Systematic Review and Meta-Analysis

Medicine®

OPEN

Prognostic value of neutrophil to lymphocyte ratio and clinicopathological characteristics for multiple myeloma

A meta-analysis

Qiang Zeng, MD, Zhigang Liu, MD, Qiuyang Li, MM, Ting Liu, MD*

Abstract

Background: Neutrophil to lymphocyte ratio (NLR) was reported to be an effective parameter in carcinoma prognosis. Many studies were already performed to investigate the prognostic value of NLR in patients with multiple myeloma (MM). The results, however, were still debatable.

Methods: Databases of Pubmed, Cochrane library and Embase were examined. Hazard ratio (HR) with 95% confidence interval (CI) was used to assess the results. In addition, odds ratios (ORs) with 95% CIs were used to evaluate the association of NLR with clinicopathological factors. Meta-regression, sensitivity analysis, and subgroup analysis were also performed.

Results: The results showed poor OS (HR: 1.73, 95% CI: 1.23-2.44; $P = .002$) and progression-free survival (PFS) (HR: 1.74, 95% CI: 1.11-2.73; $P = .015$) when pretreatment NLR elevated. Our pooled ORs suggested that NLR had association with International Staging System (ISS), isotype and response to treatment.

Conclusion: The meta-analysis results demonstrated that NLR could predict prognosis in MM patients.

Abbreviations: CI = confidence interval, HR = hazard ratio, IL = interleukin, ISS = International Staging System, MM = multiple myeloma, NLR = neutrophil to lymphocyte ratio, NOS = Newcastle-Ottawa Scale, OR = odds ratios, OS = overall survival, PFS = progression-free survival.

Keywords: meta-analysis, multiple myeloma, neutrophil to lymphocyte ratio, prognosis

1. Introduction

Multiple myeloma (MM) is a common hematological carcinoma characterized by malignant clone of plasma cells derived from diverse genetic events contributing to the onset, progression and prognosis of this disorder.[1] Precise and effective prognostic markers can provide an optimal treatment and benefit more patients.[2] Since prognostic markers stratify patients effectively, overall survival (OS) increased by 1.25 times after many novel drugs developed in the last few years.[3] Currently, cytogenetics, such as 17p13 deletion which indicates poor outcome,[2] is a most accurate prognostic biomarker to identify risk of MM patients. Nevertheless, its cost and convenience for prognosis limits the application. Thus, we need to seek some new prognostic markers easily acquired.

In the 19th century, Rudolf Virchow first found leukocytes among tumor cells, which implied a possible relationship between inflammation and cancer.[4] Some inflammatory factors from accessory cells in tumor milieu, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), facilitated cancer cells' invasiveness.[4] Further studies exhibited that reactive oxygen and nitrogen from inflammatory cells induced mutation of some tumor suppressor genes, and inflammatory factors such as IL-6 and prostaglandin E2 (PGE2) caused DNA methylation,[5] which both played an important role in tumorigenesis. Accordingly, neutrophil to lymphocyte ratio (NLR),[6] coinciding with rationales supported by numerous studies, could offer a precise potency in predicting prognosis of cancers. In fact, many studies already demonstrated the prognostic significance of NLR in various cancers. Consistently, a number of meta-analyses further confirmed this view in colorectal cancer,[7] lung cancer,[8] ovarian cancer,[9] breast cancer,[10] and lymphoma[11] and others.

We searched articles regarding correlation between NLR and MM. Some studies claimed that high levels of NLR indicated poor prognosis of MM, while some others did not. Whether NLR could be a prognostic biomarker of MM remained unknown, so we conducted this meta-analysis to clarify the problem.

2. Methods

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] The study protocol was approved by the Ethics Committee of West China Hospital of Sichuan University.

Editor: Ahmet Emre Eskazan.

QZ and ZL contribute equally to the article.

This article does not contain any studies with human participants or animals performed by any of the authors.

The authors have no conflicts of interest to disclose.

Department of Hematology, West China Hospital, Sichuan University, Chengdu, China.

** Correspondence: Ting Liu, Department of Hematology, West China Hospital, Sichuan University. No. 37 Guo Xue Xiang, Chengdu, Sichuan, 610041, P.R China (e-mail: liuting_57@126.comliuting@scu.edu.cn).*

Medicine (2018) 97:41(e12678)

Received: 9 May 2018 / Accepted: 7 September 2018

http://dx.doi.org/10.1097/MD.0000000000012678

Table 1

Characteristics of studies.

Study	Year	Duration	Sample size	Country	Cut-off value	NOS score	Survival analysis	Study design	Follow-up period (year)
Kelkitli	2014	2006–2012	151	Turkey	2	8	OS,PFS	R	>3
Kim	2016	2001–2013	273	Korea	2.25	6	OS	R	>3
Shi	2016	2008–2013	559	China	4	7	OS,PFS	P	>3
Li	2016	2010–2015	315	China	2	7	OS,PFS	R	<3
Onec	2017	2009–2014	52	Turkey	1.72	6	OS	R	>3
Romano	2015	2006–2012	309	Italy	2	6	OS,PFS	R	>3
Wongrakpanich	2016	2004–2014	131	USA	2.78	8	OS	R	>3
Atallah	2013	2000–2012	96	USA	2.28	6	OS	R	>3

NOS = Newcastle-Ottawa Scale, OS = overall survival, P = prospective study, PFS = progression-free survival, R = retrospective study.

2.1. Retrieval strategy

We examined databases of Pubmed, Cochrane library, and Embase for articles evaluating NLR for predicting the prognosis of MM. In addition, we searched articles by key words of "neutrophil to lymphocyte ratio," "neutrophil: lymphocyte ratio," "NLR," "MM," "Kahler Disease," "prognosis," and "prognostic." Publication date was specified before January 2018, and the references search was also done in case of any omissions.

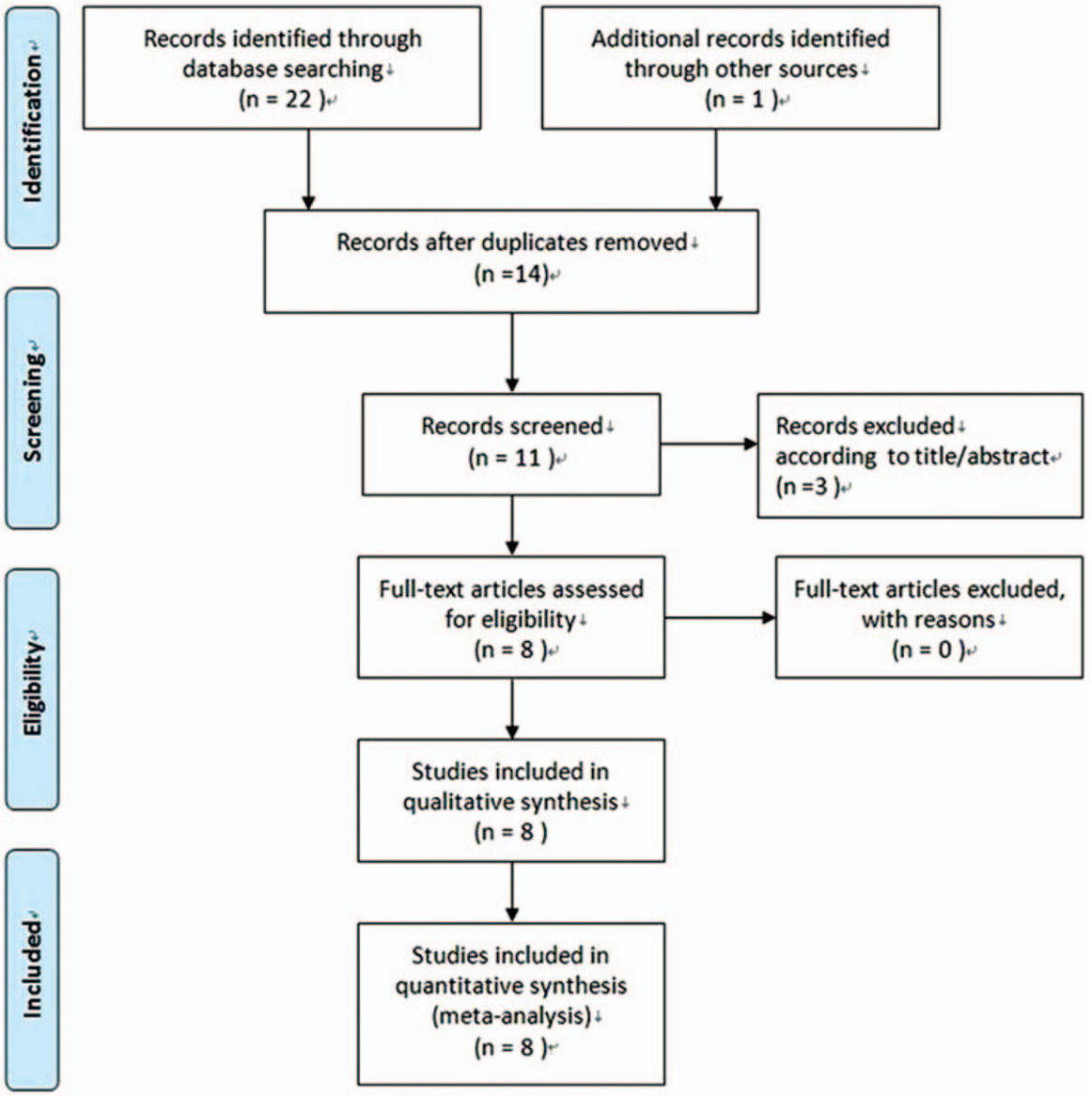

Figure 1. Flow-chart of the included articles.

2.2. Study included criteria

Two independent reviewers evaluated all potential articles. Studies were listed as candidates when they met qualifying criteria as follows:

(1) patients were confirmed as MM by the latest diagnostic criteria;
(2) studies investigated the relationship between the level of NLR before treatment and prognosis of MM;
(3) we were able to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) directly or calculate them by the data from the articles;
(4) all the texts were written in English. Moreover, differences were eliminated through discussion.

2.3. Quality assessment

We assessed these studies by Newcastle-Ottawa Scale (NOS).[13] The scale includes 3 aspects of selection, comparability and outcome ranging from 0 to 9 points. We considered 6 points and above eligible in our meta-analysis, and divergences were also resolved by discussion.

2.4. Data extraction

Data were extracted and calculated by 2 independent investigators. We extracted the data as follows: first author, study country, publication year, duration of cases, sample size, cut-off value of NLR, HR, and 95% CI, type of study design and follow-up period. Moreover, we contacted the author for original data if we were unable to calculate the effect size through the methods provided by Tierney et al.[14] Any divisions were resolved by discussion.

2.5. Statistical analysis

We used HR with 95% CI to evaluate the influence of NLR on survival of MM patients, and odds ratios (ORs) with 95% CIs were used to assess the association of NLR with clinicopathological factors. Heterogeneity tests were conducted using the I-squared statistic and $I^2 > 50\%$ was considered a significant heterogeneity. To be more conservative, we chose random effects models to calculate the pooled HRs and 95% CIs if the heterogeneity was significant, or we selected fixed effects models. We also analyzed the source of heterogeneity by meta-regression and subgroup analysis. Also, sensitivity analysis was used to assess the stability of the pooled results, and publication bias was evaluated using Begg test. All the analyses were performed by STATA 12.0 software (STATA, College, TX) and Revman 5.3 (Revman the Cochrane, Collaboration, Oxford, England).

3. Results

3.1. Study retrieval and characteristics

The flow-chart of the study screening is presented in Figure 1. We retrieved a total of 22 articles after first literature retrieval and added an article to the analysis by reference search. Nine articles were removed after deduplication, and 3 articles were eliminated when we re-screened records. According to title or abstract,

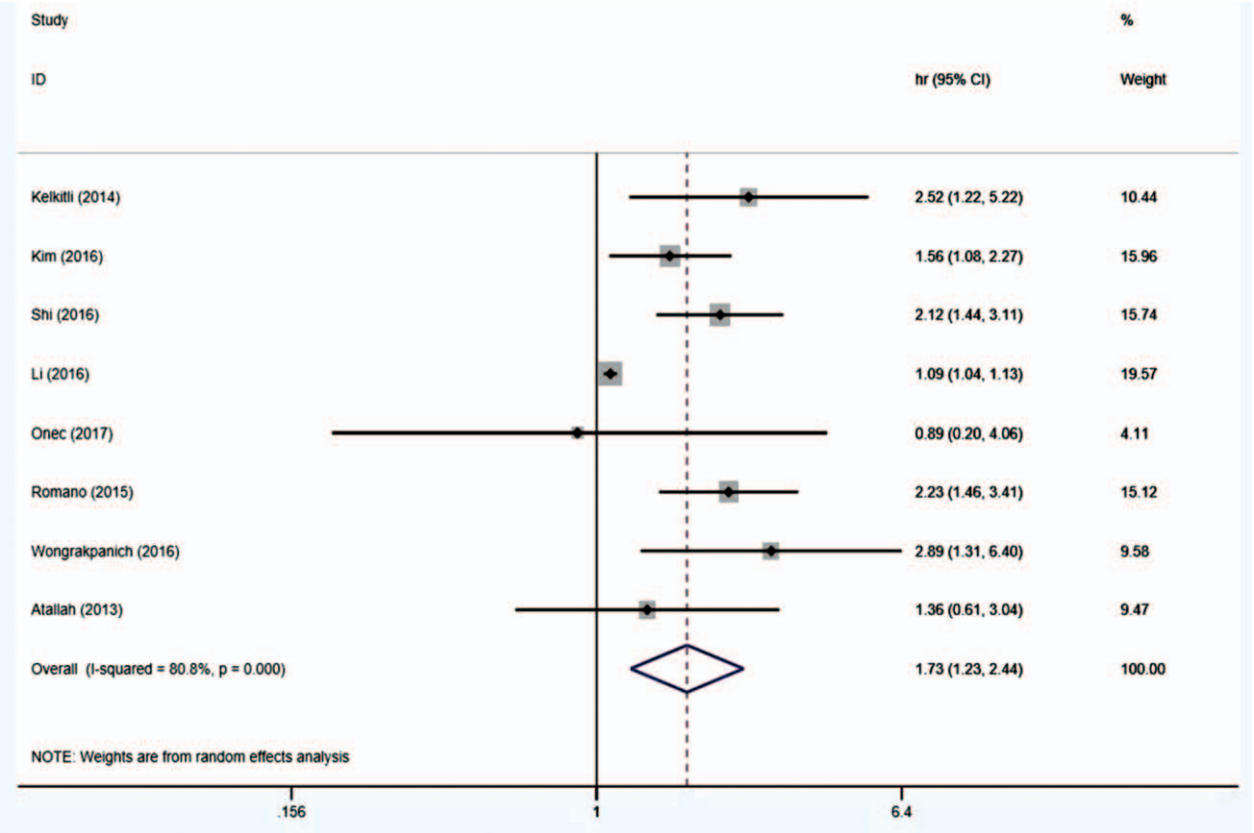

Figure 2. Forest plots of studies evaluating HR with 95% CI of NLR for OS. CI = confidence interval, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival.

3 other articles were excluded. Thus, we brought altogether 8 studies with 1886 patients published from 2013 to 2017 into our meta-analysis. The characteristics of these studies are listed in Table 1. Thereinto, the meta-analysis contained 2 studies each from the USA,[15,16] China,[17,18] and Turkey,[19,20] as well as 1 each from Korea[21] and Italy.[22] All the studies referred to each disease stage according to International Staging System (ISS). Additionally, all studies reported the link between NLR and OS, and 4 studies[17–19,22] including 1334 patients described the link between NLR and progression-free survival (PFS). The follow-up period of all studies was more than 3 years except Li's.

3.2. Association of NLR with OS and PFS

The pooled result suggested that a higher level of pretreatment NLR meant shorter OS in MM patients (pooled HR 1.73, 95% CI: 1.23–2.44, $P=.002$; Fig. 2) with a significant heterogeneity among studies ($I^2=80.9\%$, $P<.001$).

Only 4 studies described the data of pretreatment NLR for PFS. We calculated pooled HR (1.74, 95% CI: 1.11–2.73, $P=.015$; Fig. 3), perhaps indicating the significant correlation between NLR and PFS, although there is a heterogeneity among these studies ($I^2=87.9\%$, $P<.001$).

3.3. Association between clinicopathological characteristics and NLR

Further, we explored the relationship between NLR and clinicopathological characteristics. The pooled results suggested that NLR was higher in ISS stage III (OR: 2.41, 95% CI: 1.27–4.57; $P=.007$), isotype of light chain (OR: 1.74, 95% CI: 1.09–2.79; $P=.02$) and non-responders (OR: 0.50, 95% CI: 0.36–0.71; $P<.001$). It was indicated that the level of NLR was not associated with gender (OR: 1.41, 95% CI: 0.99–2.01; $P=.05$; Fig. 4). The association of NLR with cytogenetics and renal function were not investigated due to insufficient details.

3.4. Heterogeneity

We performed meta-regression, sensitivity analysis, and subgroup analysis to investigate the root of heterogeneity for PFS and OS. The results of meta-regression revealed no contributions of study country ($P=.24$), cut-off value ($P=.77$), NOS score ($P=.62$) and sample size ($P=.74$) to the source of heterogeneity. Also, sensitivity analysis manifested no weakness of our findings in the absence of any single study by turn (Figs. 5 and 6).

Next, we continued to perform subgroup analyses by country, cut-off value, sample size, NOS points, study type and follow-up period (Table 2). The subgroup analyses exhibited that HR was 1.49 (95% CI: 0.97–2.28, $P=.072$) in eastern countries, while 2.13 (95% CI: 1.57–2.87, $P<.001$) in western countries. The result of subgroup analysis by cut-off value of NLR was that pooled HR was 1.72 (95% CI: 0.93–3.20, $P=.083$) when cut-off value was 2 and 1.81 (95% CI: 1.42–2.29, $P<.001$) when cut-off value was not 2. At last, we analyzed the follow-up period and we found that the heterogeneity for OS dropped sharply ($I^2=0$, $P=.519$) after excluding Li's study, whose follow-up period was apparently shorter than others. Simultaneously, the result of

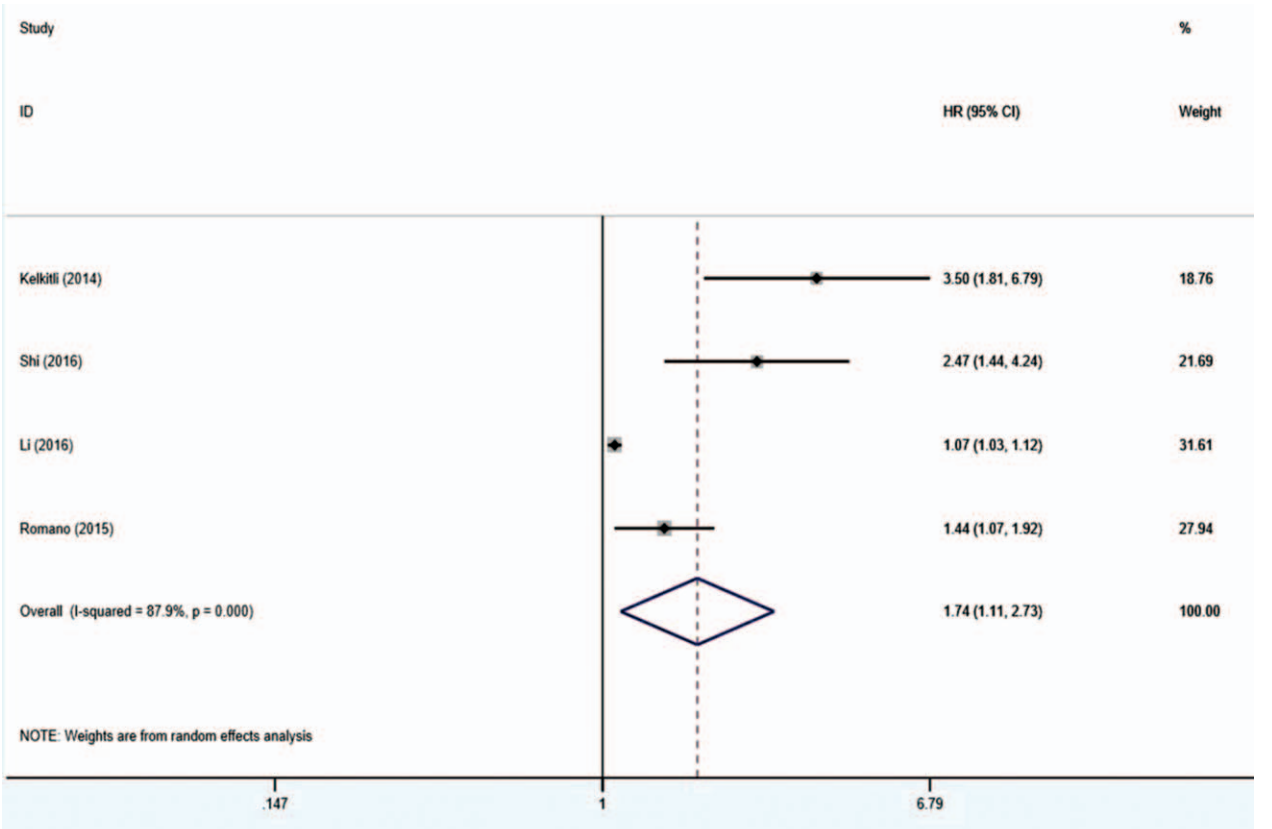

Figure 3. Forest plots of studies evaluating HR with 95% CI of NLR for PFS. CI = confidence interval, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, PFS = progression-free survival.

incorporating the remaining 7 studies was still significant (HR: 1.94, 95% CI: 1.59–2.37, $P = .002$; Fig. 7).

3.5. Publication bias

We adopted Begg's test to evaluate publication bias, which showed no significant publication bias for both OS ($P = .711$) and PFS ($P = .089$).

4. Discussion

This is a meta-analysis designed to investigate the association between NLR and prognosis of MM patients. We computed pooled HR with 95% CI for OS (1.73, 95% CI: 1.23–2.44; $P = .002$) from the data of 1886 MM cases in 8 studies and for PFS (1.74, 95% CI: 1.11–2.73; $P = .015$) from 1334 MM patients in 4 studies. These results were thus supportive of NLR as a

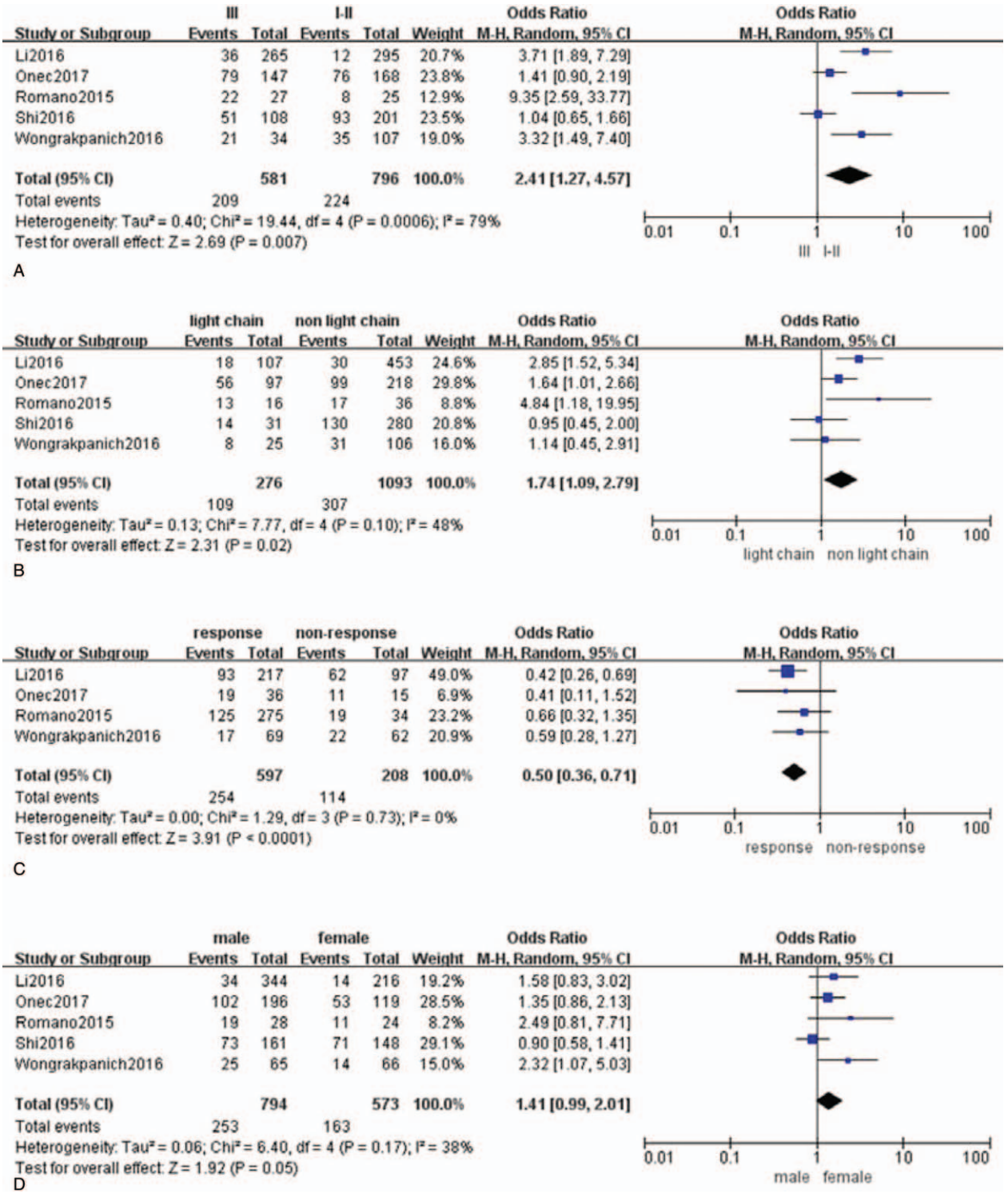

Figure 4. Forest plots for correlation between NLR and clinicalpathological characteristics. (A) ISS stage; (B) isotype; (C) response; (D) gender. ISS = International Staging System, NLR = neutrophil to lymphocyte ratio.

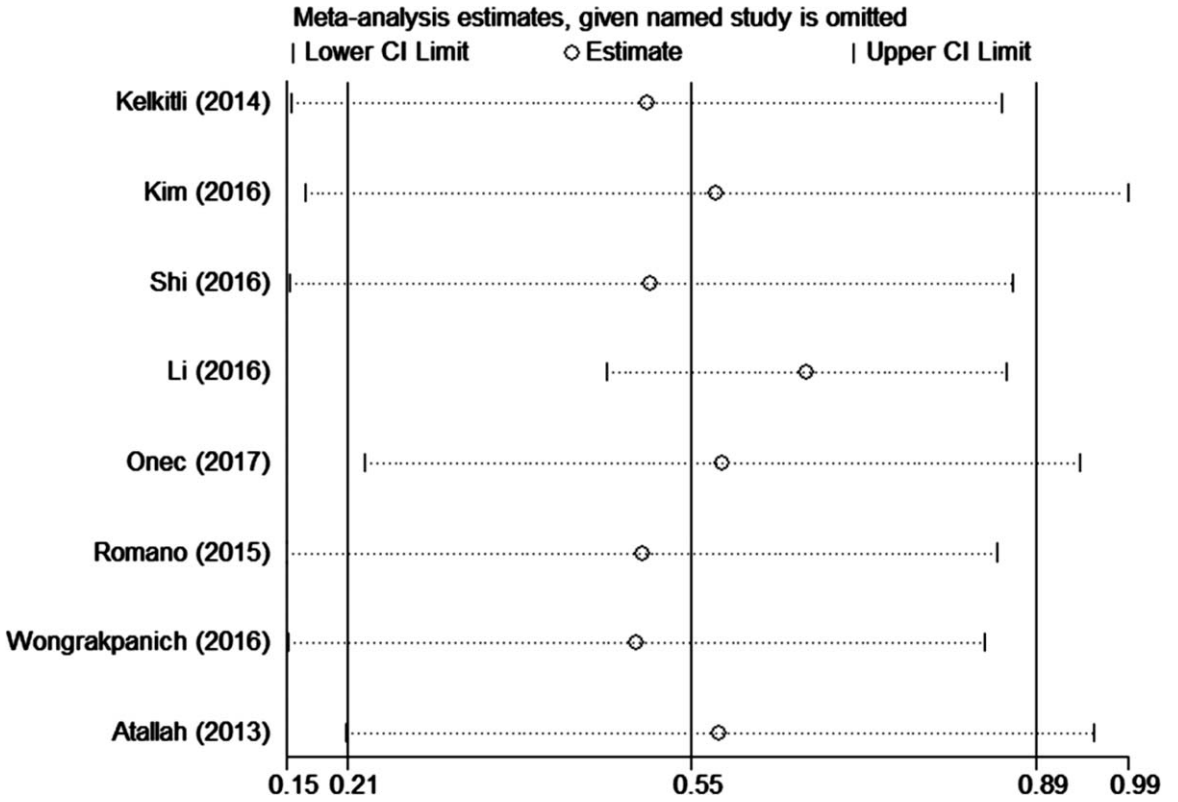

Figure 5. Sensitivity analysis on the correlation between NLR and OS. NLR = neutrophil to lymphocyte ratio, OS = Overall survival.

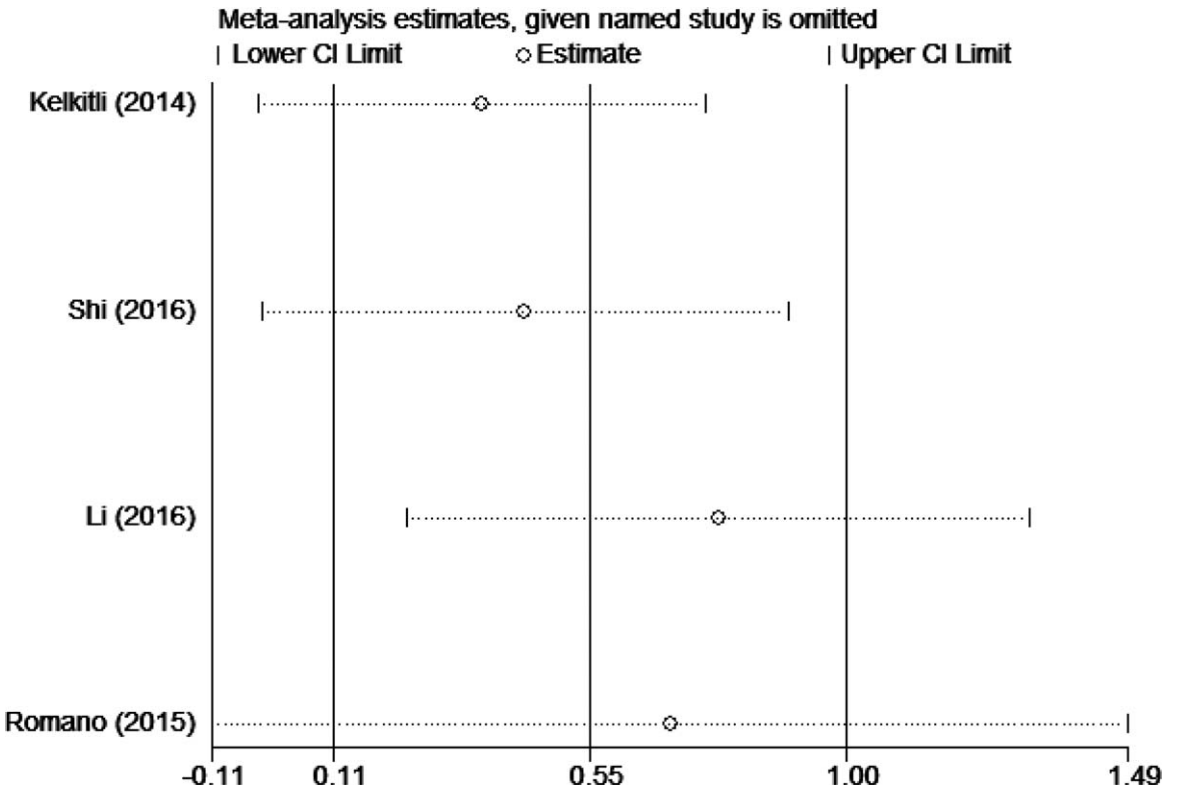

Figure 6. Sensitivity analysis on the correlation between NLR and PFS. NLR = neutrophil to lymphocyte ratio, PFS = progression-free survival.

Table 2

Subgroup analysis for OS.

Subgroup	Number of studies	Number of patients	HR (95% CI)	P value	Heterogeneity
Location					
west	5	739	2.13 (1.57–2.87)	<0.001	I^2=0%; P=.507
east	3	1147	1.49 (0.97–2.28)	0.072	I^2=86.6%; P<.001
Cut-off value					
=2	3	775	1.72 (0.93–3.20)	0.084	I^2=87.5%; P<.001
≠2	5	1111	1.81 (1.42–2.29)	<0.001	I^2=0%; P=.414
NOS score					
≥7	4	1156	1.88 (1.08–3.27)	0.025	I^2=86.5%; P<.001
<7	4	730	1.73 (1.34–2.24)	<0.001	I^2=0%; P=.426
Sample size					
≥200	4	1456	1.64 (1.08–2.48)	0.021	I^2=88.3%; P<.001
<200	4	430	2.01 (1.29–3.14)	0.002	I^2=6.6%; P=.360
Study type					
Prospective	1	559	2.12 (1.44–3.11)	<0.001	/
Retrospective	7	1327	1.66 (1.16–2.39)	<0.001	I^2=76.5%; P<.001
Follow-up period					
<3 years	1	315	1.09 (1.03–1.14)	<0.001	/
>3 years	7	1571	1.94 (1.59–2.37)	<0.001	I^2=0%; P=.519

CI=confidence interval, HR=hazard ratio, NOS=Newcastle-Ottawa Scale.

prognostic biomarker which can benefit MM patients in clinical management.

Cumulative evidence demonstrated that cancers had an association with leukocyte count. During the last decades, researchers detected that different forms of inflammation recruited immune cells (neutrophils, lymphocytes, natural killer cells, and macrophages) within the tumor microenvironment,[23] which controlled and shaped tumor growth by way of direct contact and cytokine production.[4] Cytokines, including IL-6, IL-17, IL-21, IL-22, and IL-23, were detected at a high level in

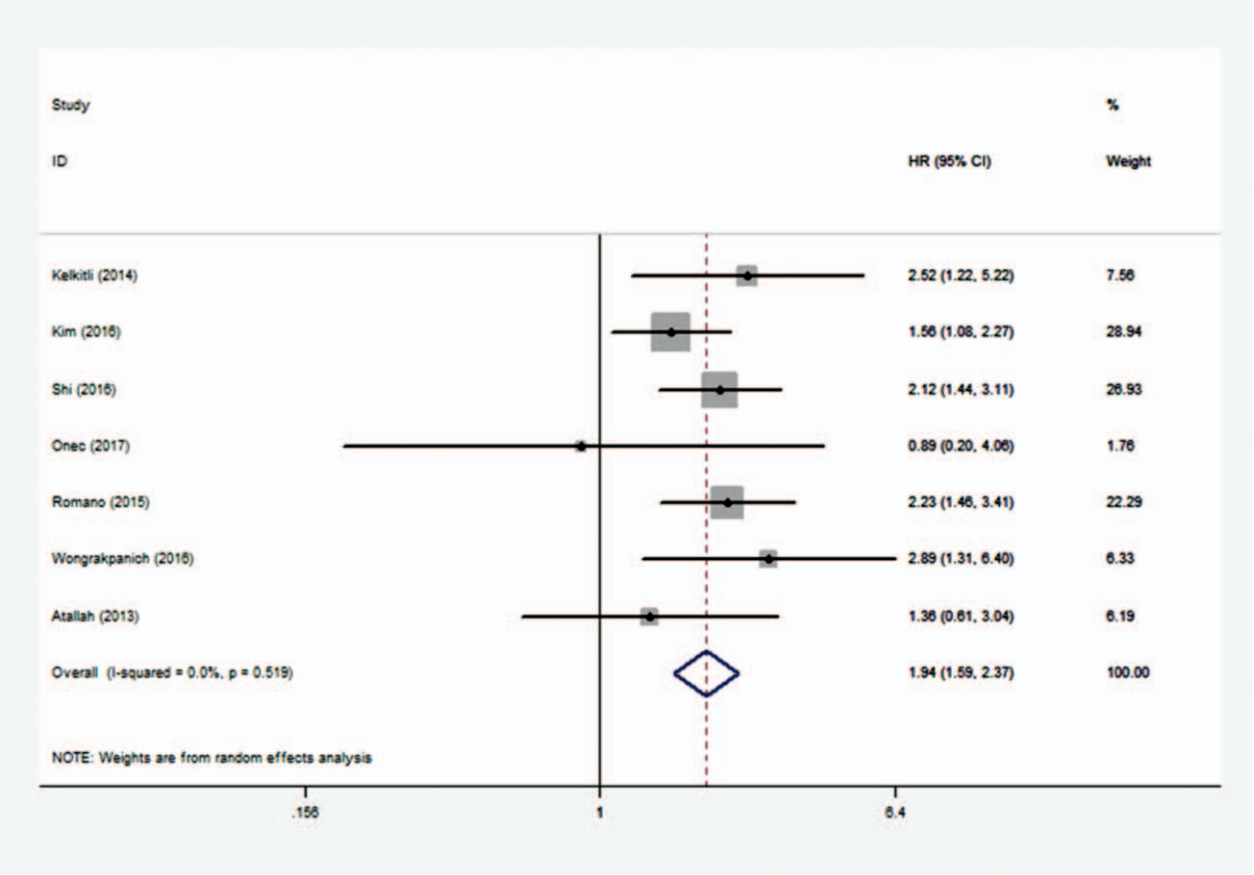

Figure 7. Forest plots of studies about HR with 95% CI of NLR for OS excluding Li's study. CI=confidence interval, HR=hazard ratio, NLR=neutrophil to lymphocyte ratio, OS=Overall survival.

MM patients. And inflammatory elements, combined with accessory cells in milieu, protected tumor cells from the check of immunocytes and simultaneously promoted the development of tumors.[24] These alterations of components of tumor microenvironment urged patients to respond in the form of change of leukocyte count in the peripheral blood. Further research suggested that macrophages and neutrophils stimulated the tumor cells,[25–27] whereas B and T lymphocytes inhibited them.[28,29] Therefore, NLR, which was a new index and altered obviously in many cancers, perhaps played an important role in the onset, proliferation, and metastasis of cancers.

In the last few years, several studies about the association between NLR and survival of MM patients were performed in different countries. Most of them concluded that elevated NLR could predict poor prognosis. However, 2 of these studies (Onec and Atallah) suggested negative results of correlation between NLR and OS. We hypothesized that their conclusions were both restricted by the small sample size. As illustrated in Figures 5 and 6, our trial suggested a robust finding which lent support to the benefits of NLR as a prognostic marker for MM. Furthermore, the consistency of pooled HR did not weaken despite different types of study design, cut-off values and locations. In summary, our meta-analysis, coinciding with the theories and findings mentioned above, showed that high levels of NLR were associated with short OS and PFS, implying poor prognosis of MM patients.

Nevertheless, several limitations must be considered in interpreting our findings. First, a significant heterogeneity indeed existed in the pooled outcome. Through the subgroup analysis and meta-regression analysis, we excluded some confounding factors, such as cut-off value of NLR, study country, NOS score, sample size, and study type, finding that the heterogeneity came from a study with a short follow-up period. Second, we only investigated the relationship between NLR and clinicopathological factors, including sex, response, isotype and ISS. However, we did not explore the association of cytogenetics, the level of beta-2 microglobulin, and renal function due to inadequate materials. Third, our meta-analysis did not solve the problem of what the appropriate cut-off value of NLR was for stratification, which was important for clinical application.

In conclusion, our findings inferred that higher level of NLR had an association with shorter OS and PFS, which might indicate poorer prognosis of MM patients. Elevated NLR was also associated with ISS, isotype, and the response to treatment. Using the index, we could offer an optimal regime to benefit patients. Owing to these limitations mentioned above, however, we suggest that more large-scale and well-designed investigations should be performed to go deeper into the value of NLR in predicting the prognosis of MM patients clinically.

Acknowledgments

We thank all patients and clinical investigators who were involved in the studies for this meta-analysis.

Author contributions

The study was conceived and designed and performed by Qiang Zeng and Zhigang Liu. Zhigang Liu analyzed the data and Qiuyang Li contributed to the materials and tools. Qiang Zeng wrote this paper and also took part in Software and Formal analysis. Qiuyang Li retrieved all the text articles. All the work was performed under Prof. Liu's instructions.
Data curation: Zhigang Liu.
Formal analysis: Zhigang Liu.
Investigation: Zhigang Liu, Qiuyang Li.
Methodology: Qiuyang Li.
Software: Qiuyang Li.
Supervision: Zhigang Liu, Ting Liu.
Writing – original draft: Qiang Zeng.

References

[1] Rollig C, Knop S, Bornhauser M. Multiple myeloma. Lancet (Lond Engl) 2015;385:2197–208.
[2] Hanbali A, Hassanein M, Rasheed W, et al. The evolution of prognostic factors in multiple myeloma. Adv Hematol 2017;2017:4812637.
[3] Fonseca R, Abouzaid S, Bonafede M, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. Leukemia 2017.
[4] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
[5] Hussain SP, Amstad P, Raja K, et al. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Res 2000;60:3333–7.
[6] Proctor MJ, McMillan DC, Morrison DS, et al. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 2012;107:695–9.
[7] Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer 2014;134:2403–13.
[8] Gu XB, Tian T, Tian XJ, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis. Sci Rep 2015;5:12493.
[9] Yang Z, Gu JH, Guo CS, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival of epithelial ovarian cancer: a systematic review and meta-analysis of observational studies. Oncotarget 2017;8:
[10] Ethier JL, Desautels D, Templeton A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res BCR 2017;19:2.
[11] Wang J, Zhou X, Liu Y, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in diffuse large B-cell lymphoma: A meta-analysis. PloS One 2017;12:e0176008.
[12] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg (Lond Engl) 2010;8:336–41.
[13] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[14] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
[15] Azab B, Vivekanandarajah A, Naboush A, et al. Elevated neutrophil: lymphocyte ratio does not predict survival in multiple myeloma patients. Blood 2013;122:5336–15336.
[16] Wongrakpanich S, George G, Chaiwatcharayut W, et al. The prognostic significance of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in patients with multiple myeloma. J Clin Lab Anal 2016;30:1208–13.
[17] Li Y, Li H, Li W, et al. Pretreatment neutrophil/lymphocyte ratio but not platelet/lymphocyte ratio has a prognostic impact in multiple myeloma. J Clin Lab Anal 2016;31:
[18] Shi L, Qin X, Wang H, et al. Elevated neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio and decreased platelet-to-lymphocyte ratio are associated with poor prognosis in multiple myeloma. Oncotarget 2017;8:18792–801.
[19] Kelkitli E, Atay H, Cilingir F, et al. Predicting survival for multiple myeloma patients using baseline neutrophil/lymphocyte ratio. Ann Hematol 2014;93:841–6.
[20] Onec B, Okutan H, Albayrak M, et al. The predictive role of the neutrophil/lymphocyte ratio in survival with multiple myeloma: a single center experience. J Clin Lab Anal 2017;31:
[21] Kim DS, Yu ES, Kang KW, et al. Myeloma prognostic index at diagnosis might be a prognostic marker in patients newly diagnosed with multiple myeloma. Korean J Intern Med 2016.
[22] Romano A, Parrinello NL, Consoli ML, et al. Neutrophil to lymphocyte ratio (NLR) improves the risk assessment of ISS staging in newly diagnosed MM patients treated upfront with novel agents. Ann Hematol 2015;94:1875–83.

[23] van Kempen LC, de Visser KE, Coussens LM. Inflammation, proteases and cancer. Eur J Cancer (Oxf Engl 1990) 2006;42:728–34.
[24] Prabhala RH, Pelluru D, Fulciniti M, et al. Elevated IL-17 produced by TH17 cells promotes myeloma cell growth and inhibits immune function in multiple myeloma. Blood 2010;115:5385–92.
[25] DeNardo DG, Andreu P, Coussens LM. Interactions between lymphocytes and myeloid cells regulate pro- versus anti-tumor immunity. Cancer Metastasis Rev 2010;29:309–16.
[26] Egeblad M, Nakasone ES, Werb Z. Tumors as organs: complex tissues that interface with the entire organism. Dev Cell 2010;18:884–901.
[27] Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol 2010;11:889–96.
[28] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
[29] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436–44.