

Comparison of the prognostic value of the neutrophil to lymphocyte ratio with other prognostic indices in the prognosis of patients diagnosed with multiple myeloma

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Abstract. The high neutrophil to lymphocyte ratio (NLR) is a poor prognostic factor for patients with multiple myeloma (MM); however, it has yet to be widely recognized in clinical practice. The present study was conducted to determine the value of NLR in the prognosis of patients with MM, compared with other prognostic indices. In total, 109 patients with newly diagnosed MM who were undergoing chemotherapy were recruited in the present retrospective cohort study. The prognostic factors subjected to analysis for survival time were determined at the time of pre-treatment. The results of the univariate and multivariate analyses revealed that only a high bone marrow plasma cell percentage ($\geq 40\%$), a low platelet count ($< 150 \times 10^9/l$), a high NLR (≥ 2.1) and a high calcium level (≥ 2.75 mmol/l) were poor prognostic factors for both overall survival (OS) and progression-free survival (PFS). In the OS analysis, the hazard ratios (HRs) of a high bone marrow plasma cell percentage ($\geq 40\%$), low platelet count ($< 150 \times 10^9/l$), high NLR (≥ 2.1) and high calcium level (≥ 2.75 mmol/l) were 1.900, 1.839, 2.605 and 2.665, with $P=0.039$, 0.049, 0.003 and 0.003, respectively. The absolute value of standardized coefficient β values for OS were 0.065, 0.039, 0.141 and 0.212, respectively. In the PFS analysis, the HRs of high bone marrow plasma cell percentage ($\geq 40\%$), low platelet count ($< 150 \times 10^9/l$), high NLR (≥ 2.1) and high calcium level (≥ 2.75 mmol/l) were 1.721, 1.876, 2.326 and 2.354, with $P=0.044$, 0.026, 0.002 and 0.004, respectively. Moreover, values for the absolute value of standardized coefficient β (for PFS) were 0.149, 0.099, 0.186 and 0.207. Collectively, the results of the present study revealed that a high

NLR (≥ 2.1) may exhibit a higher potential for determining a poor prognosis than a high bone marrow plasma cell percentage ($\geq 40\%$) and a low platelet count ($< 150 \times 10^9/l$); however, it may be less useful than high calcium levels (≥ 2.75 mmol/l).

Introduction

Multiple myeloma (MM) is a malignant hematological disease characterized by the proliferation of monoclonal plasma cells in bone marrow with the accumulation of genetic changes, and the interaction between abnormal plasma cells and bone marrow microenvironment (1-3). The interaction with the bone marrow environment and the accumulation of genetic alterations allows these cells to evade immune surveillance, leading to long-term persistence of malignant cells in the bone marrow microenvironment and resistance to conventional chemotherapeutics. Although numerous patients may achieve long-term remission with the introduction of new regimens, relapsed/refractory MM remains challenging, and is therefore considered an incurable disease (4-6). However, due to recent improvements in treatment strategies and the application of new drugs, the overall survival (OS) of patients has significantly increased, leading to requirements for novel prognostic factors and the measurement of progression-free survival (PFS) rather than OS when evaluating the survival rates of patients (7-9).

To date, the International Staging System (ISS) and the Revised International Staging System (R-ISS) have been considered the two most critical and widely used systems in the prognosis of MM. However, ISS was developed from the results of treatment prior to the use of the current regimen, and it was not as strongly associated with PFS as it was with OS (10-12). Despite its suitability for current treatment strategies, R-ISS requires fluorescence *in situ* hybridization (FISH) techniques that are time consuming and costly (13,14). Moreover, the second revision (R2-ISS) that includes gain/amplification of 1q21 is also time consuming and costly (15). Thus, numerous studies have focused on determining novel prognostic factors that are suitable for updated treatment strategies, ensuring both convenience and cost. Notably, the high neutrophil to

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lymphocyte ratio (NLR) has been proposed as a poor prognostic factor. Over the past 10 years, numerous previous studies have evaluated NLR; however, an accurate cut-off value is yet to be established, while numerous other prognostic factors have exhibited its use in clinical practice, with well-established cut-off values; for example, hemoglobin (<100 g/l) and platelet count (<150x10⁹/l) (16-27). Thus, the prognostic value of NLR has yet to be widely used in clinical practice. Moreover, recent studies with large datasets did not include NLR in the prognosis of MM (28-31), and two studies even demonstrated that NLR did not play a key role in predicting the short-term survival of patients diagnosed with MM (32,33). It appears that the prognostic role of NLR in multiple myeloma warrants further investigation. Thus, the present study aimed to determine the value of NLR in the prognosis of patients with diagnosed MM, compared with other prognostic indices.

Patients and methods

Patients. The present study was a retrospective cohort study conducted at the Hematology and Blood Transfusion Center, Bach Mai Hospital, Hanoi, Vietnam. In total, 109 patients newly diagnosed with MM who underwent chemotherapy from January, 2019 to June, 2023 were recruited in the present study. Patients received specific treatment regimens, such as bortezomib, cyclophosphamide and dexamethasone (VCD), bortezomib, thalidomide and dexamethasone (VTD) and bortezomib, lenalidomide and dexamethasone (VRD), and the response to chemotherapy was evaluated after four to eight cycles. Moreover, patient follow-up was carried out for a further 4 years to assess OS and PFS. In the present study, patients who received autologous stem cell transplantation were excluded. The study protocol was approved by the Institutional Review Board of Bach Mai Hospital (approval no. 7219/QĐ-BM, dated December 31, 2024). Patients, or their guardians and family members were informed and consented to participate in the study. They were called to request consent.

Data collection. Pre-treatment laboratory indices included peripheral blood cell indices, such as hemoglobin level, white blood cell (WBC) count, platelet count and NLR, bone marrow cell indices, such as bone marrow count (BMC) and bone marrow plasma cell percentage, and biochemical blood indices, such as albumin, creatinine, calcium, lactate dehydrogenase (LDH) and β 2 microglobulin (β 2M) levels. Prior to treatment, the performance status (PS) of the patients was recorded using the Eastern Cooperative Oncology Group (ECOG) criteria (34), and stage was recorded according to the ISS criteria (10). The data were collected from the medical records of the patients, which are stored at the hospital. Data collection began after the study received ethics approval (after December 31, 2024).

Definitions. Patients were diagnosed with MM according to the criteria of the International Myeloma Working Group (IMWG) 2014 (14). Patients were evaluated on response to chemotherapy, according to IMWG 2016 (35). OS was calculated from the time of diagnosis to death or the last follow-up. PFS was calculated from the beginning of treatment to relapse, death or the last follow-up.

Statistical analysis. Differences in pre-treatment laboratory indices, including hemoglobin level, WBC count, platelet count, NLR, BMC, bone marrow plasma cell percentage, albumin, creatinine, calcium, LDH and β 2M levels among ISS groups (ISS I, II and III) were analyzed using one-way ANOVA or the Kruskal-Wallis test, depending on whether variables followed a normal or non-normal distribution. Bonferroni post-hoc tests were applied for parametric data, whereas Dunn's post-hoc tests were used for non-parametric data. The Kolmogorov-Smirnov test was used to assess data normality.

Univariate and multivariate analyses were performed to identify prognostic factors for OS and PFS. Prognostic variables included established clinical factors; namely, ISS stage, ECOG PS score \geq 2, low hemoglobin level (<100 g/l), low platelet count (<150x10⁹/l), high bone marrow plasma cell percentage (\geq 40%), elevated creatinine level (\geq 177 μ mol/l), elevated calcium level (\geq 2.75 mmol/l), increased LDH level (upper normal limit >240 U/l according to institutional criteria) and high β 2M level (\geq 5.5 mg/l). To determine the optimal cut-off value for NLR, receiver operating characteristic curve analysis was performed to identify the value associated with a significant difference in OS beyond 4 years. The area under the curve was 0.63 (P=0.021). Based on the highest Youden index [$J = \max (Se + Sp - 1)$], the optimal NLR cut-off value was determined to be 2.1, with a sensitivity of 71.1% and a specificity of 62.5% (Fig. 1).

The authors used a single NLR threshold to evaluate both OS and PFS. This was also for consistency across survival endpoints and ease of use, therefore this NLR cut-off value (\geq 2.1) was applied in both univariate and multivariate analyses for OS and PFS. Kaplan-Meier survival curves and log-rank tests were used to identify factors associated with OS and PFS. Variables that were statistically significant in univariate analysis were subsequently included in multivariate analysis using the Cox proportional hazards model. The aim was to find an index that is meaningful for both OS and PFS. Therefore, multivariate analysis were only performed on those metrics that were significant for both OS and PFS. The relative effects of prognostic factors on OS and PFS were compared based on hazard ratio (HR) and the absolute values of standardized regression coefficients (β). Statistical analyses were performed using SPSS (version, 25; IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient data. A total of 109 patients newly diagnosed with MM were enrolled in the present study, including 54 males and 55 females. The median age of the patients was 61 years (range, 35-84 years), and the median follow-up duration was 26 months (range, 5-55 months). Patient distributions according to ECOG PS, type, ISS stage, treatment regimen and response to chemotherapy are summarized in Table I. Patients with ISS stage III accounted for the largest proportion of the cohort (67%). The proportion of patients achieving a treatment response of very good partial response or better was 44.9%. The estimated median OS was 37.3 months, with a 4-year OS rate of 36%. The number of events for OS was 45. The number of events for PFS was 60. The estimated median PFS was 30.6 months, with a 4-year PFS rate of 25.7% (Table I). The differences in laboratory indices among the ISS groups

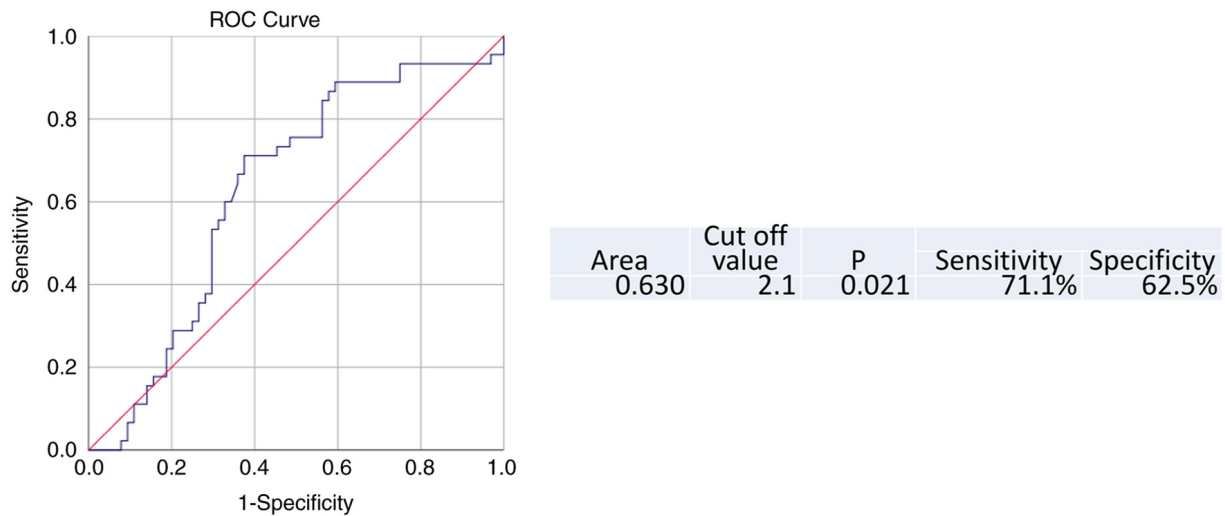


Figure 1. Receiver operating characteristic curve analysis demonstrating the ability of NLR (neutrophil to lymphocyte ratio) to discriminate between survival and mortality.

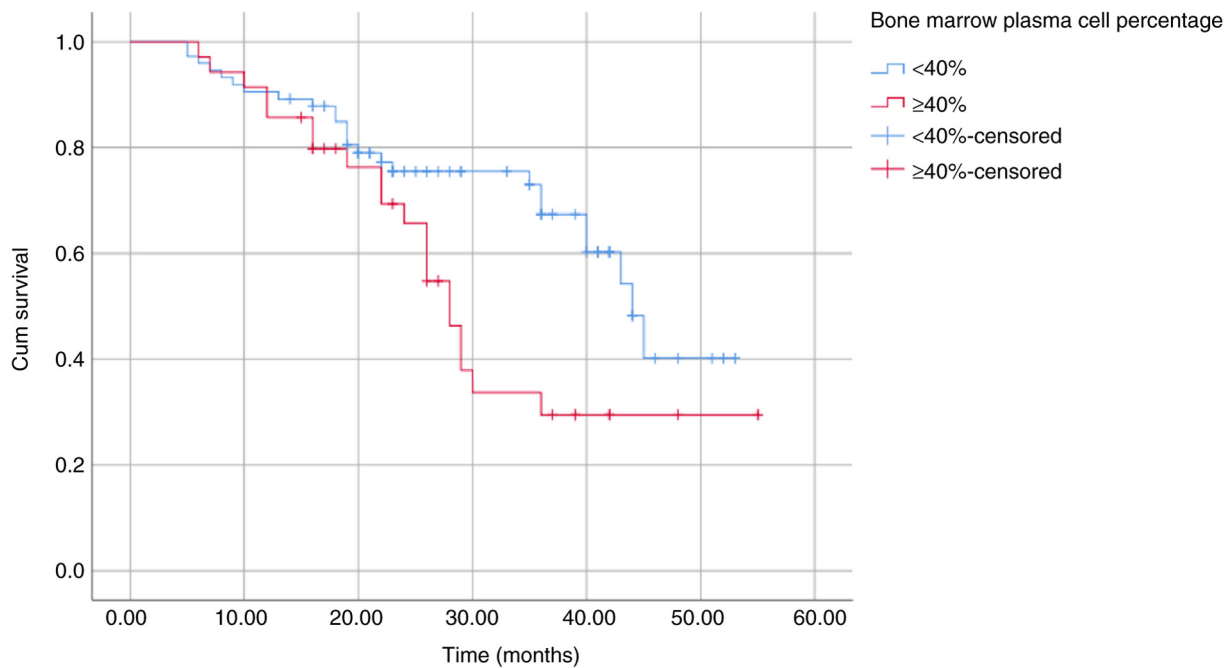


Figure 2. Patient overall survival according to the bone marrow plasma cell percentage ($\geq 40\%$ vs. $< 40\%$).

are shown in Table II. Statistically significant differences were observed in hemoglobin, albumin, creatinine, calcium, $\beta 2M$ levels and bone marrow plasma cell percentage.

Prognostic factors. The results of the univariate analysis demonstrated that a low hemoglobin level (< 100 g/l), low albumin level (< 35 g/l) and high creatinine level (≥ 177 $\mu\text{mol/l}$) were not associated with survival outcomes in the present study cohort. This analysis indicated that a high $\beta 2M$ level (≥ 5.5 mg/l), PS score ≥ 2 , elevated LDH level and high ISS stage were associated with a poor OS; however, these were not significantly associated with PFS. Among all variables examined, only a high bone marrow plasma cell percentage ($\geq 40\%$), low platelet count ($< 150 \times 10^9/l$), high NLR (≥ 2.1) and

a high calcium level (≥ 2.75 mmol/l) were factors for a poor prognosis and significantly associated with both OS and PFS (Table III). These differences were further illustrated using Kaplan-Meier survival curves (Figs. 2-9).

Multivariate analysis demonstrated that a high bone marrow plasma cell percentage ($\geq 40\%$), low platelet count ($< 150 \times 10^9/l$), high NLR (≥ 2.1) and a high calcium level (≥ 2.75 mmol/l) were independent adverse prognostic factors for both OS and PFS in patients with MM (Table IV). In the present study, ISS stage, $\beta 2M \geq 5.5$ mg/l, elevated LDH level and ECOG PS ≥ 2 were only significant for OS, not for PFS; therefore, they were not used in the multivariate analysis.

In the OS analysis, the HRs for high bone marrow plasma cell percentage ($\geq 40\%$), low platelet count ($< 150 \times 10^9/l$), high

Table I. Characteristics of the patients in the present study.

| Characteristics | No. of patients (n=109) | Percentage | |
|----------------------------|-------------------------|----------------------|-------------------|
| Sex | | | |
| Male | 54 | 49.5 | |
| Female | 55 | 50.5 | |
| ECOG PS | | | |
| <2 | 27 | 24.8 | |
| ≥2 | 82 | 75.2 | |
| Type | | | |
| IgG | 58 | 53.2 | |
| IgA | 21 | 19.1 | |
| Lambda light chain | 17 | 15.6 | |
| Kappa light chain | 13 | 11.9 | |
| ISS | | | |
| ISS I | 8 | 7.3 | |
| ISS II | 28 | 25.7 | |
| ISS III | 73 | 67.0 | |
| Treatment regimen | | | |
| VTD | 50 | 45.9 | |
| VRD | 23 | 21.1 | |
| VCD | 35 | 33.0 | |
| Response to chemotherapy | | | |
| ≥VGPR (after four cycles) | 49 | 44.9 | |
| ≥VGPR (after eight cycles) | 49 | 44.9 | |
| Survival rate | | | |
| | Estimate (months) | Rate for 4 years (%) | No. of events (n) |
| OS | 37.3 | 36.0 | 45 |
| PFS | 30.6 | 25.7 | 60 |

The age of the patients was as follows Median, 61 years; min, 35 years; max, 84 years ECOG, Eastern Cooperative Oncology Group; PS, performance status; ISS, International Staging System; VTD, bortezomib, thalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone; VCD, bortezomib, cyclophosphamide and dexamethasone; VGPR, very good partial response; OS, overall survival; PFS, progression-free survival.

Table II. Laboratory indices of the patients according to ISS.

| Indices | ISS I (n=8) | ISS II (n=28) | ISS III (n=73) | Total (n=109) | P-value ^a |
|---|--------------|---------------|----------------|---------------|----------------------|
| Hemoglobin (g/l), mean ± SD | 114.75±21.10 | 95.11±18.15 | 81.57±20.35 | 87.48±22.10 | <0.001 |
| WBC (x10 ⁹ /l), median | 6.80 | 6.10 | 7.10 | 6.83 | >0.05 |
| Platelet count (x10 ⁹ /l), median | 262.50 | 199.50 | 191.00 | 199.50 | >0.05 |
| NLR, median | 1.37 | 1.99 | 2.06 | 1.98 | >0.05 |
| Creatinine (μmol/l), median | 81.00 | 77.50 | 133.50 | 99.00 | <0.001 |
| Albumin (g/l), median | 36.30 | 29.45 | 32.35 | 33.50 | 0.023 |
| LDH (U/l), median | 175.00 | 167.00 | 171.00 | 167.00 | >0.05 |
| β2M (mg/l), median | 2.21 | 4.02 | 9.15 | 6.86 | <0.001 |
| Calcium (mmol/l), median | 2.07 | 2.13 | 2.31 | 2.24 | 0.045 |
| Bone marrow count (x10 ⁹ /l), median | 32.94 | 33.94 | 43.07 | 40.15 | >0.05 |
| Bone marrow plasma cell percentage, median | 19.00 | 12.00 | 32.00 | 24.50 | 0.003 |

^aP-values indicate differences among the ISS I, II and III groups. ISS, International Staging System; WBC, white blood count; NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; β2M, β 2 microglobulin.

Table III. Prognostic factors used in univariate survival analysis.

| Factor | OS | | PFS | |
|--------------------------------------|--------|-------------------------|--------|-------------------------|
| | Months | P-value (log-rank test) | Months | P-value (log-rank test) |
| Bone marrow plasma cell percentage | | | | |
| <40% | 39.41 | 0.016 | 33.38 | 0.011 |
| ≥40% | 32.01 | | 23.43 | |
| Platelet count (x10 ⁹ /l) | | | | |
| ≥150 | 39.81 | 0.035 | 32.84 | 0.028 |
| <150 | 30.47 | | 23.86 | |
| NLR | | | | |
| <2.1 | 43.30 | 0.003 | 35.14 | 0.003 |
| ≥2.1 | 31.21 | | 25.83 | |
| Calcium level (mmol/l) | | | | |
| <2.75 | 40.41 | <0.001 | 33.26 | <0.001 |
| ≥2.75 | 23.54 | | 19.35 | |
| β2M level (mg/l) | | | | |
| <5.5 | 43.73 | 0.005 | 34.55 | >0.05 |
| ≥5.5 | 33.85 | | 28.54 | |
| LDH level (U/l) | | | | |
| Normal | 40.19 | 0.021 | 31.42 | >0.05 |
| Elevated | 30.51 | | 26.10 | |
| ECOG PS | | | | |
| ≤2 | 45.62 | 0.006 | 35.13 | >0.05 |
| >2 | 32.89 | | 28.45 | |
| ISS | | | | |
| ISS I | 49.75 | 0.014 | 34.19 | >0.05 |
| ISS II | 41.18 | | 34.33 | |
| ISS III | 33.85 | | 28.54 | |
| Hemoglobin level (g/l) | | | | |
| ≥100 | 39.63 | >0.05 | 29.21 | >0.05 |
| <100 | 36.31 | | 30.14 | |
| Creatinine level (μmol/l) | | | | |
| <177 | 37.92 | >0.05 | 30.99 | >0.05 |
| ≥177 | 36.12 | | 28.83 | |
| Albumin level (g/l) | | | | |
| ≥35 | 38.85 | >0.05 | 31.31 | >0.05 |
| <35 | 35.50 | | 30.01 | |

OS, overall survival; PFS, progression-free survival; NLR, neutrophil to lymphocyte ratio; β2M, β 2 microglobulin; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ISS, International Staging System.

NLR (≥2.1) and a high calcium level (≥2.75 mmol/l) were 1.900, 1.839, 2.605 and 2.665, respectively, with corresponding P-values of 0.039, 0.049, 0.003 and 0.003. The absolute value of standardized coefficient (β) values for OS were 0.065, 0.039, 0.141 and 0.212, respectively. These findings indicated that the prognostic impact of a high NLR (≥2.1) on OS was greater than that of high bone marrow plasma cell percentage (≥40%) and low platelet count (<150x10⁹/l), but lower than that of high calcium levels (≥2.75 mmol/l; Table IV).

In addition, the HRs for a high bone marrow plasma cell percentage (≥40%), low platelet count (<150x10⁹/l),

high NLR (≥2.1) and a high calcium level (≥2.75 mmol/l) in the PFS analysis were 1.721, 1.876, 2.326 and 2.354, respectively, with corresponding P-values of 0.044, 0.026, 0.002 and 0.004. The absolute values of standardized coefficient β (for PFS) were 0.149, 0.099, 0.186 and 0.207, respectively. These results further demonstrated that the prognostic value of a high NLR (≥2.1) on PFS exceeded that of high bone marrow plasma cell percentage (≥40%) and a low platelet count (<150x10⁹/l); however, the values were lower than those of high calcium levels (≥2.75 mmol/l; Table IV).

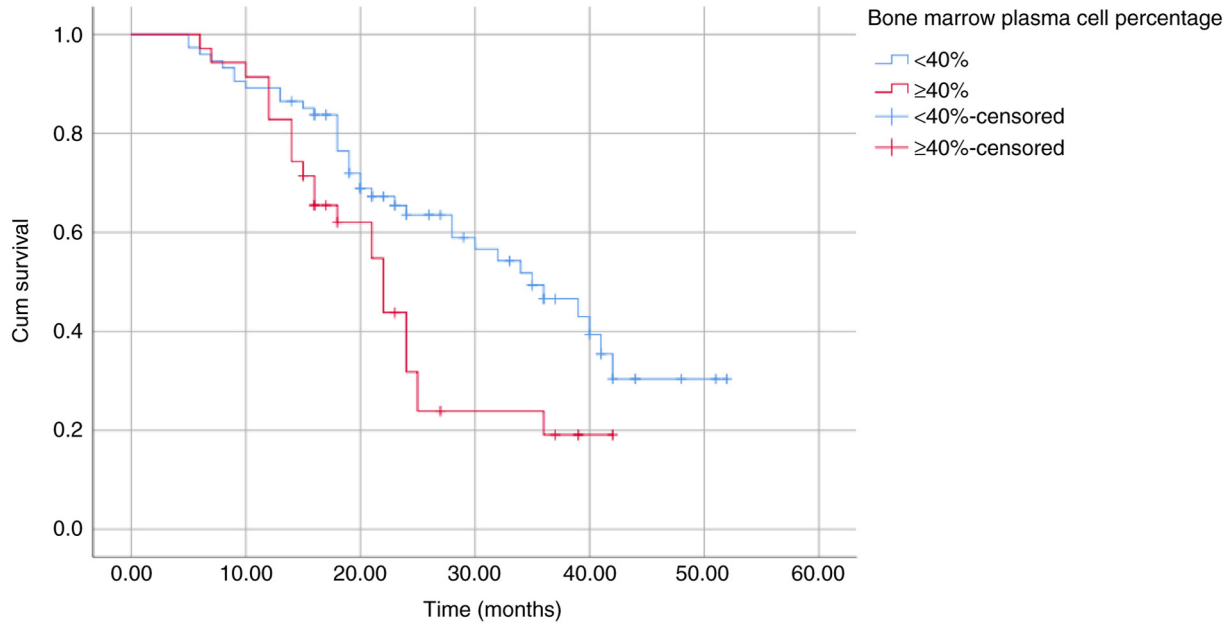


Figure 3. Patient progression-free survival according to bone marrow plasma cell percentage ($\geq 40\%$ vs. $< 40\%$).

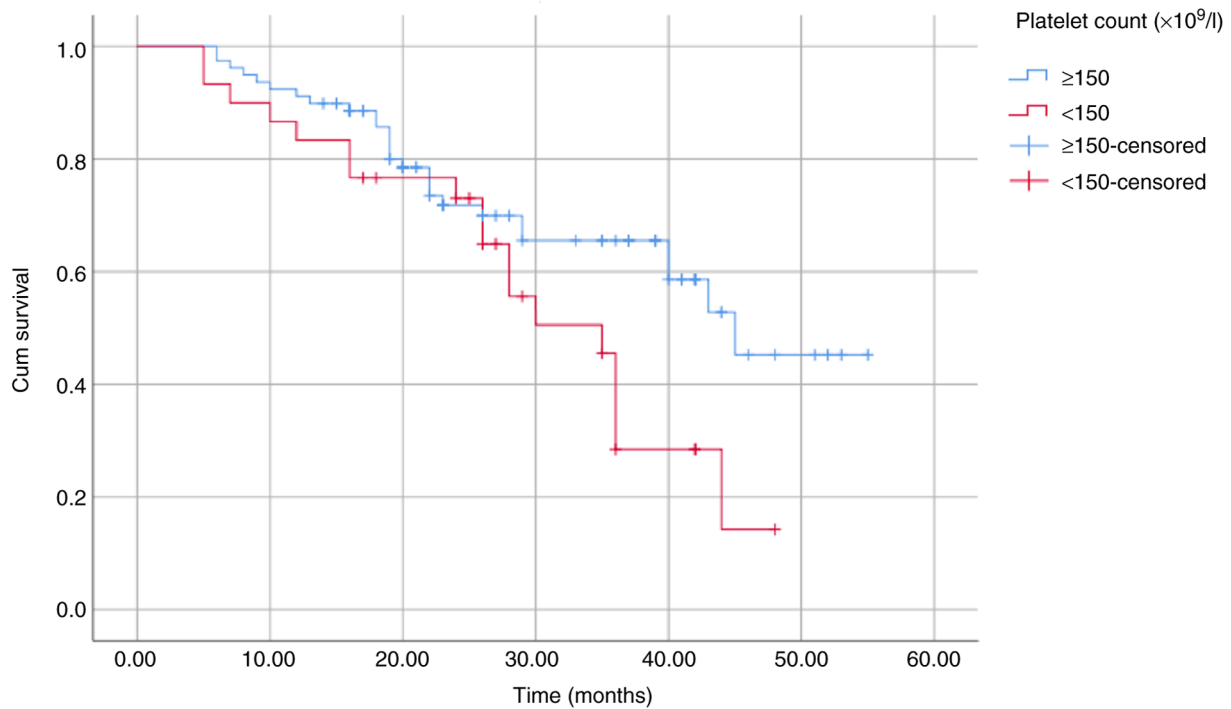


Figure 4. Patient overall survival according to platelet count ($< 150 \times 10^9/l$ vs. $\geq 150 \times 10^9/l$).

Discussion

Kelkitli *et al* (16) initially documented an association between NLR and survival rates in patients with MM. Since then, several studies have supported this finding (17-27), although a small number have reported contradictory results (32,33). These studies were based on the hypothesis that an imbalance in immune responses within the bone marrow microenvironment in MM supports plasma cell proliferation. T-cells play a crucial role in immune surveillance; therefore, increased

T-cell infiltration within the bone marrow microenvironment at tumor sites is considered a favorable prognostic indicator. By contrast, interactions between malignant plasma cells and the bone marrow microenvironment enable immune evasion. Plasma cells secrete chemokines, such as IL-6, which stimulate neutrophil mobilization and recruitment. Neutrophils can suppress T-cell function, thereby exerting an adverse effect on survival. Consequently, an elevated NLR provides indirect evidence of impaired T-cell recruitment to tumor sites and suppression of antitumor immune activity, creating a

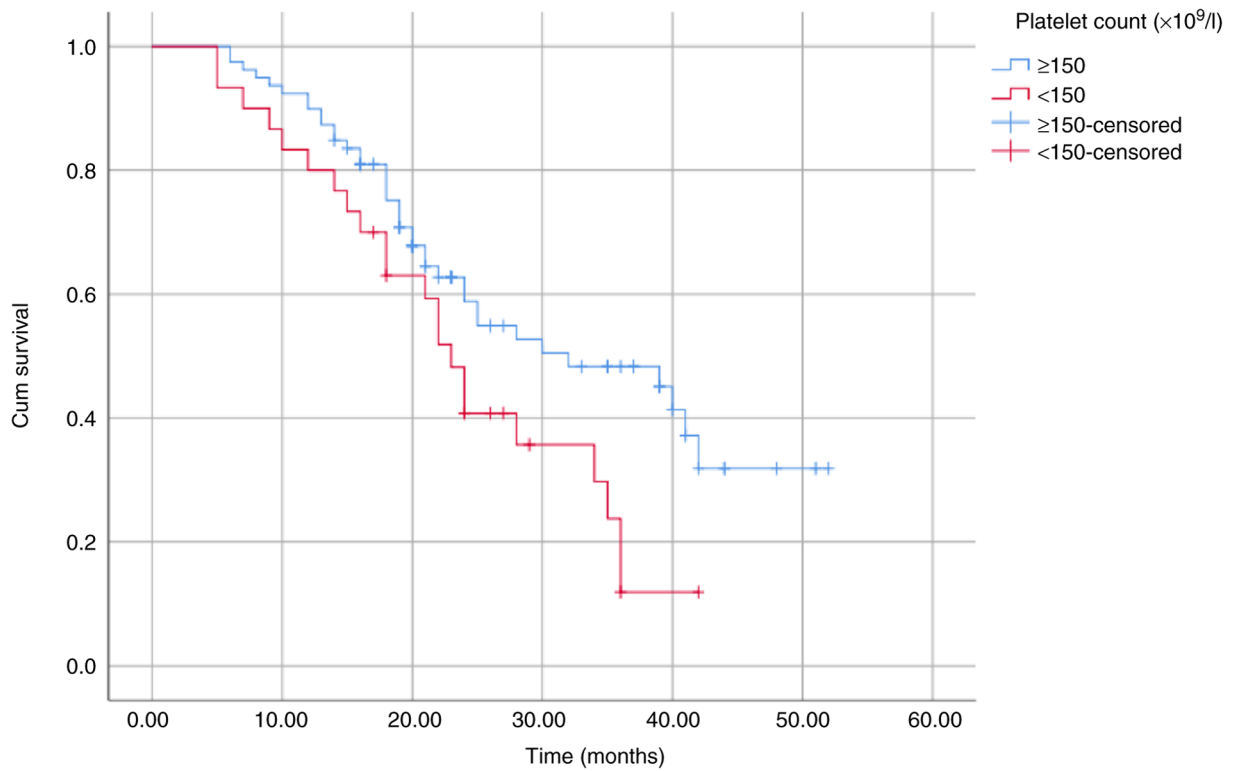


Figure 5. Patient progression-free survival according to platelet count (<150x10⁹/l vs. ≥150x10⁹/l).

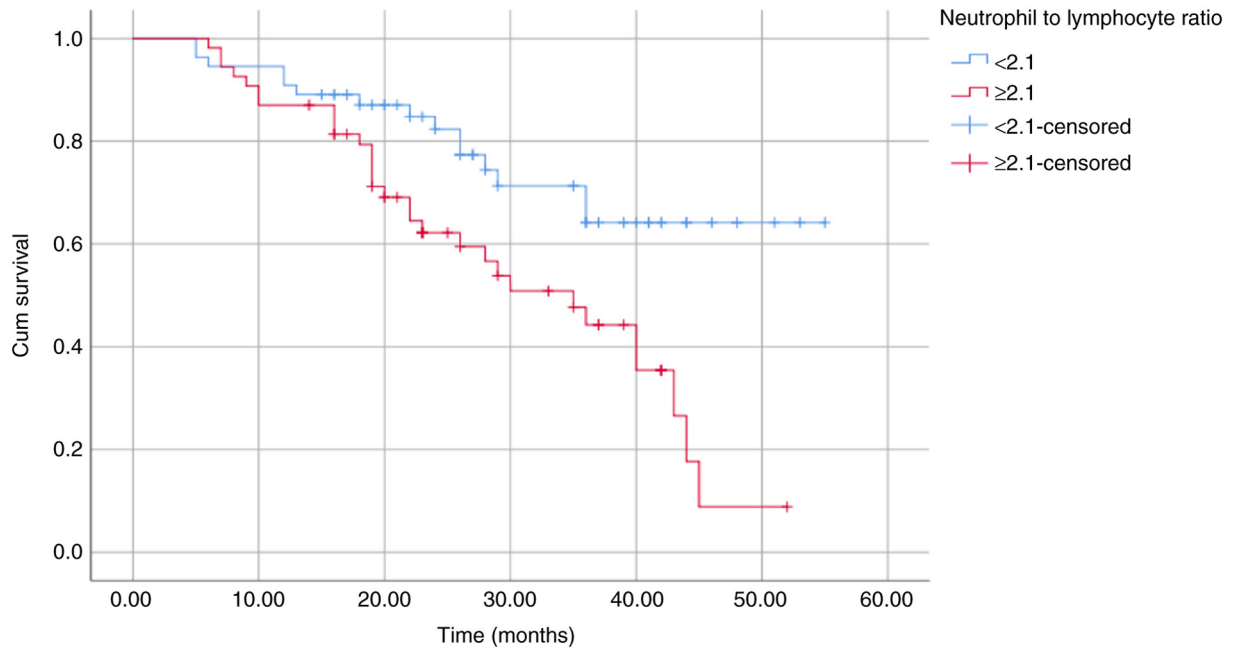


Figure 6. Patient overall survival according to neutrophil to lymphocyte ratio (≥2.1 vs. <2.1).

microenvironment conducive to plasma cell proliferation and dissemination (17,18,36,37).

Although Zhou *et al* (32) and Avagyan *et al* (33) reported no association between a high NLR and survival rates in MM, numerous other studies have suggested that NLR may serve as a prognostic biomarker (16-27). Notably, the two studies (32,33) reporting negative findings were conducted with relatively small sample sizes of 76 and 54 patients,

respectively, which may have limited their statistical power. Collectively, these studies reinforce the hypothesis that immune dysregulation in MM markedly affects patient survival.

In the present study, a high NLR was defined using a cut-off value of 2.1, whereas previously reported cut-off values ranged from 1.72 to 4 (16-27). To facilitate clinical application, the standardization of the NLR cut-off value

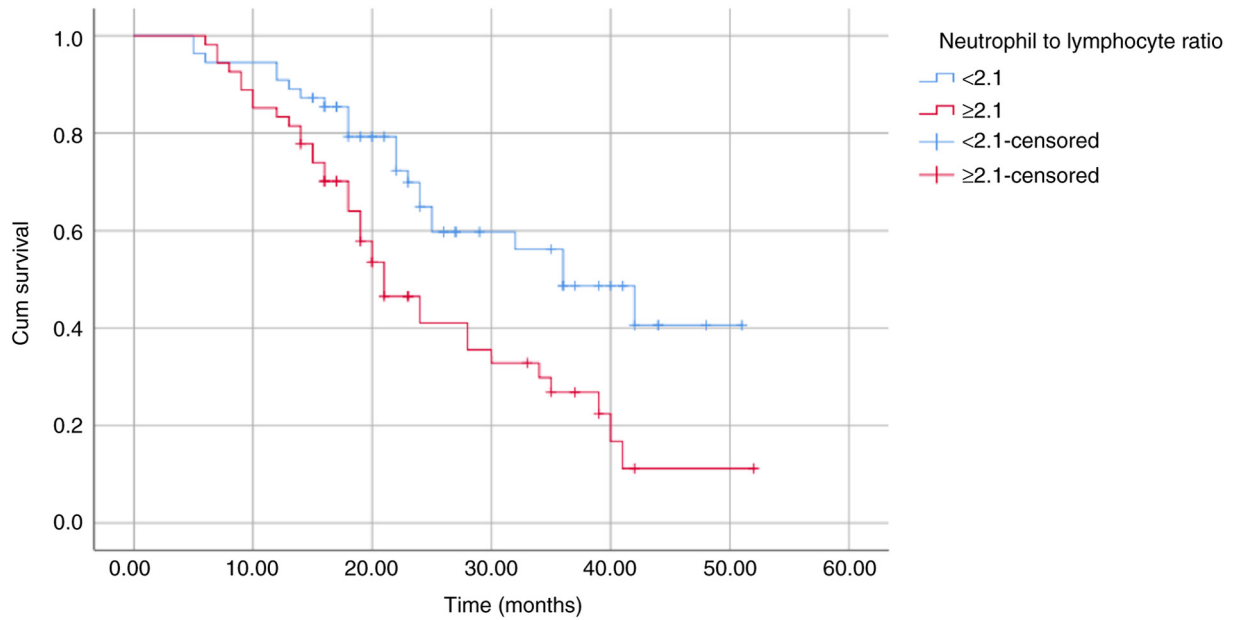


Figure 7. Patient progression-free survival according to neutrophil to lymphocyte ratio (≥ 2.1 vs. < 2.1).

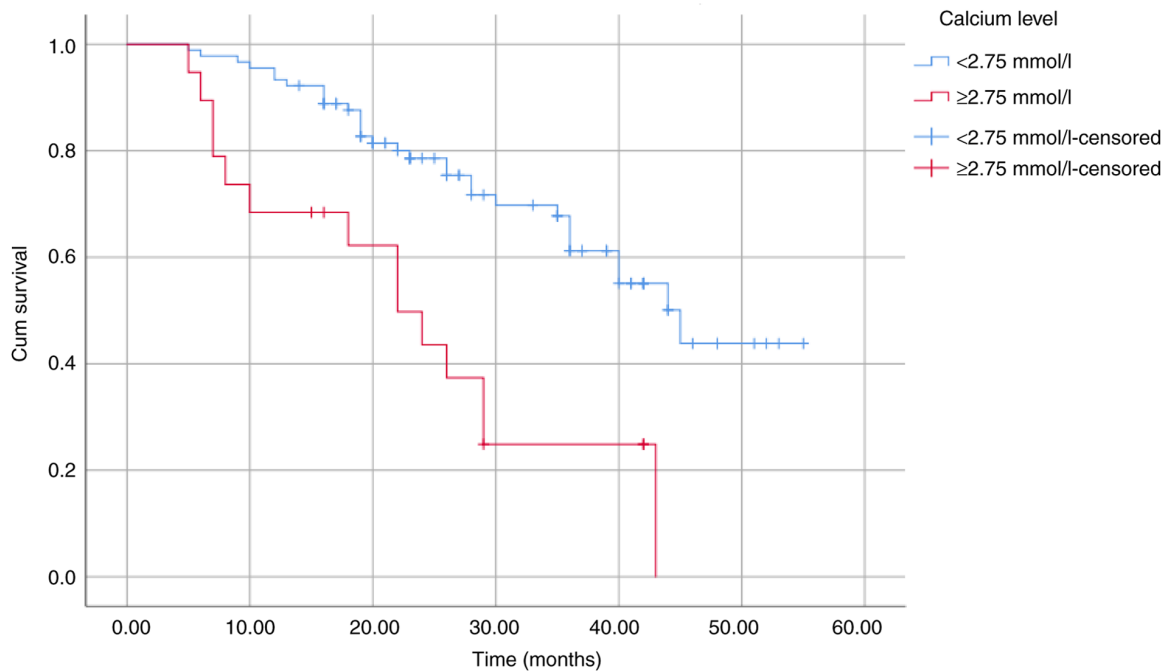


Figure 8. Patient overall survival according to the calcium level (≥ 2.75 mmol/l vs. < 2.75 mmol/l).

is required (38). In addition, several influential studies, such as those by Abdallah *et al* (28), Kumar *et al* (29,31) and Ferri *et al* (30) did not include NLR alongside other prognostic factors in MM, such as low platelet count and high bone marrow plasma cell percentage. As a result, the prognostic value of NLR may have been underestimated relative to these variables. By contrast, the present study demonstrated that the HR and absolute value of standardized coefficient β associated with a high NLR exceeded those of low platelet count and high bone marrow plasma cell percentage, through Cox proportional hazards analysis

for both OS and PFS. In the OS analysis, the HRs for high NLR, low platelet count and high bone marrow plasma cell percentage were 2.605, 1.839 and 1.900, respectively, with corresponding absolute values of standardized coefficient (β) for OS of 0.141, 0.039 and 0.065. In the PFS analysis, the HRs were 2.326, 1.876 and 1.721, respectively, with absolute values of standardized coefficient β of 0.186, 0.099 and 0.149. These findings indicated that a high NLR had a greater prognostic significance than a low platelet count and high bone marrow plasma cell percentage in patients with MM.

Table IV. Prognostic factors used in multivariate survival analysis.

A, OS

| Factor | β | B | SE | Wald | P-value (Cox analysis) | HR | 95% CI |
|---|---------|-------|-------|-------|------------------------|-------|-------------|
| High bone marrow plasma cell percentage ($\geq 40\%$) | 0.065 | 0.642 | 0.312 | 4.243 | 0.039 | 1.900 | 1.032-3.501 |
| Low platelet count ($< 150 \times 10^9/l$) | 0.039 | 0.609 | 0.310 | 3.871 | 0.049 | 1.839 | 1.002-3.373 |
| High NLR (≥ 2.1) | 0.141 | 0.958 | 0.326 | 8.652 | 0.003 | 2.605 | 1.376-4.931 |
| High calcium level (≥ 2.75 mmol/l) | 0.212 | 0.980 | 0.328 | 8.959 | 0.003 | 2.665 | 1.403-5.065 |

B, PFS

| Factor | β | B | SE | Wald | P-value (Cox analysis) | HR | 95% CI |
|---|---------|-------|-------|-------|------------------------|-------|-------------|
| High bone marrow plasma cell percentage ($\geq 40\%$) | 0.149 | 0.543 | 0.270 | 4.040 | 0.044 | 1.721 | 1.014-2.922 |
| Low platelet count ($< 150 \times 10^9/l$) | 0.099 | 0.625 | 0.280 | 4.982 | 0.026 | 1.867 | 1.079-3.231 |
| High NLR (≥ 2.1) | 0.186 | 0.844 | 0.273 | 9.590 | 0.002 | 2.326 | 1.363-3.970 |
| High calcium level (≥ 2.75 mmol/l) | 0.207 | 0.856 | 0.296 | 8.358 | 0.004 | 2.354 | 1.318-4.207 |

OS, overall survival; PFS, progression-free survival; B, unstandardized coefficient; β , absolute value of standardized coefficient; NLR, neutrophil to lymphocyte; SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval.

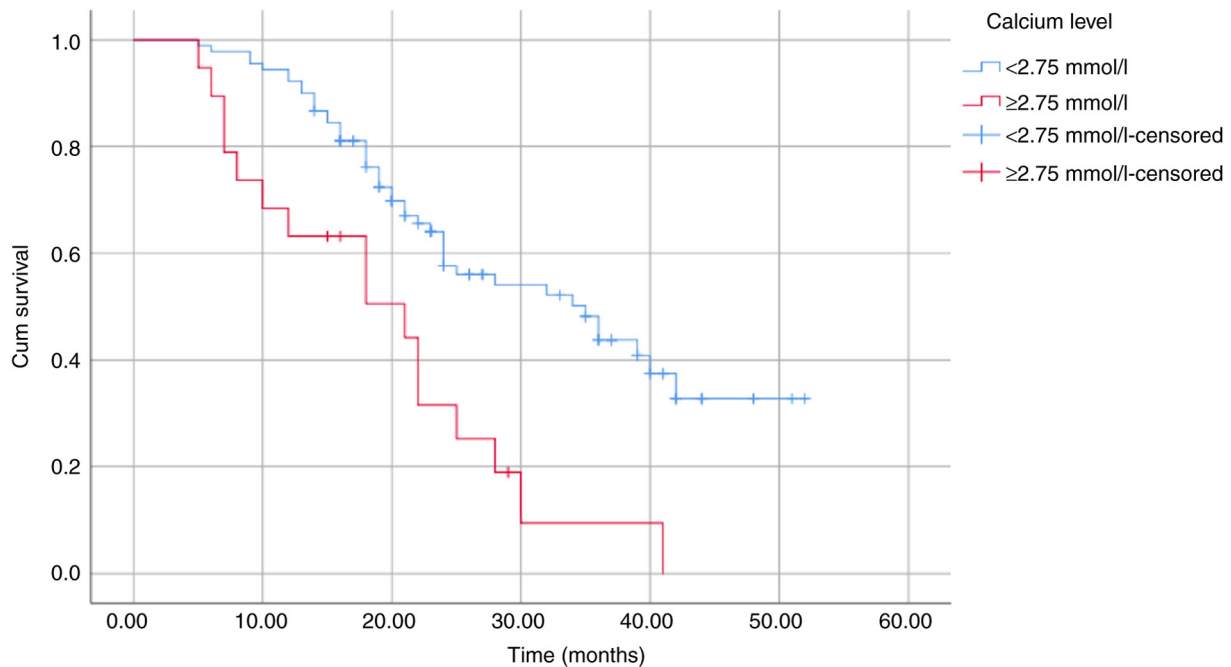


Figure 9. Patient progression-free survival according to the calcium level (≥ 2.75 mmol/l vs. < 2.75 mmol/l).

The association between thrombopoiesis and MM is complex. On one hand, malignant plasma cells secrete cytokines, such as IL-6 and VEGF, which promote thrombocytosis. On the other hand, monoclonal immunoglobulins secreted by plasma cells exert inhibitory effects on platelet production. The balance between these opposing mechanisms complicates interpretation of the association between platelet count and disease progression, although clinical

evidence consistently indicates that low platelet count is a poor prognostic factor in MM (37-39). Bone marrow plasma cell percentage reflects disease burden; however, the findings of the present study suggest that its prognostic value is inferior to that of NLR. Overall, MM progression results from dynamic interactions between malignant plasma cells and the bone marrow microenvironment, in which inflammatory mediators play a pivotal role. Inflammatory cytokines, such

as IL-6, TNF α and other mediators, promote cell adhesion, angiogenesis and may impair treatment efficacy, rendering inflammatory markers, such as NLR, valuable indicators of poor prognosis.

The results of the present study also demonstrated that a high NLR had a lower prognostic impact than elevated calcium levels in MM. For OS, the HRs were 2.605 compared with 2.665, and the absolute values of standardized coefficients β were 0.141 compared with 0.212 for high NLR and high calcium, respectively. For PFS, the HRs were 2.326 compared with 2.354, and the absolute values of standardized coefficients β were 0.186 compared with 0.207, respectively. In MM, plasma cell-derived cytokines stimulate osteoclast activation, leading to bone resorption and calcium release. Concurrent renal impairment reduces calcium clearance, contributing to hypercalcemia (40). Hypercalcemia is therefore directly associated with MM progression, whereas NLR represents an indirect marker reflecting immune dysregulation, the mechanisms of which require further clarification.

Notably, the present study exhibits several limitations. As a retrospective cohort study, it is subject to selection and information bias. In addition, due to financial constraints, comprehensive cytogenetic evaluation using FISH was not performed, precluding the analysis of the association between NLR and R-ISS or R2-ISS. Future studies incorporating complete cytogenetic data are required to enable the more objective evaluation of the prognostic role of NLR. The association between NLR and chromosomal abnormalities of multiple myeloma, as detected using FISH techniques and staging classifications, such as R-ISS or R2-ISS, is an exciting area of research. Zuo *et al* (41) demonstrated that a NLR ≥ 2 was strongly associated with R-ISS. However, their study also demonstrated that there were no significant differences between the value of NLR and the presence of 1q21 amplification, therefore, there was also no association between NLR and R2-ISS (41). Thus, the association between NLR and the presence of chromosomal abnormalities, as well as staging classifications based on chromosomal abnormalities, such as R-ISS or R2-ISS, is a worth considering. The authors hope to further develop the study, exploring the association between NLR and chromosomal abnormalities of multiple myeloma, as well as with R-ISS or R2-ISS. The present study was conducted in Vietnam, a developing country, where limited drug availability necessitated use of multiple treatment regimens, including VTD, VCD and VRD, resulting in heterogeneous treatment outcomes. Consequently, adjustment for treatment regimens in prognostic analyses was limited. Larger prospective studies stratified by treatment protocol are required to address these issues.

In conclusion, a high NLR is a valuable adverse prognostic factor in MM and appears to have greater prognostic significance than a low platelet count and bone marrow plasma cell percentage. However, further large-scale studies are required to determine the most appropriate and standardized NLR cut-off value for routine clinical application.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MPV conceived the study. NDN, MPV, HV, PTP and TTN designed the study. HV, PTP, TVOK, HYD, TTMN and THH participated in data collection and processing. NDN, MPV, HV and PTP participated in data analysis and interpretation. All authors participated in the literature search in the writing of the manuscript. All authors have read and approved the final manuscript. HV and PTP confirm the authenticity of the raw data.

Ethics approval and consent to participate

The study protocol was approved by The Institutional Review Board of Bach Mai hospital (no. 7219/QĐ-BM: date 31 December 2024). All patients were informed and consented to participate in this study. Patients, their guardians or family members were called to request consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that have no competing interests.

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