | 3 (13.6%) | 9 (30%) | 0.10 |
| VGPR | 15 (28.8%) | 8 (36.4%) | 7 (23.3%) | |
| PR | 10 (19.2%) | 7 (31.8%) | 3 (10%) | |
| SD | 8 (15.4%) | 3 (13.6%) | 5 (16.6%) | |
| Prog. D | 7 (13.5%) | 1 (4.5%) | 6 (20%) | |
| CRP (mg/l) | 10.0 (0.5–118.0) | 5.6 (1.0–39.2) | 12.6 (0.5–118.0) | 0.02 |
| ESR (mm/hr) | 93 (17–157) | 104 (17. –157.) | 91 (17–146) | 0.53 |
| Hb (g/dl) | 9.4 (6.5–14.5) | 9.5 (6.5–14.5) | 9.3 (7.2–14.0) | 0.90 |
| Albumin (g/l) | 3.8 (1.9–5.1) | 3.8 (1.9–5.1) | 3.7 (1.9–4.8) | 0.57 |
| Ca (mg/dl) | 9.8 (4.2–14.9) | 9.5 (4.2–13.2) | 10.1 (8.2–14.9) | 0.018 |
| LDH(U/l) | 210 (3.7–532) | 233.5 (137.0–525) | 205.5 (3.7–532.0) | 0.47 |
| Urea (mg/dl) | 42.0 (19.0–238.0) | 33.0 (19.0–139.0) | 47.0 (23.0–238.0) | 0.011 |
| Creatinine (mg/dl) | 1.1 (0.21–8.3) | 0.9 (0.5–5.1) | 2.3 (0.2–8.3) | 0.002 |
| eGFR (ml/min/1.73 $m^2$) | 61.6 (4.6–322.2) | 73.9 (9–107.6) | 37.7 (4.6–322.2) | 0.019 |

Ig, Immunoglobulin; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, Hemoglobin; Ca, Calcium; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate; CR, complete remission; VGPR, Very good partial response; PR, partial response; SD, stable disease; Prog. D, progressive disease.

[a]Statistical significance of comparisons between two NLR groups.

[b]VAD: Vincristine + Adriamycin + Dexamethasone.

[c]Bortezomib-based therapy: Bortezomib + dexamethasone/bortezomib + cyclophosphamide + dexamethasone.

[d]Other therapies: Dexamethasone only/melphalan + prednisolone/melphalan + thalidomide + prednisolone.

0.026). The baseline CRP was assessed as a marker for the systemic inflammatory response, and as expected, was found to be higher in the high NLR group ($P = 0.02$), but the ESR was not any different between the two groups. While there was no significant difference between the Hb and the LDH groups, which were considered to be the prognostic factor for the myeloma, it was noted that the levels of Ca, urea, and creatinine were significantly high, and the eGFR was significantly low in the NLR > 1.72 group ($P$ 0.018, 0.011, 0.002, and 0.019, respectively).

The treatment distribution reflects reimbursement policies which do not allow for bortezomib treatment for first line therapies in patients younger than 65 years of age in our country. Nearly 60% of all the patients had vincristine, adriamycin, and dexamethasone (VAD) therapy for first line, and 35% of the patients had bortezomib-based therapies, such as bortezomib and dexamethasone, bortezomib, cyclophosphamide, and dexamethasone. Only 5.8% of the patients had received other therapies, such as dexamethasone only, melphalan and prednisolone, or melphalan, thalidomide, and prednisolone. There was no statistically significant difference between the NLR groups in the treatment groups ($P$: 0.86). The only novel agent we could compare was bortezomib in this study. We regrouped the patients as "Patients treated with bortezomib" and "Patients treated with conventional agents" in order to evaluate the effect of the novel agents on the OS rates in the low- and high-NLR groups. Because only one patient had died in the bortezomib group, the estimated OS could not be reached, and the OS could not be compared between the low- and high-NLR groups. In the other treatment group, the OS was significantly better in the low-NLR group ($P = 0.02$). We think that larger studies, with a much longer follow up, are needed to interpret whether the novel agents could turn over the impact of the high NLR or not.

The NLR at the diagnosis was found to be a predictor of OS. The whole group's OS was estimated as 35.1 months, while the patients with a NLR ≤ 1.72 at diagnosis had better OS rates when compared to those with a NLR > 1.72 (42.75 and 26.14 months, respectively, $P$: 0.04, Fig. 1). The univariate analysis of the NLR, and some other clinical characteristics on OS are in Table 2. Neither age nor gender were associated with OS ($P = 0.66$ and $P = 0.09$). LDH, creatinine, albumin, and hemoglobin, did not have significant prognostic effect on the OS ($P > 0.05$). However, the urea seemed to be associated with OS ($P$: 0.03). The β2 microglobulin grouped as low (<3.5), intermediate (3.5–5.5), and high (>5.5) and like the ISS classification, had a statistically significant effect on OS. The low β2 microglobulin group had a median OS of 46.2 months, while the intermediate and high β2 microglobulin group had 40.7 and 25.3 months, respectively ($P$: 0.025). Another well-known prognostic factor was that the serum calcium levels were also associated with the OS with a mean of 44.1 and 26.9 months in the lower and higher Ca levels using the median Ca level as a cut-off point ($P$: 0.01). When the patients were evaluated for the ISS and Durie–Salmon stages, although a decreasing OS time was observed with both the higher ISS and the Durie–Salmon stages, the difference had no statistical significance ($P = 0.076$ and $P = 0.054$, respectively). This was possibly because of the limited number and unequal distribution of the patients with only seven (13.5%) in the ISS I group, 18 (34.6%) in the ISS II, and 27 (51.9%) in the ISS III groups. Likewise, it was difficult to examine the effect of the NLR on the OS in the different ISS groups. We did not find a significant difference between the OS in the low- and high-NLR groups in each of the ISS stages, although we could not give the exact estimated OS time for the ISS I group because of the low number of cases and for statistical reasons ($P = 0.62$ for ISS I, $P = 0.45$ for ISS II, and $P = 0.52$ for the ISS III groups, Table 1). When we put the univariate factors, such as the Durie–Salmon stage, β2 microglobulin, Ca, urea, and NLR, we could not obtain any statistically significant results (Table 3).

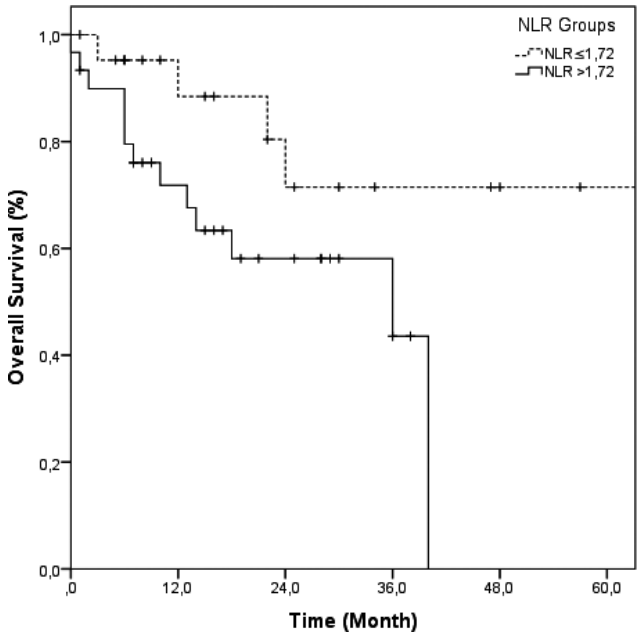


**Fig. 1.** Overall survival (OS) based on the neutrophil/lymphocyte ratio (NLR) at diagnosis. The patients with NLR > 1.72 had significantly shorter OS than the patients who had a NLR ≤ 1.72 ($P = 0.04$).

**TABLE 2. Univariate Analysis of Clinical Characteristics on Overall Survival**

| Characteristics | HR (95%CI) | *P* |
|---|---|---|
| Age | | |
| <65.5 | 1.00 | 0.66 |
| ≥65.5 | 0.81 (0.31–2.11) | |
| Gender | | |
| Male | 1.00 | 0.09 |
| Female | 0.41 (0.14–1.17) | |
| ECOG | | |
| 0–1 | 1.00 | 0.24 |
| 2–4 | 1.78 (0.68–4.69) | |
| ISS Stage | | |
| I | 1.00 | 0.10 |
| II (1) | 1.76 (0.20–15.83) | 0.62 |
| III (2) | 4.87 (0.61–37.93) | 0.13 |
| Durie–Salmon Stage | | |
| I | 1.00 | 0.77 |
| II (1) | 2.10 (0.55–7.78) | 0.28 |
| III (2) | 4.10 (1.19–14.0) | 0.03 |
| Treatment | | |
| VAD | 1.00 | 0.87 |
| Non-VAD regimens | 0.90 (0.25–3.17) | |
| CRP | | |
| <10.0 | 1.00 | 0.33 |
| ≥10.0 | 0.60 (0.21–1.70) | |
| ESR | | |
| <93 | 1.00 | 0.26 |
| ≥93 | 0.50 (0.15–1.68) | |
| β2 Microglobulin | | |
| <3.5 | 1.00 | 0.05 |
| 3.5–5.5 (1) | 1.49 (0.13–16.80) | 0.74 |
| >5.5 (2) | 6.48 (0.81–52.13) | 0.08 |
| Hg | | |
| ≤10 | 1.00 | 0.24 |
| >10 | 0.54 (0.20–1.49) | |
| Albumin | | |
| ≤3.5 | 1.00 | 0.12 |
| >3.5 | 0.46 (0.18–1.23) | |
| Ca | | |
| ≤9.8 | 1.00 | 0.01 |
| >9.8 | 3.57 (1.30–9.82) | |
| LDH | | |
| ≤210 | 1.00 | 0.70 |
| >210 | 1.22 (0.46–3.26) | |
| Urea | | |
| ≤42 | 1.00 | 0.03 |
| >42 | 3.13 (1.08–9.01) | |
| Creatinine | | |
| ≤1.1 | 1.00 | 0.14 |
| >1.1 | 2.11 (0.77–5.72) | |
| eGFR | | |
| ≤60 | 1.00 | 0.48 |
| >60 | 0.71 (2.27–1.86) | |
| NLR | | |
| ≤1.72 | 1.00 | <0.05 |
| >1.72 | 3.14 (1.01–9.94) | |

HR, Hazard ratio; VAD, Vincristine + Adriamycin + Dexamethasone; ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, Hemoglobin; Ca, Calcium; LDH, lactate dehydrogenase; eGFR, estimated glomerular filtration rate; NLR, neutrophil/lymphocyte ratio.

**TABLE 3. Multivariate Analysis of Clinical Characteristics on Overall Survival**

| Characteristics | HR (95%CI) | *P* |
|---|---|---|
| Durie–Salmon Stage | | |
| I | 1.00 | 0.17 |
| II (1) | 5.01 (0.94–27.50) | 0.06 |
| III (2) | 2.82 (0.62–12.84) | 0.18 |
| β2 Microglobulin | | |
| <3.5 | 1.00 | 0.05 |
| 3.5–5.5 (1) | 1.49 (0.13–16.80) | 0.4 |
| >5.5 (2) | 6.48 (0.81–52.13) | 0.79 |
| Ca | | |
| ≤9.8 | 1.00 | 0.15 |
| >9.8 | 2.52 (0.71–8.92) | |
| Urea | | |
| ≤42 | 1.00 | 0.50 |
| >42 | 1.68 (0.38–7.40) | |
| NLR | | |
| ≤1.72 | 1.00 | 0.88 |
| >1.72 | 0.89 (0.20–4.06) | |

HR, Hazard ratio; Ca, Calcium; NLR, neutrophil/lymphocyte ratio.

The median bone marrow plasma cell percentage (BMPCP) was 57.5% (10–90), and the patients were divided through the median BMPCP to define the two groups as the low- and high BMPCP. The median BMPCP was 47.5 (20–90) in the low-NLR group, and 60.0 (10–90) in the high-NLR group. However, the difference was not significant ($P = 0.78$). Although the OS was slightly better in the low-NLR subgroups, both in the low- and high- BMPCP groups, this difference did not have any statistical significance ($P = 0.19$ and $P = 0.2$).

We combined the NLR and CRP in order to investigate whether we could improve the predicting efficacy of the NLR or not. We decided to classify the three different groups as Group 1 with low NLR and CRP levels, Group 2 with one high level (either NLR or CRP), and Group 3 with both high NLR and CRP levels. We used 1.72 as the cut off for the NLR and median level for the CRP. The number of patients in these groups was 15, 18, and 19, respectively. Although the first group had the longest OS time (67, 35, and 24 months, respectively), the difference was not statistically significant ($P = 0.503$, Fig. 2A). We similarly combined NLR and β2 microglobulin in the three groups using the cut-off levels 1.72 for the NLR and median level (6.63 mg/L) for β2 microglobulin. The patients in Group 1 had both low NLR and β2 microglobulin ($n = 12$), Group 2 had a high NLR or β2 microglobulin ($n = 18$), and Group 3 had both a high NLR and β2 microglobulin ($n = 22$). The estimated mean OS was 72, 38, and 25 months, for Groups 1, 2, and 3, respectively, but the difference was not statistically significant ($P = 0.14$, Fig. 2B).

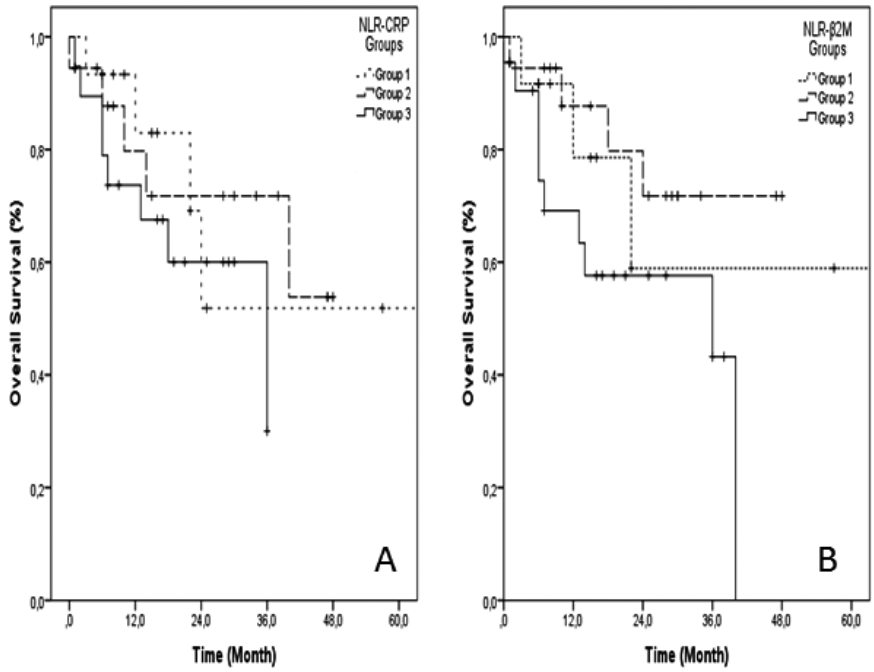


**Fig. 2.** (A) Overall survival (OS) based on the neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) at diagnosis ($P = 0.503$) (B) Overall survival (OS) based on the neutrophil/lymphocyte ratio (NLR) and β2 microglobulin at diagnosis.

The treatment response rates were evaluated according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for MM. The responses were grouped as complete remission (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD). All the response rates in the low- and high-NLR groups are shown in Table 1. The rates of the VGPR were greater in the low-NLR group (36% of all the responses were VGPR in the low-NLR group, while 23% of all the responses were VGPR in the high-NLR group). The same pattern was also seen in the PR rates (31% vs. 10%) while the stable and progressive diseases were more frequent in the high-NLR group. Despite these rates, when all the groups were evaluated, there was no statistically significant difference between the low- and high-NLR groups' responses ($P = 0.1$). Considering the small size of the sample, we combined the VGPR and PR responses, and the difference became more obvious, but was still not statistically significant ($P = 0.07$).

## DISCUSSION

The associations between chronic immune stimulation, autoimmune disorders, and the risk of multiple myeloma have been evaluated in several epidemiological studies, but no established causal link has been demonstrated (12). The sedimentation rate, inflammatory markers, such as CRP (5), and various markers and scores derived from the proportions of the inflammatory cells are found to be related to the prognosis in various solid tumors in addition to the absolute number of inflammatory cells. The neutrophil/lymphocyte ratio (NLR) obtained by the absolute neutrophil count divided by the absolute lymphocyte count has also been suggested as a prognostic marker related to the systemic inflammatory response in solid malignancies (6–8, 13–15). A meta-analysis covering 100 studies reported that a high NLR is associated with an adverse OS in many solid tumors (16).

Despite the huge number of studies conducted on solid tumors, NLR has recently begun to be investigated in hematological malignancies, and there has been very little research done, mostly on lymphomas. In their study where Porrata et al. examined 255 diffuse large B-cell lymphoma (DLBCL) patients, they reported that the patients had better OS and EFS for which NLR < 3.5 at diagnosis (17). Recently, Troppan et al. (10) used the derived NLR (dNLR) which was calculated by neutrophil to (leukocyte – neutrophil) the ratio in a cohort of 290 patients, and reported that dNLR was a prognostic factor of both OS and disease-free survival (DFS) in DLBCL. Another study on classic Hodgkin lymphoma (cHL) reported that a high NLR (≥4.3) was correlated with a poor OS ($P < 0.001$; 9).

Myeloma is a heterogeneous disease with a complex pathogenesis including interactions between myeloma cells and a bone marrow microenvironment, in which NLR might express a particular and more important meaning. The patients who have a greater immunocompetence and a distinct immunological profile, which consists of T-cell clonal expansions, a higher T helper 17, and lower T-regulatory cells seem to survive longer. (18). However, a subpopulation of neutrophils and immature myeloid cells are defined as myeloid-derived suppressor cells (MDSC) and can suppress the T-cell function in MM having an adverse effect on survival (19). The peripheral absolute neutrophil count may represent the MDSCs, and the absolute lymphocyte count may be associated with the T-cell activity, making NLR a potential marker to measure both (20). However, this issue is not widely understood, and has been investigated with only two retrospective clinical studies (11, 20).

Although cytogenetic and FISH analyses have taken part in risk stratifications of international guidelines, and are the undeniable requirements of proper myeloma treatment, they are extremely costly. Because advanced examinations are not accessible for most of the centers, determining the prognosis using simple measurements has attracted attention in recent years (21). Blood cell counts and scores, such as NLR, which are also simple and available for every patient, can probably never take the place of cytogenetic analyses, but may give additional information and be an easy way of predicting the prognosis based on the interactions between the MDSCs and lymphocytes. To our knowledge, only two studies investigated NLR as a prognostic factor on MM (11, 20).

In our study, we aimed to find out the relationship of NLR to other proven prognostic factors in MM patients, and its effect on OS in the patients followed at our newly opened center. We scanned a total of 80 newly diagnosed MM patients, and excluded patients with diseases or medications that could affect the NLR. Among the remaining 52 patients, we found that NLR is associated with well-known prognostic factors such as CRP and β2 microglobulin ($P = 0.02$ and $P = 0.001$, respectively). In order to investigate whether we could improve the power of NLR in predicting the prognosis, we tried to combine these parameters. We combined NLR and CRP. Although the patients who had both low NLR and CRP had the longest OS time (67 months), and the patients who had both high NLR and CRP had the shortest OS (24 months), there was not any difference in statistical significance ($P = 0.503$). the results were similar in the NLR and β2 microglobulin combination, with the estimated mean the OS of 72 months in both the low group, and 25 months in both the high group ($P = 0.14$). The reason for the lack of statistical significance may be due to the small size of the sample causing difficulties in estimating the median OS in the six subgroups.

Another interesting result was, as in the study by Kelkitli et al. (11), the patients with NLR > 1.72 had the worse ISS stages and kidney functions. We also find that higher NLR is associated with a worse ECOG performance status. These are defined as tumor load and patient-related prognostic factors according to the Mayo Clinic risk stratification (2), and are routinely used to predict survival in clinical practice. NLR is not directly affected in any of these three clinical parameters, but might be directing us to a higher risk population. Although a decreasing OS was observed in both the higher ISS and Durie–Salmon stages in our study, the difference did not reach any statistical significance. This is possibly because of the limited number and unequal distribution of the patients. Interestingly, Romano et al. (20) also mentioned that ISS staging could not provide a clear distinction for the outcomes in their series. In order to improve stratification, they proposed an addition of NLR to the ISS staging, but their results demonstrated that this combination particularly works for stage I and younger patients. Our small sample size, with only seven patients in ISS stage I, did not allow us to combine NLR and ISS. Because we had an older and advanced staged population, it was unlikely to improve our results according to Romano's suggestions.

The NLR at the diagnosis was found to be a predictor for OS, and consistent with the other two studies focusing on NLR and myeloma (11, 20). The whole group's OS was estimated as 35.1 months, while the patients with a NLR ≤ 1.72 at diagnosis had better OS rates when compared to those with a NLR > 1.72 ($P$: 0.04). Despite more frequent good responses, such as VGPR and PR, in the low-NLR group, this was not statistically significant. Romano et al. described better response rates in the lower NLR groups in their study, which particularly investigates the responses in the patients treated with novel agents, but they could not reach a statistical significance either. Despite these features making our population completely different from Romano's series, we concluded that NLR predicts OS, but does not significantly affect the overall response rates, like in Romano's study. The other study from our country reported by Kelkitli et al. probably represents relatively similar (but younger) patients, and so the treatment trends are, with the exception of more frequent ASCTs, quite similar. However, the authors did not mention the response rates. As in the other two trials, we did not find a relationship between the bone marrow plasma cell percentage and the NLR.

The limitations of this study were EFS could not be investigated because of the missing data for the progression time and the relatively small number in the patient group did not allow for proper multivariate analysis. Genetic markers, flow cytometric features, and free light chain levels were not available for most of the patients. Another common problem shared by all the NLR studies concerns the cut-off point. NLR do not have a validated cut off, and researchers have to calculate their own using statistical methods, which could cause different cut-off points. Larger studies are needed in order to determine a single and validated NLR cut off.

We concluded that NLR, which is related to ISS, ECOG, and kidney functions, is also associated with overall survival, and it might be a simple and costless additional prognostic factor, especially for the centers where flow cytometry, cytogenetic analysis, and free light chain ratio cannot be done. Despite the need for further larger prospective studies on this subject, simply adding NLR to the routine charts might be helpful in directing attention to the patients' inflammatory response status associated risk, and thus may enrich our data for larger studies.

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