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ORIGINAL RESEARCH

Prognostic role of neutrophil–lymphocyte ratio in multiple myeloma: a dose–response meta-analysis

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Background: The neutrophil–lymphocyte ratio (NLR), a biomarker for systematic inflammation, has been recently identified as a prognostic factor for various types of both solid and hematologic malignancies. Our study presented here was the first meta-analysis assessing the prognostic role of NLR in multiple myeloma (MM).

Methods: We systematically searched PubMed, Embase, and ISI Web of Science for relevant studies. Odds ratios (ORs) or hazards ratios (HRs) with corresponding 95% CIs are pooled to estimate the association between NLR and clinicopathological parameters or survival of MM patients.

Results: Seven trials with 1,971 MM patients were enrolled in the meta-analysis, and the results indicated that elevated pretreatment NLR was significantly associated with advanced tumor stages (International Staging System [ISS] III vs ISS I–II: OR 2.427, 95% CI: 1.268–4.467; and Durie–Salmon III vs Durie–Salmon I–II: OR 1.738, 95% CI: 1.133–2.665). Moreover, increased NLR also predicted poorer overall survival (HR 2.084, 95% CI: 1.341–3.238) and progression-free survival (HR 1.029, 95% CI: 1.016–1.042). And two-stage dose–response meta-analysis revealed linear association between increased NLR and risk of mortality in MM patients.

Conclusion: We can conclude that MM patients with higher NLR are more likely to have poorer prognosis than those with lower NLR.

Keywords: neutrophil–lymphocyte ratio, multiple myeloma, prognosis, dose–response meta-analysis

Introduction

Multiple myeloma (MM) is well known as a malignant neoplasm of plasma cells derived from a single clonal expansion in the bone marrow (BM), which is characterized by bone destruction, renal failure, anemia, and hypercalcemia.[1] In the USA in 2016, the American Cancer Society estimated that there were 30,280 newly diagnosed MM patients and 12,590 deaths caused by MM, and MM accounted for more than 18% of all hematologic malignancies.[2] For optimal personalized treatment, accurate assessment of prognosis is urgently required in the clinical practice. However, high variability exists in the prognosis of patients with MM.

As we all know, the International Staging System (ISS) was developed on the basis of a multicenter study, which reported that β2-microglobin (β2-MG) and serum albumin were most closely correlated with the prognosis by the multivariate analysis. Although ISS overcame several limitations of Durie–Salmon (D-S) staging system, and was applied worldwide for many years, the Revised ISS is now widely accepted as the new standard prognostic model for MM patients in case of therapeutic innovation and technical development. However, clinical progress of myeloma patients and their survival are so highly variable that we cannot get exact prognosis just based

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on the state at the time of diagnosis. Besides, BM biopsy is invasive and some further clinical examinations, such as fluorescence in situ hybridization (FISH), are too expensive to be affordable. Therefore, researchers pay more attention to combining some patient-related factors to develop new prognostic models.

Recently, the systemic inflammation has been presented as a critical component of tumor progression.[3] In this context, several studies have investigated effective markers to measure the correlation between inflammation and survival of various cancer patients, including C-reactive protein, albumin, as well as the neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio, and platelet–lymphocyte ratio, and so on.[4–7] The NLR, simply neutrophil count (cells/μL) divided by lymphocyte count (cells/μL), has been recently identified as a prognostic factor for both solid tumors and hematologic malignancies.[8–11]

Elevated level of NLR may predict poor clinical outcome in MM. Meanwhile, due to the variance in the study design and sample size, direct impact of NLR level on patients' survival and tumor's clinicopathological parameters remains inconclusive. In this study, we searched PubMed (Medline), Embase, and ISI Web of Science databases for relevant studies and performed a meta-analysis in order to determine the prognostic role of NLR in MM and investigate the association between NLR and some clinicopathological parameters.

Methods

Search strategy

We conducted the systematic search strategies described by Dickersin et al[12] to identify all relevant electric publications until April 2017 throughout databases, including PubMed (Medline), Ovid (EMBASE), and ISI Web of Science databases. The search strategy included terms as follows: "NLR" (eg, "neutrophil to lymphocyte ratio", "neutrophil lymphocyte ratio", and "neutrophil-to-lymphocyte ratio"), "prognosis" (eg, "outcome", "survival", and "mortality"), and "MM" (eg, "multiple myeloma", "myeloma", "plasmacytoma", "myelomatosis", and "Kahler's disease"). Furthermore, we manually checked the reference lists of retrieved studies to identify more potential pertinent studies.

Selection criteria

Studies were included in the meta-analysis if they met all of the following criteria: 1) patients were diagnosed with MM according to International Myeloma Working Group criteria 2014;[13] 2) association between the pretreatment NLR and overall survival (OS), progression-free survival (PFS), or other clinicopathological parameters was reported; 3) studies that were not directly reporting hazards ratios (HRs) and 95% CI were allowed if we could reconstruct them by *p*-values and other data reported;[14] 4) the publication language was confined to English. Exclusion criteria were 1) abstracts, letters, reviews, case reports, and so on; 2) studies with insufficient data for analysis; 3) studies without specific data concerning MM or NLR; and 4) multiple published reports. When there were several reports concerning the same cohort, we included the most recent publication in our meta-analysis.

Data extraction

Two investigators (FJF and SDM) independently identified the eligible studies for this meta-analysis. Any disagreement was resolved by discussion with the third party (SDM and LSA). The qualities of the included studies were assessed according to the Newcastle–Ottawa Quality Assessment Scale (NOS). This scale uses a star system (with a maximum of nine stars) to evaluate a study in three domains: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. NOS scores of ≥6 were assigned as high-quality studies. For each study, the following relevant data were extracted in a predefined table: 1) first author's name, year of publication, country of the population, sample size, patient age, gender, therapy, follow-up period; 2) clinicopathological parameters including β2-MG level, ISS stages, and D-S stages; 3) survival data including OS and PFS (OS was calculated from the medical treatment until the death of patient or the last follow-up. PFS was defined as the interval between the date of treatment and the detection of the recurrence tumor or death from any cause); 4) cut-off value used to define "elevated NLR".

Statistical analysis

HR and 95% CIs were obtained directly from each literature or from estimation according to the methods by Parmer et al.[14] The combined odds ratio (OR) and its 95% CIs were used to evaluate the association between NLR and clinicopathological parameters.[15]

A two-stage dose–response meta-analysis was conducted to assess whether NLR was associated with higher risks of mortality from MM, based on specific cut-off values, distribution of death cases and person-years, and adjusted HRs with 95% CIs. We used the generalized least-square regression described by Orsini et al to calculate the study-specific linear trend and 95% CIs for higher NLR within each study from the natural logs of adjusted HRs and 95% CIs, and pooled HRs and 95% CIs were obtained under the random-effects model.[16] We approximately derived person-years from

follow-up duration and the number of participants at each NLR level. The midpoint of the higher NLR category was set at 1.2 times the lower boundary (specific cut-off value in each study). And we set the lower boundary to zero in the lower NLR category.

Heterogeneity among included studies was checked by the χ^2-based Q-test and I^2 test.[17] The fixed-effect model was used for analysis without any significant heterogeneity between studies ($p>0.10$, $I^2=0\%$). Otherwise, the random-effects model was chosen. Subgroup analysis and metaregression were further performed to explore the source of heterogeneity. Sensitivity analysis was also performed to examine the effect of each study on the overall pooled results. All statistical tests were two sided and the significance level was set at 5%.

The Begg's funnel plot was used to visually evaluate the publication bias of all studies included in our meta-analysis. And then the Egger's bias indicator test was performed for each of the pooled study groups.[18] All analyses were carried out using STATA statistical software package version 14.0 (STATA, College Station, TX, USA).

Results

Selection and characteristics of included studies

As shown in Figure 1, the initial search algorithm retrieved a total of 125 studies. After excluding the duplicates (n=21), abstracts, letters, reviews, and so on (n=13), and the studies not related to research topics (n=41), the remaining studies (n=50) were further reviewed by reading the full text.

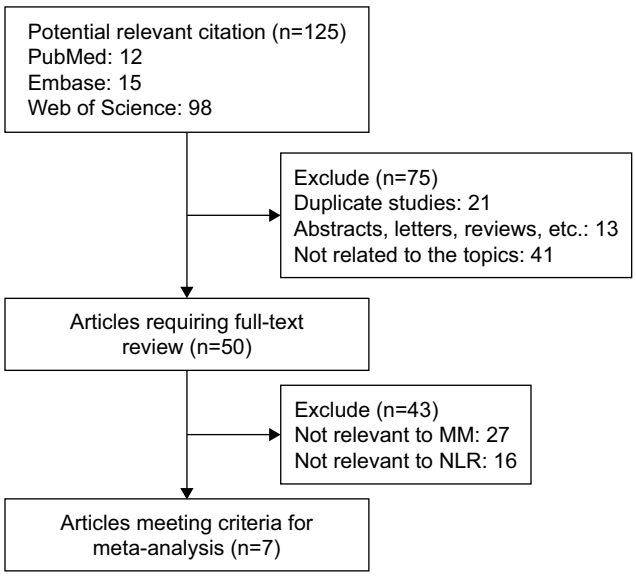

Figure 1 Flow diagram of the selection of relevant published works regarding NLR in MM.
Abbreviations: MM, multiple myeloma; NLR, neutrophil–lymphocyte ratio.

Additional studies were then excluded because they did not provide specific data concerning MM (n=27) or NLR (n=16). Therefore, seven studies[10,16,19–23] between 2014 and 2017 with a total of 1,971 MM patients were enrolled in our meta-analysis.

Summary on the characteristics of the included studies is shown in Table 1. The publication periods of all included studies range from 2014 to 2017. Three studies were from the eastern region (two from China[21,22] and one from Korea[20]) and four from the western region (two from Turkey,[16,19] one from the USA,[23] and one from the USA and Italy). Three studies[16,19,23] enrolled <200 patients and four studies[10,20–22] had >200 patients. Five studies[10,19,20,22,23] directly reported HR and 95% CIs in the original literature. NOS score was above 7 in four studies.[10,20–22]

Association between NLR and clinicopathological parameters

We next analyzed the association between NLR and clinicopathological parameters. Among seven studies in our meta-analysis, five studies[10,16,20–23] indicated a significant correlation between high NLR and advanced ISS staging of MM patients (ISS III vs ISS I–II: pooled OR 2.427, 95% CI: 1.268–4.467) with significant heterogeneity ($\chi^2=19.44$, $p=0.001$; $I^2=79.4\%$) (Figure 2A).

Moreover, three studies[16,21,22] examined the association between high NLR and advanced D-S staging of MM patients. The results showed a significant association (D-S III vs D-S I–II: pooled OR 1.738, 95% CI: 1.133–2.665) with no heterogeneity ($\chi^2=0.92$, $p=0.631$; $I^2=0.0\%$) (Figure 2B).

Association between NLR and survival of MM patients

Seven studies[10,16,19–23] in our analysis examined the association between NLR and survival of MM patients. With heterogeneity ($\chi^2=57.64$, $p<0.0001$; $I^2=89.6\%$), the pooled HR of 2.084 (95% CI: 1.341–3.238) indicated that MM patients with elevated NLR were expected to have shorter OS (Figure 3A). Furthermore, we conducted a dose–response meta-analysis to evaluate the prognostic role of NLR on specific cut-off value using generalized least squares. And the results showed linear association between higher NLR and shorter OS in MM patients (HR =1.568, 95% CI: 1.205–2.04, $p=0.001$) (Figure 3B).

To explore the source of heterogeneity, subgroup analysis and metaregression were performed by the study location (eastern vs western region), sample size (≥200 vs <200), cut-off value defining "elevated NLR" (2 vs not 2), and NOS score (≥8 vs <8). The subgroup analysis did not alter

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country	Follow-up[a] median (range)	Age	Cases (male/female)	Sample size	Cut-off value	Therapy	Outcome	Survival analysis	Method[b]	NOS score
Kelkitli et al[19]	2014	Turkey	41 (1–100)	63 (35–89)	83/68	151	2	NR	OS	No	2	7
Kim et al[20]	2017	Korea	>10 years	64 (30–83)	160/113	273	2.25	Chemotherapy including novel agents and/or eligible ASCT	OS	M	I	8
Li et al[21]	2017	China	25 (1–64)	NR	196/119	315	2	Bortezomib-based or conventional chemotherapy, such as thalidomide, doxorubicin, or vincristine	OS, PFS	U, M	I	8
Onec et al[16]	2017	Turkey	(1–60)	65.5 (34–88)	28/24	52	1.72	VAD and/or bortezomib-based therapies, such as BD and BCD	OS	U, M	I	7
Romano et al[10]	2015	Italy and USA	(1–60)	63 (28–88)	161/148	309	2	(V)TD/Rd + ASCT or VMP	OS, PFS	No	I	9
Shi et al[22]	2017	China	64 (1–96)	NR	344/216	560	4	NR	OS, PFS	M	I	8
Wongrakpanich et al[23]	2016	USA	(1–140)	69 (56–78)	62/69	131	2.783	NR	OS	U, M	I	7

Notes: [a]Denoted as obtaining estimated follow-up ranges from Kaplan–Meier curves in the corresponding publications. [b]1 denoted as obtaining HRs directly from publications; 2 denoted as estimating HRs from Kaplan–Meier curves, using GetData Graph Digitizer 2.26 (http://getdata-graph-digitizer.com/) to digitize and extract the relevant survival data.

Abbreviations: ASCT, autologous stem cell transplantation; BCD, bortezomib, cyclophosphamide, and dexamethasone; BD, bortezomib and dexamethasone; HR, hazards ratio; M, multivariate analysis; NOS, Newcastle–Ottawa Quality Assessment Scale; NR, not reported; PFS, progression-free survival; OS, overall survival; Rd, lenalidomide and dexamethasone; U, univariate analysis; VAD, vincristine, adriamycin, and dexamethasone; VMP, bortezomib, melphalan, and prednisone; (V)TD, (bortezomib), thalidomide, and dexamethasone.

the prognostic role of NLR in OS substantially (Table 2), with significant heterogeneity across studies in most subgroups. Metaregression analysis figured out that study location (p=0.064) might partially explain the source of the heterogeneity.

Furthermore, three studies[10,21,22] were pooled to estimate the correlation between NLR and PFS in MM patients. The results showed that there was no significant relationship between high NLR and shorter PFS (HR =1.434, 95% CI: 0.923–2.227), with significant heterogeneity (χ^2=20.13, $p<0.0001$; I^2=90.1%) (Figure 4A). The dose–response meta-analysis revealed linear association between higher NLR and shorter PFS in MM patients (HR =1.029, 95% CI: 1.016–1.042, $p<0.001$) (Figure 4B). Because of the limited original literature, subgroup analysis and metaregression cannot be performed to explore the source of significant heterogeneity. So, more relevant studies are warranted to validate our present meta-analytic results.

Sensitivity analysis

Sensitivity analyses were performed next. A single study involved in the meta-analysis was deleted each time to unveil the influence of the individual data set on the pooled HRs. It was shown that one study from Li et al[21] impacted the results obviously, indicating the main source of heterogeneity to some extent (Figure 5).

Publication bias

Based on the results of sensitivity analysis, the outlier study from Li et al[21] was excluded from the analysis of publication bias. The Begg's funnel plot showed that there was no significant asymmetry for OS (p=0.260) (Figure 6). The p-value of Egger's test also indicated that there was no publication bias in OS (p=0.077) among the studies included in our meta-analysis.

Discussion

Previous studies have demonstrated the biological and prognostic importance of a proinflammatory tumor microenvironment in cancer progression.[3,24–26] Numerous studies[27,28] and several meta-analyses[11,29,30] have provided solid evidence on the correlation between elevated pretreatment NLR and poor prognosis in different tumors, including colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, non-small-cell lung cancer, and urinary cancer.

Our study presented here was the first meta-analysis assessing the association between NLR and clinicopathological parameters as well as prognosis in MM. Seven trials

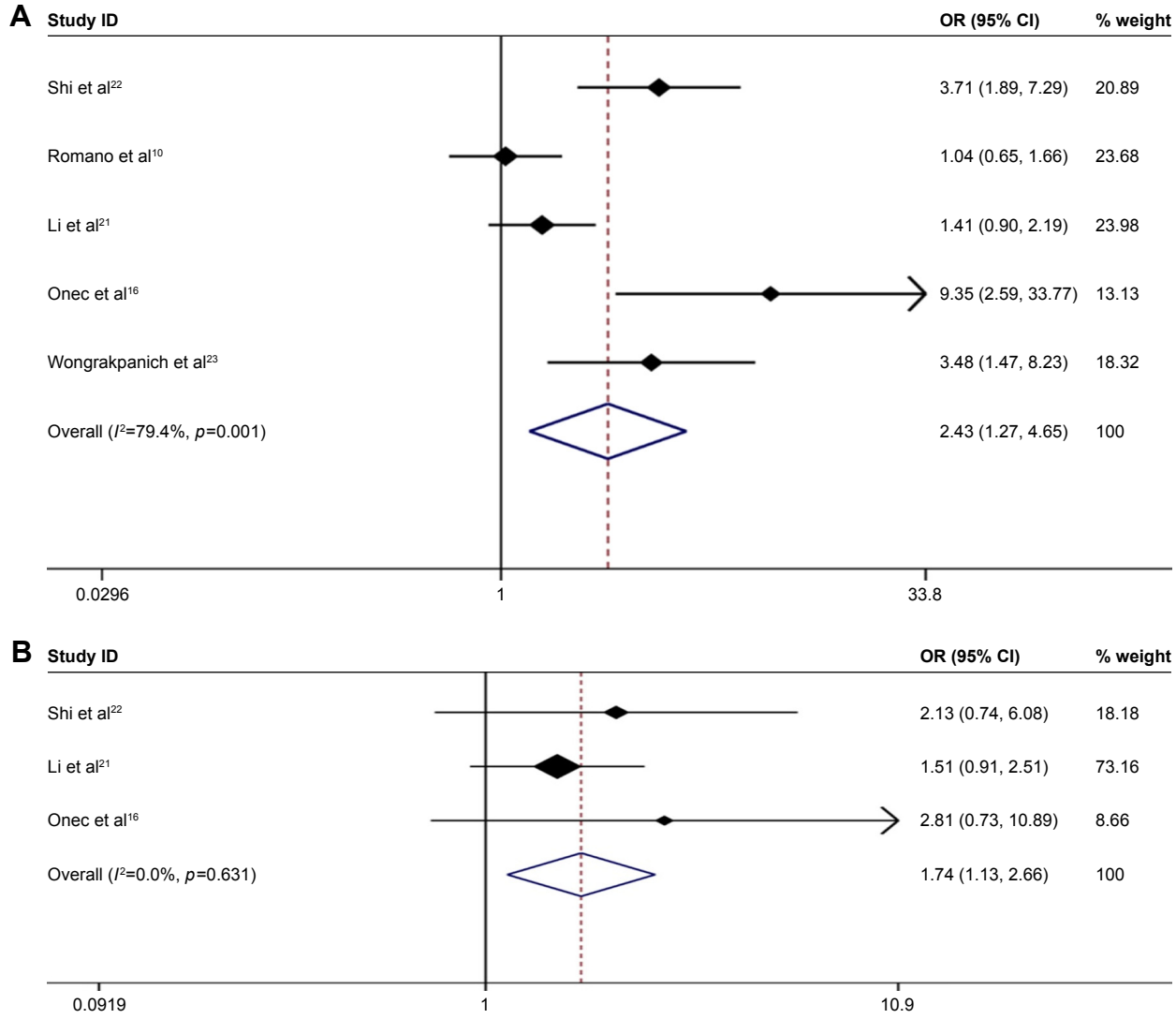

Figure 2 Forest plots showing the association between elevated NLR and clinicopathological parameters. (**A**) ISS staging (III vs I–II); (**B**) D-S staging (III vs I–II).
Abbreviations: OR, odds ratio; NLR, neutrophil–lymphocyte ratio; ISS, International Staging System.

with a total of 1,791 patients were included in this meta-analysis, demonstrating that there was also a significant association between NLR and clinicopathological parameters (Figure 2). What is more, elevated NLR predicted shorter OS and PFS in MM patients (Figures 3 and 4). The results were consistent with previous reports, indicating that NLR is also a promising prognostic biomarker for MM treatment and outcomes.

This heterogeneity among these included studies may be partially explained by study location, sample size, cut-off value of NLR, and NOS score. Significant heterogeneity in selection bias is inevitable in studies with smaller sample sizes. However, the subgroup analysis showed that the prognostic value of NLR was unaffected by the above factors included in the analysis. Moreover, baseline pretreatment, types and doses of chemotherapy regimens, and dichotomized cut-off values also differed among the studies. Although different treatments for MM patient might affect the OS outcome, patients were divided into two groups according to the pretreatment NLR in every study. Thus, treatment protocol is not a confounding factor in the meta-analysis. Definitely, more studies are warranted to further investigate the prognostic role of NLR in MM patients undergoing different therapies. In addition, the sensitivity analysis identified the study from Li et al,[21] impacting the results obviously, while, after excluding the outlier study, the analytic results were not apparently affected, thus indicating the robustness of pooled results in our meta-analysis.

NLR has the advantage of low economic cost and wide availability, thereby drawing increasing attention. Mechanically, an elevated NLR is usually caused by neutrophilia and lymphopenia. Neutrophilia can prompt secreting active

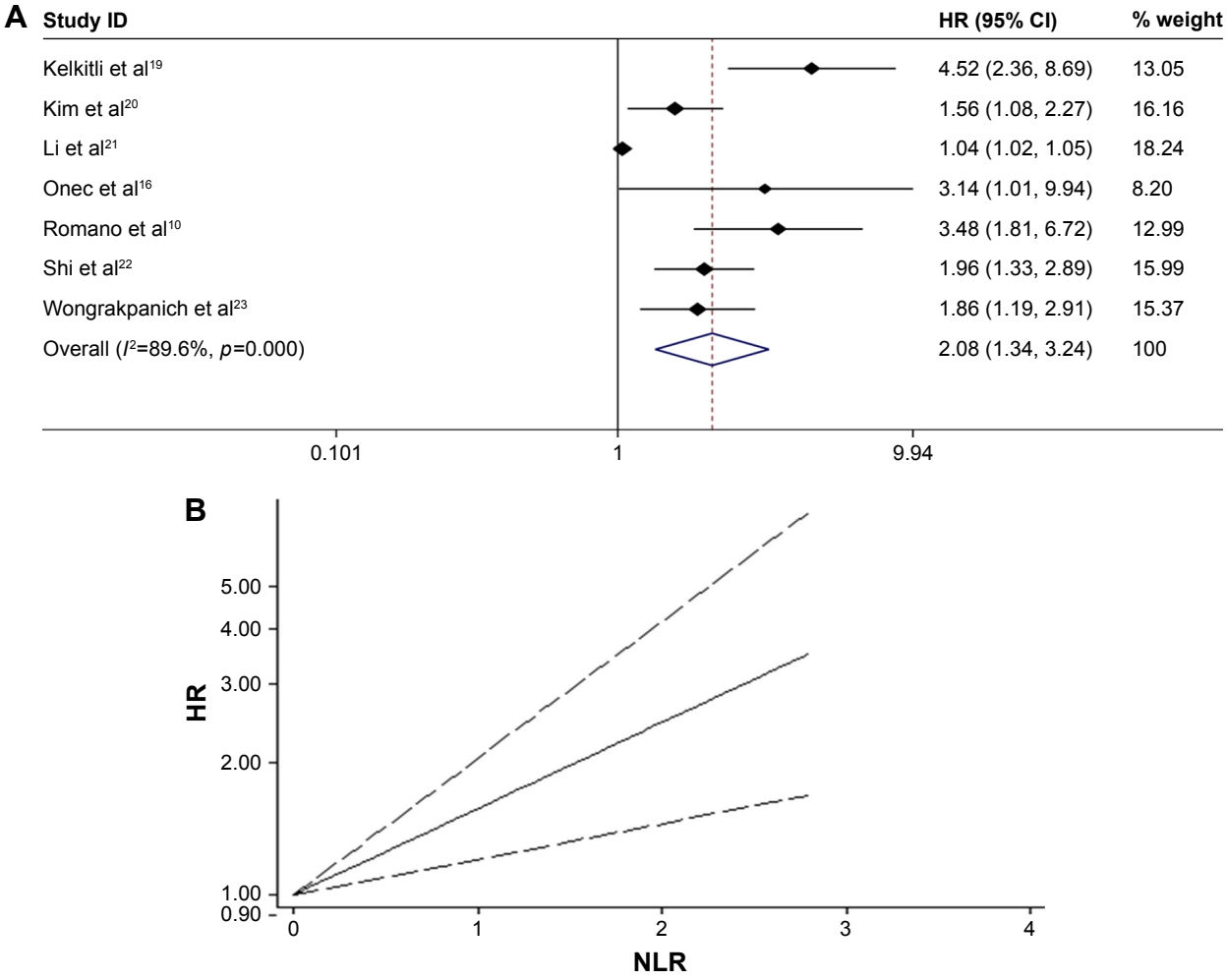

Figure 3 (**A**) Meta-analysis of the association between elevated NLR and OS of MM. (**B**) Dose-response analysis of the prognostic role of NLR in OS of MM.
Abbreviations: HR, hazards ratio; NLR, neutrophil–lymphocyte ratio; MM, multiple myeloma; OS, overall survival.

cytokines such as vascular endothelial growth factor and therefore accelerate tumor progression.[31] Lymphopenia is regarded to correlate with disease severity and is linked to the immune escape of tumor cells from tumor-infiltrating lymphocytes.[32,33] Therefore, an elevated NLR generates a favorable immune microenvironment that promotes vascular invasion and host immune suppression, thereby correlating to poor prognosis of patients.

Table 2 Subgroup analysis and metaregression of pooled hazard ratios for overall survival in MM patients with high NLR

Subgroup analysis	No of studies	No of patients	Pooled HR (95% CI)	Metaregression (*p*-value)	Heterogeneity	
					I^2, %	*p*-value
Region						
Western	4	643	2.714 (1.992–3.699)		47.5	0.126
Eastern	3	1,148	1.421 (0.924–2.185)	0.064	86.6	0.001
Sample size						
<200	3	334	2.832 (1.504–5.330)	0.259	60.0	0.082
≥200	4	1,457	1.706 (1.053–2.764)		89.3	<0.001
Cutoff value						
=2.0	3	775	1.038 (1.020–1.056)	0.773	99.3	<0.001
≠2.0	4	1,016	1.811 (1.445–2.269)		0.0	0.641
NOS score						
≥8	4	1,457	1.706 (1.053–2.764)	0.259	89.3	<0.001
<8	3	334	2.832 (1.504–5.332)		60.0	0.082

Abbreviations: HR, hazards ratio; MM, multiple myeloma; NLR, neutrophil–lymphocyte ratio; NOS, Newcastle–Ottawa Quality Assessment Scale.

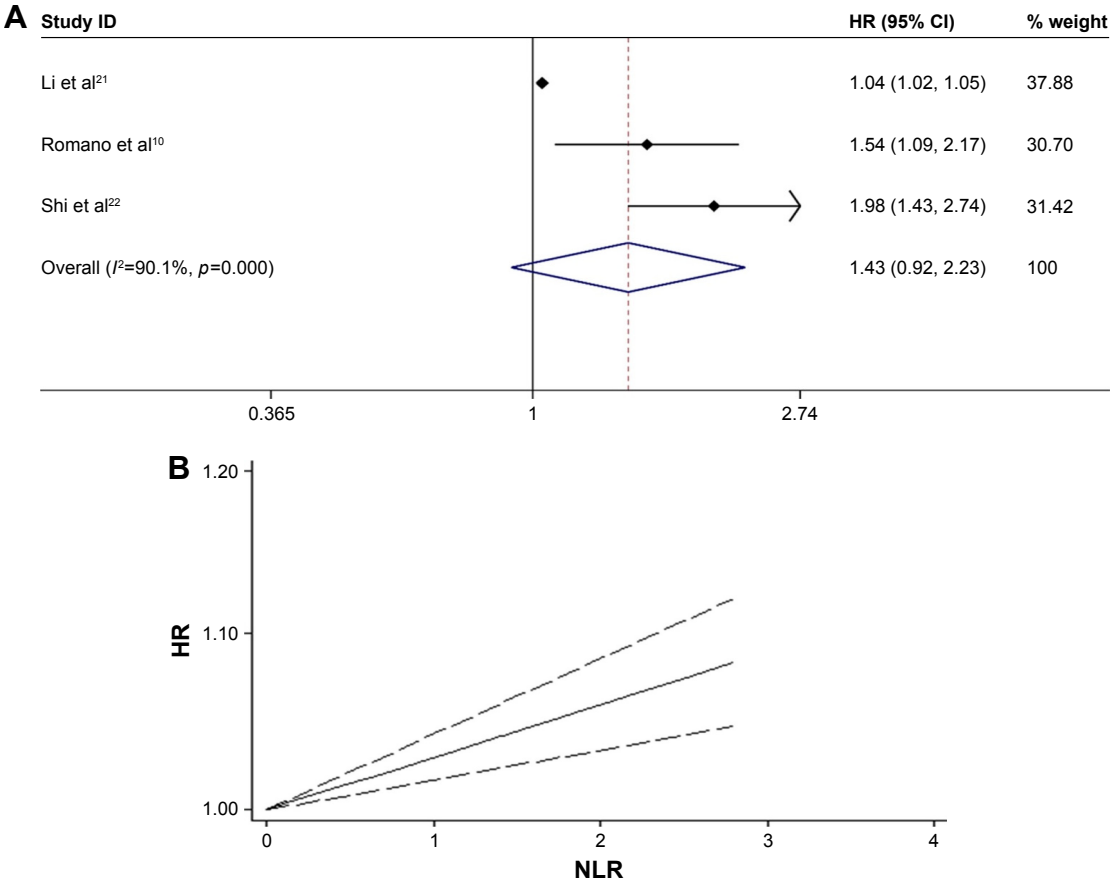

Figure 4 (**A**) Meta-analysis of the association between elevated NLR and PFS of MM. (**B**) Dose-response analysis of the prognostic role of NLR in PFS of MM.
Abbreviations: HR, hazards ratio; NLR, neutrophil–lymphocyte ratio; MM, multiple myeloma; PFS, progression-free survival.

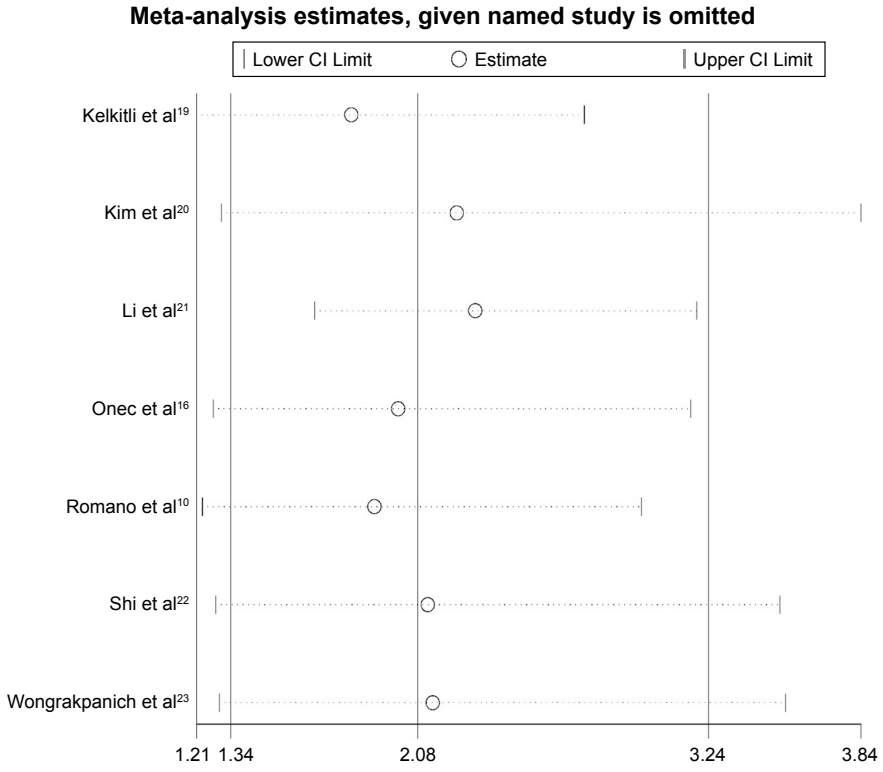

Figure 5 Sensitivity analysis of the overall pooled study for OS.
Abbreviation: OS, overall survival.

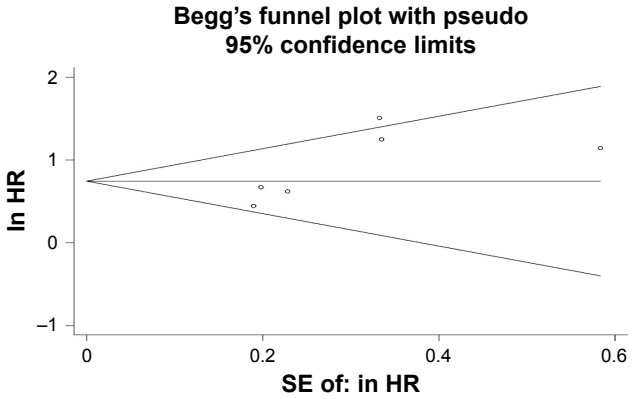

Figure 6 Publication bias of the present meta-analysis.
Abbreviation: HR, hazards ratio.

Limitations

It is noteworthy that our meta-analysis had some limitations that call for cautious interpretation of the results. First, only seven studies published in full text were included in this meta-analysis. Second, the cut-off value for defining high NLR in each study was not the same (Table 1), which may have contributed to heterogeneity. Third, some studies provided only a Kaplan–Meier curve and did not report HR or 95% CI, possibly causing inaccurate HR estimation. Fourth, differences of paper quality and sample size across the studies might cause bias in the meta-analysis, although subgroup analysis and metaregression did not show the above factors as the resource of heterogeneity. Fifth, most of the included studies reported positive results; therefore, our results might overestimate the prognostic significance of NLR to some degree.

Despite the above limitations, our meta-analysis supports the values of NLR for predicting survival outcome in MM patients. NLR can be easily obtained from routine blood tests, and thus may be widely applied in clinic as an alternative to cytogenetic and FISH analysis, gene expression profiling, plasma cell labeling index, serum free light chain ratio, and early interim analysis with positron emission tomography for evaluating risk stratification of MM patients.

Conclusions

Here, we searched electronic databases for relevant studies, and enrolled seven studies with a total of 1,791 patients in meta-analysis, drawing a conclusion that patients with higher NLR are more likely to have shorter OS and PFS under more advanced stages. Taken together, the results from our meta-analysis suggest that NLR gains a prognostic value for patients with MM. More multicenter, prospective cohorts are warranted to further validate the role of the NLR in MM.

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Disclosure

The authors report no conflicts of interest in this work.

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