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META-ANALYSIS OF OBSERVATIONAL STUDIES IN EPIDEMIOLOGY

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Pretreatment Neutrophil to Lymphocyte Ratio as a Prognostic Predictor of Urologic Tumors

A Systematic Review and Meta-Analysis

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Abstract: The relationship between inflammation and tumor development and progression has been recognized in recent decades. NLR is an easily reproducible and widely used inflammatory response marker. The prognostic value of NLR for urologic tumors has been reported in succession. Here, we perform a systematic review and meta-analysis to summarize the association between the NLR and prognosis of urologic tumors.

We conducted a computerized search of PubMed, Embase, and ISI Web of Knowledge to identify clinical studies that had evaluated the association between the pretreatment NLR and prognosis in urologic tumors. Prognostic outcomes included overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), progression-free survival (PFS), and metastasis-free survival (MFS). We extracted and synthesized corresponding hazard ratios (HRs) and confidence intervals (CIs) using Review Manager 5.3 and STATA 13.

We identified 34 retrospective cohort studies and conducted the meta-analysis. The results showed that all OS, CSS, RFS, PFS, and MFS risks were significantly different between patients with an elevated NLR and those with a low NLR in various urologic tumors. A high NLR portended poor prognosis. However, no significance was observed for CSS in patients with renal cell carcinoma (HR = 1.38, 95% CI: 0.96–1.99).

Our meta-analysis suggests that NLR could be a prognostic predictor for urologic tumors. Patients with a high NLR were deemed to have a poor prognosis.

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Abbreviations: BC = bladder cancer, 95%CI = 95% confidence interval, CSS = cancer-specific survival, HR = hazard ratio, MFS = metastasis-free survival, NLR = neutrophil to lymphocyte ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, PCa = prostate cancer, PFS = progression-free survival, RCC = renal cell carcinoma, RFS = recurrence-free survival, UTUC = upper tract urothelial carcinoma.

INSTRUCTION

The relation between inflammation and tumor development and progression has been recognized in recent decades.[1,2] As a typical representative of inflammatory reactions, C-reactive protein (CRP) has been reported to be significantly associated with the prognosis of several cancers.[3–7] Other systematic inflammation markers have been validated as predictive in various types of cancer.[8–10] The neutrophil to lymphocyte ratio (NLR) is also a widely used inflammatory marker that is defined as the absolute neutrophil count divided by the absolute lymphocyte count and can be easily acquired from complete blood cell parameters.[11] It is a cheap and easily acquired marker compared with other inflammatory markers, such as CRP. Prognostic factors are essential for the stratification of cancer risk, medical treatment, and clinical research. Hence, we aimed to conduct a systematic review and meta-analysis to reveal the predictive effect of NLR on urologic tumor prognosis. Adding NLR to the inflammation-based prognostic score model may lead to improved patient management. This study is complied with Meta-analysis of Observational Studies in Epidemiology (MOOSE).[12]

MATERIALS AND METHODS

Search and Filtration Strategy

A systematic literature search of PubMed, Embase, and ISI Web of Knowledge (Web of Science + BIOSIS Previews + MEDLINE + SciELO Citation Index + KCI-Korean Journal Database) was conducted to retrieve clinical studies up to January 2015. We used Mesh terms and text words of neutrophil, lymphocyte, renal cancer, upper tract urothelial carcinoma, bladder cancer, prostate cancer, and urinary cancer to search for related articles (http://links.lww.com/MD/A446). Citations in the retrieved articles were also searched for any relevant studies. The initial selection was performed to eliminate obviously irrelevant articles and retain potentially relevant articles about NLR or urologic tumor prognostic risk factors by an analysis of the title and abstract by 2 independent investigators (YL and D-LS). Thereafter, the full text was reviewed according to eligibility criteria. For inclusion in this analysis, studies should contain an evaluation of the relationship between pretreatment NLR and urologic cancer prognosis. Studies with the following criteria were excluded: duplicated literature, overlapping patients, or duplicated data presented in conferences; no available data; and abstract only. Meeting abstracts were not included based on their lack of sufficient detailed

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information to assess the methodological bias or quality before the quantitative meta-analysis. All data and analyses were based on the previous published studies; thus, ethical approval and patient consent are waived.

Quality Assessment and Data Extraction

There are no standard quality assessment tools for prognostic studies in systematic reviews. The quality assessment of included studies was independently applied using the "Newcastle-Ottawa Scale (NOS)" for cohort studies,[13] which includes 3 domains with 8 items. Each item was awarded 1 to a maximum of 2 stars, and the total possible score was 9 stars. Studies with >5 stars were deemed as being of good quality. Data extraction and cross-checking were also performed by 2 independent investigators (YL and D-LS). Additionally, any disagreement or uncertainty was brought to a group discussion where a consensus was reached. Data extracted from these citations included the name of the first author, year of publication, tumor category, cutoff value of NLR, prognostic outcomes, sample size, region, statistic model, follow-up time, and NOS score. The data were extracted from the original articles. Situations lacking exact data were resolved in a number of ways: multivariate outcomes were preferred to univariate outcomes when both were provided, but if no multivariate results were presented, univariate outcomes were used instead; and given survival or mortality curves were used to calculate the estimated HR and 95% CI provided by Tierney et al[14] or the corresponding author was contacted to obtain the original data or results. Finally, before the meta-analysis, we rechecked the data and potential studies for overlapping patients to avoid an over-analysis.

Statistical Analysis

Review Manager 5.3 (The Cochrane Collaboration, Copenhagen) was used to carry out the synthesis analysis. Quantitative small-study effect detection with Egger regression intercept test was merely performed on outcomes with >10 studies by using STATA 13 (Stata Corp LP, College Station, TX).[15,16] Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated as the time-to-event effect estimate for the survival analysis. First, Cochran's Q test and Higgins I^2 statistic were performed for heterogeneity.[15] $P \geq 0.1$ and $I^2 \leq 50\%$ meant no significant heterogeneity, and thus, a fixed-effects model was used. Otherwise, a random-effects model was used to calculate pooled HRs. A sensitivity analysis was performed using the method of leave-one-out to leave-all-out of univariate or estimated outcomes to test the feasibility of the pooled results. If a small-study effect existed, a trim and fill method was also performed. A 2-tailed $P < 0.05$ was considered statistically significant. All the results are presented in the forest plots.

RESULTS

Eligible Studies and Quality Assessment

A total of 1017 articles were retrieved by the initial search strategy in PubMed, Embase, and ISI Web of Knowledge. Overall, 747 of 1017 articles were retained after removing duplicates. After reading the title and abstract, 550 articles were excluded for unrelated information, and the remaining 197 were screened by skimming the full-text. Then, 49 potential studies were screened and validated by reading the full-text. Finally, 34 studies[17–50] were included according to the inclusion and exclusion criteria.

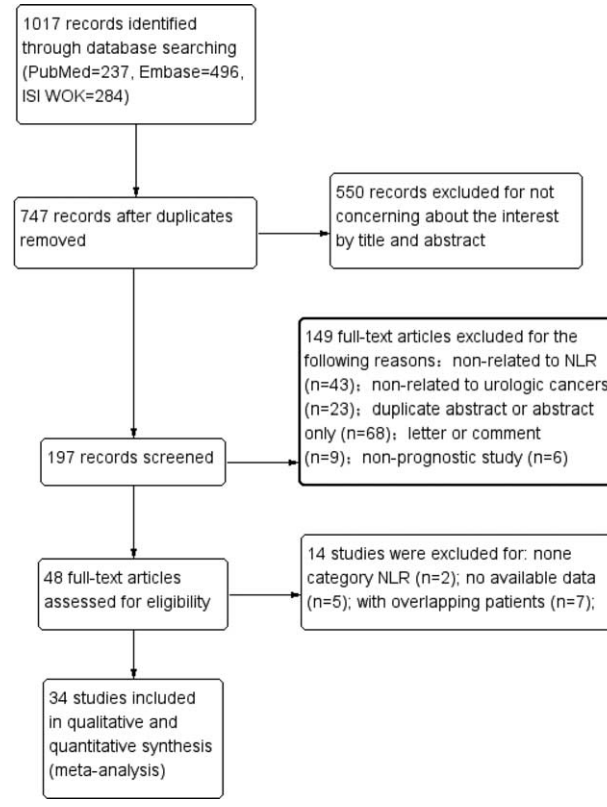

FIGURE 1. Literature screening flowchart.

Two studies were excluded for lacking dichotomous NLR variables,[51,52] 5 studies had no available data,[53–57] and 7 studies[58–64] included overlapping patients with 5 other studies.[19,21,29,38,42] The screening diagram is shown in Figure 1. Table 1 tabulates the characteristics and quality assessment of the included studies. The majority of the included studies were adjusted for potential confounders using the COX proportion hazard model, but the adjusted factors did not conform to each study. Univariate and estimated outcomes were acquired from the article when no multivariate outcomes were reported. The urological tumors were defined as renal cell carcinoma, upper tract urothelial carcinoma, bladder cancer, and prostate cancer.

Survival Outcome

Prognostic outcomes, including overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), progression-free survival (PFS), and metastasis-free survival (MFS), were quantitatively synthesized. The meta-analysis results are displayed in Figures 2–6. Heterogeneity is illustrated in each forest plot. In Figure 2, OS outcomes were available from 23 studies on renal cell carcinoma, upper tract urothelial carcinoma, bladder cancer, and prostate cancer. The synthesized hazard risk for each type of cancer consistently favored the low NLR patients (pooled HR: 1.79, 95% CI: 1.61–2.00 for renal cell carcinoma; pooled HR: 2.48, 95% CI: 1.31–4.70 for upper tract urothelial carcinoma; pooled HR: 1.68, 95% CI: 1.45–1.94 for bladder cancer; and pooled HR: 1.44, 95% CI: 1.28–1.62 for prostate cancer), which meant that patients with a higher NLR had a higher all-cause mortality risk than those with a low NLR.

TABLE 1. Characteristics and Quality Assessment Results of the Included Studies

Study	Country	Tumors	Duration	n	Age, y	Cutoff	Results	Estimated	Uni/Multi	Follow-up	NOS Score
Wang et al,[50] 2014	China	mRCC	2006.12–2011.3	41	Md = 53 (24–81)	4	PFS	No	Multi	NA	7
Viers et al,[49] 2014	USA	Localized ccRCC	1995–2008	827	Md = 65 (56–73)	4 (C)	CSS OS MFS	Yes	Uni	Md = 9.3 (IQR: 6.3–12.8 y)	8
Viers et al,[48] 2014	USA	BC	1994–2005	899	Md = 69 (IQR:62–76)	2.7 (C)	CSS OS	Yes	Uni	Md = 10.9 (IQR: 8.3–13.9 y)	8
Templeton et al,[47] 2014	Canada	mCRPC	2001.2–2011.11	357	Md = 71 (44–90)	3 (C)	OS	No	Multi	NA	7
Santoni et al,[42] 2015	Italy	mRCC	2005.1–2014.6	151	Md = 64 (29–88)	3	PFS OS	No	Multi	Md = 51.6 mo	8
Pichler et al,[41] 2013	Austria	nmccRCC	2000.1–2010.12	678	Mn = 63.7 ± 11.9	3.3	CSS OS MFS	No	Multi	Mn = 44 (0–130 mo)	8
Nuhn et al,[37] 2014	USA	mCRPC	1998.1–2010.12	238	Md = 68.3 (44.6–84.5)	3	OS	No	Multi	Md = 15 (1.5–90.2 mo)	8
Mano et al,[36] 2014	Israel	NMIBC	2003–2010	107	Md = 68 (IQR:61–78)	2.41, 2.43	PFS RFS	No	Multi	Md = 15 (23–51 mo)	
Luo et al,[35] 2014	Taiwan	UTUC	2005–2010	234	Mn = 67 ± 10.7	3	CSS MFS	No	Multi	Mn = 37.5 ± 22.1 mo	7
Lorente et al,[34] 2014	Multi–national	mCRPC	2007.1–2008.10	755	Md = 67 (IQR:62–73)	3 (C)	OS	No	Multi	Md = 12.8 (IQR: 7.8–16.9 mo)	7
Linton et al,[33] 2013	Multi–national	mCRPC	2007–2009	112	(54.1–88.7)	5 (C)	OS	No	Multi	NA	6
Krane et al,[31] 2013	USA	BC	2005.4–2011.10	68	Mn = 67.4 ± 10.1	2.5	CSS OS	No	Multi	NA	7
Hong et al,[28] 2013	China	RCC	2008–2011	129	Mn = 56 (IQR: 17–90)	5	OS	No	Multi	Md = 15 (1–39 mo)	7
Hermanns et al,[27] 2014	Canada	BC	1992.1–2012.12	424	Md = 70.1 (IQR: 60.6–76.3)	3	RFS CSS OS	No	Multi	MD = 58.4 (IQR: 21.3–94.5 mo)	8
Grivas et al,[25] 2014	Greece	RCC	2009–2011	114	Md = 63.5	2.7	PFS OS	No	Multi	Md = 69 (1–179 mo)	8
Fox et al,[23] 2013	Australia	Advanced RCC	2002.12–2005.2	362	Md = 62 (IQR: 19–84)	3	OS	No	Multi	NA	7
Forget et al,[22] 2013	Belgium	RCC	1993.7–2005.12	227	Mn = 63 ± 12	5	RFS OS	No	OS (Multi) RFS (Uni)	Md = 74.5 (IQR: 31–112 mo)	7
De Martino et al,[20] 2013	USA	nccRCC	1995–2012	281	Md = 63 (IQR: 54–72)	3.6 (C)	RFS	No	Uni	Md = 37 (IQR: 15–71 mo)	7
Dalpiaz et al,[19] 2014	Austria	nmUTUC	1990.9–2012.7	182	Mn = 69.3 ± 10.3	2.7	CSS OS	No	Multi	Mn = 45 (0–199 mo)	7
Cetin et al,[18] 2013	Turkey	mRCC	2008.2–2011.12	100	Md = 58 (IQR: 24–80)	3.04	PFS OS	No	Multi	Md = 15 (1–53 mo)	7
Dirican et al,[21] 2013	Turkey	mRCC	2006.3–2011.9	53	Md = 61 (IQR: 40–79)	3.4	OS	No	Multi	Md = 34 (5–58 mo)	7
Gunduz et al,[26] 2014	Turkey	mRCC	2009.5–2013.9	45	Md = 63 (IQR: 41–90)	2	PFS	No	Multi	Md = 23.9 mo	6
Sumbul et al,[44] 2014	Turkey	CRPC	2009–2013	33	Mn = 71.24 ± 7.34	3	PFS	Yes	Uni	NA	6
Ku et al,[32] 2015	Korea	BC	1999–2011	419	Md = 65.1 (IQR: 58.3–70.4)	5	CSS OS	No	Multi	Md = 37.7 (0.1–176.2 mo)	7
Sung et al,[45] 2014	Korea	UTUC	1994–2011	460	Md = 64 (IQR:55–72)	2.5	PFS	No	Multi	Md = 40.2 (IQR: 33–66.1 mo)	7
Park et al,[40] 2014	Korea	mccRCC	2005.12–2011.12	109	Md = 61 (IQR:49–67)	2.5	CSS	No	Multi	Md = 24 (IQR: 10–35 mo)	8
Azuma et al,[17] 2013	Japan	UTUC	1994–2008	137	Mn = 69.4 (IQR: 40–88)	2.5	RFS CSS	No	Multi	Md = 60.9 (1.9–187.3 mo)	8
Tanaka et al,[46] 2014	Japan	Localized UTUC	1993–2011	665	Md = 70 (IQR:62–76)	3	RFS CSS	No	Multi	Md = 28 (IQR: 14–57 mo)	7
Ohno et al,[39] 2014	Japan	mRCC	1990–2008	73	(34–88)	4	OS	No	Multi	Md = 11.7 (IQR: 1–114 mo)	7
Ohno et al,[38] 2010	Japan	nmRCC	1986–2000	192	Mn = 60 (IQR: 24–84)	2.7	RFS	No	Multi	Mn = 93 (IQR: 6–232 mo)	8
Kobayashi et al,[30] 2013	Japan	mRCC	2008.5–2012.6	58	Md = 64 (IQR: 53–81)	3.32	PFS OS	No	PFS (Uni) OS (Multi)	Md = 12 (IQR: 1.1–48.9 mo)	7
Gondo et al,[24] 2012	Japan	BC	2000.1–2009.9	189	Md = 70 (IQR: 38–85)	2.5	CSS	No	Multi	Md = 25.1 (IQR: 2.1–127.9 mo)	7
Sonpavde et al,[43] 2014	Multi–national	mCRPC	2008.7–2010.8	848	Md = 68 (IQR: 39–90)	5	PFS OS	No	Multi	NA	7
Keizman et al,[29] 2014	Multi–national	mRCC	2004.2–2013.3	244	Md = 63 (IQR: 22–87)	3	PFS OS	No	Multi	Md = 55 (IQR: 12–109 mo)	8

BC = bladder cancer, CRPC = Castration resistant prostate cancer, CSS = cancer specific survival, Cutoff row = 'C' in brackets meant that continuous variable was also analyzed, Md = median; Mn = mean, MFS = metastasis-free survival, Multi = multivariate analysis, NOS score = Newcastle-Ottawa Scale score, exceeding 5 meant relative good quality, OS = overall survival, PFS = progres-progression-free survival, RCC = renal cell carcinoma, RFS = recurrence-free survival, Uni = univariate analysis, UTUC = upper tract urothelial carcinoma. Brackets in Age row and Follow-up row was written range or mean ± standard deviation. Prefixes: n = non; m = metastatic; cc = clear cell; NMI = non-muscle invasive.

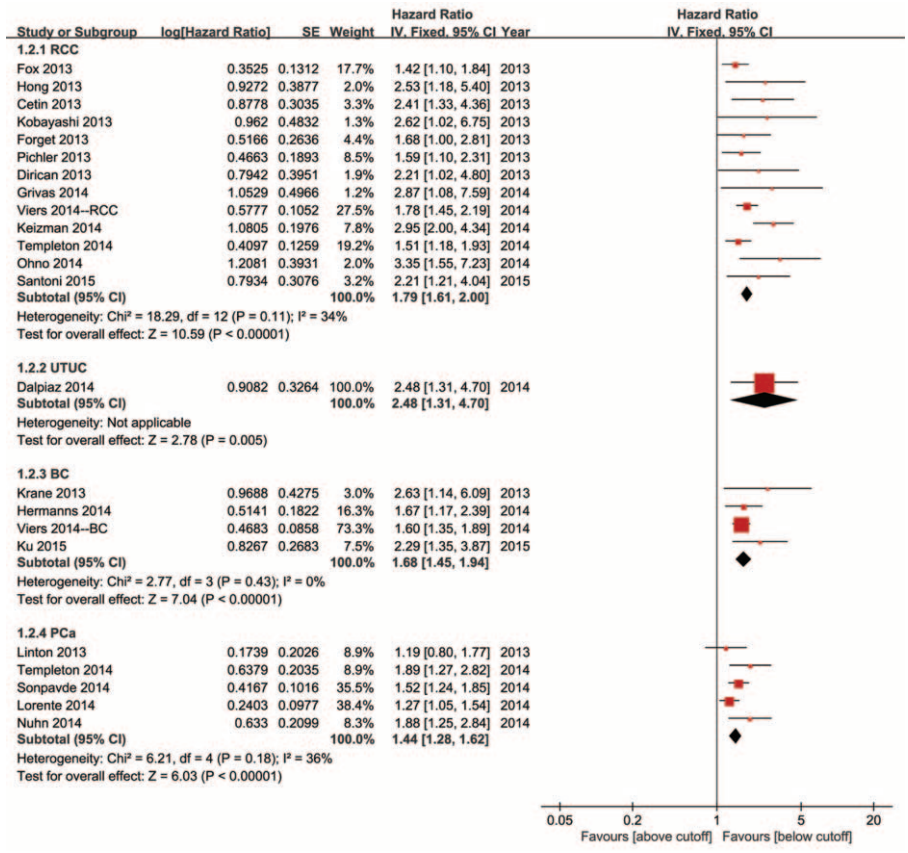

FIGURE 2. Overall survival based on the dichotomous NLR.

Figure 3 shows that 13 studies provided sufficient data on CSS outcome. Pooled results showed significant superiority of a low NLR in upper tract urothelial carcinoma (pooled HR: 2.52, 95% CI: 1.41–4.52) and bladder cancer (pooled HR: 1.70, 95% CI: 1.45–1.99) but not in renal cancer (pooled HR: 1.38, 95% CI: 0.96–1.99). No significant difference was observed in renal cell carcinoma for CSS. No study reported CSS in prostate cancer.

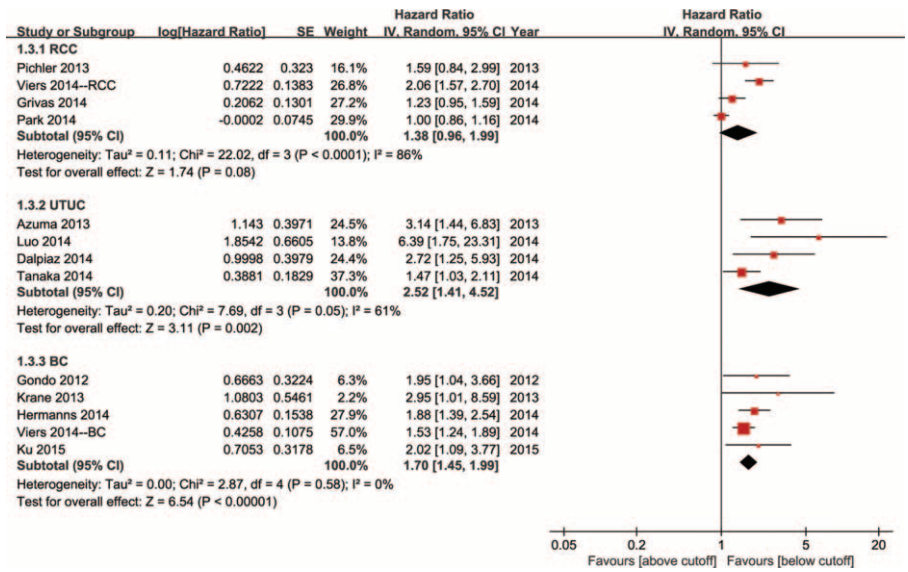

FIGURE 3. Cancer-specific survival based on the dichotomous NLR.

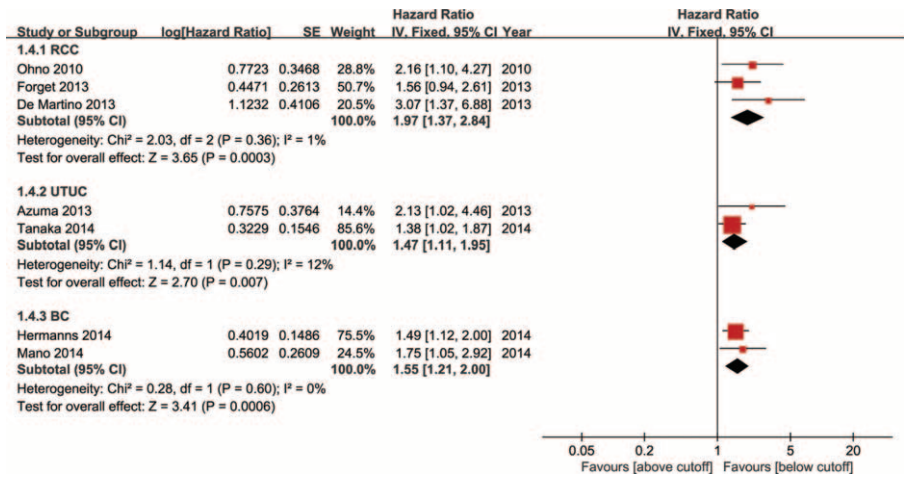

FIGURE 4. Recurrence-free survival based on the dichotomous NLR.

According to Figure 4, 7 studies reported RFS in renal cancer, upper tract urothelial carcinoma, and bladder cancer. Each pooled result showed a significantly higher risk of tumor recurrence in patients with a high NLR (pooled HR for renal cell carcinoma: 1.97, 95% CI: 1.37–2.84; pooled HR for upper tract urothelial carcinoma: 1.47, 95% CI: 1.11–1.95; pooled HR for bladder cancer: 1.55, 95% CI: 1.21–2.00). No study reported RFS for prostate cancer.

Similarly, in Figure 5, 7 studies provided PFS information in renal cancer: 1 study each in upper tract urothelial carcinoma and bladder cancer and 2 studies in prostate cancer. All the pooled HRs favored patients with a low NLR (pooled HR: 1.85, 95% CI: 1.24–2.77 in renal cell carcinoma; pooled HR: 1.70, 95% CI: 1.14–2.56 in upper tract urothelial carcinoma; pooled HR: 3.52, 95% CI: 1.33–9.33 in bladder cancer; and pooled HR: 1.29, 95% CI: 1.04–1.59 in prostate cancer).

In Figure 6, only 3 studies showed MFS in renal cancer and upper tract urothelial carcinoma, and the pooled results also favored patients with a low NLR (pooled HR: 1.60, 95% CI: 1.29–1.98 in renal cell carcinoma; pooled HR: 2.47, 95% CI: 1.16–5.29 in upper tract urothelial carcinoma). In summary, the majority of the synthesized results showed a significantly higher risk for patients with a high NLR in terms of prognostic outcome.

Small-Study Effect and Sensitivity Analysis

Quantitative small-study effect detection was conducted by Egger asymmetric test only for OS of renal cell carcinoma. The *P* value of the linear regression was 0.015. A significant small-study effect was observed, and the funnel plot was omitted, which potentially contributed to selective outcome reporting or publication bias. Thus, we conducted the trim

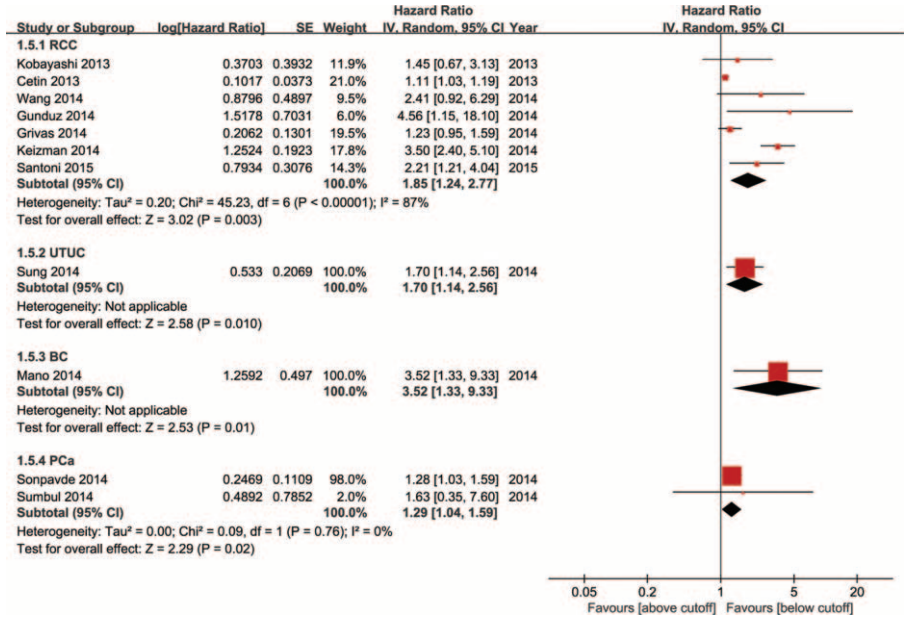

FIGURE 5. Progression-free survival based on the dichotomous NLR.

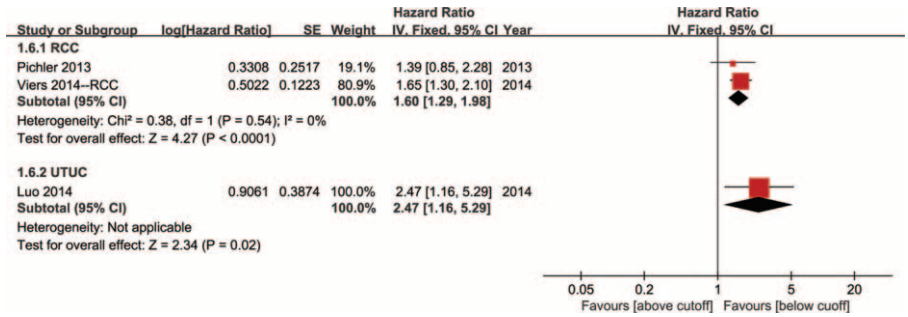

FIGURE 6. Metastasis-free survival based on the dichotomous NLR.

and fill method to test the stability of the pooled outcome. The HR was HR = 1.63 (1.48–1.80) for OS of renal cell carcinoma (Figure 7). The significance of the results was not altered. A sensitivity analysis of the univariate and estimated outcomes was also performed manually as described, and no pooled outcomes were altered except MFS in renal cell carcinoma (results were omitted).

DISCUSSION

Many studies have revealed the correlation between cancer and inflammation.[65–67] A hypothesis was proposed that chronic inflammation promotes tumor development and suppresses immune activity.[68–70] Hanahan et al[71] summarized an important hallmark of cancer is that cancer cells evade immunological attack from lymphocytes, macrophages, and natural killer cells, etc. High NLR represents systemic and local inflammation that provides a favorable microenvironment for tumor invasion and metastasis[72] and suppresses the host immune surveillance.[73] It is also associated with high infiltration of tumor-associated macrophages (TAMs)[74] that contribute to tumor growth, invasion, and evasion.[72,75] During inflammatory procedure, neutrophilia as an important component of inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells.[76,77] Additionally, neutrophils and macrophages produce tumor growth factors including epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), interleukin (IL)-6, and IL-8, which promote stimulating tumor microenvironment.[71,72] In addition, these cells may produce proangiogenic and proinvasive matrix-degrading enzymes, including matrix metalloproteinase,[78] elastases,[79] cysteine cathepsin proteases, and heparanase[80,81] that promote tumor metastasis.

Nonsteroidal anti-inflammatory drug (NSAID) consumption was confirmed to reduce the risk of colorectal cancer.[82] As a systematic inflammatory marker, NLR has been recognized to be associated with solid tumor prognosis.[83] Additionally, other inflammatory markers have been reported to be significantly associated with tumor development and prognosis. For example, CRP is correlated with urologic cancer prognosis,[3,84] and ESR and PLR are associated with renal cell carcinoma prognosis.[85] The Glasgow prognostic score is an inflammation-based prognostic score that can predict the prognosis of several types of cancer.[33,86,87]

NLR is an easily reproducible and widely available marker obtained from peripheral complete blood cell counts because cell separation has been widely applied. However, the feasibility of the NLR was seldom researched in the included studies,[48] and the volatility of the pretreatment NLR is not clear. Additionally, NLR changes followed by tumor changes during anticancer management are also essential to understand for its application as an indicator of treatment efficacy.

The majority of the included studies used the dichotomous NLR to determine the prognostic value. Several studies used both continuous and dichotomous NLR variables to determine the direct prognostic value. The continuous NLR also significantly portended the prognosis of urologic tumors in various studies.[21,35,37,43,48,49] The use of a continuous variable reflected a small intrinsic effect. However, the cutoff value seemed to adjust itself in various studies. The NLR threshold was calculated in each study to acquire the most significant effect, and the final significance of the outcomes seemed to be created, not intrinsic. Additionally, it is difficult to interpret and compare different studies when different cutoff values were used. Thus, we recommend using a continuous NLR variable rather than a categorical variable in future studies.

Our study has several limitations. First, all the included studies in our meta-analysis were retrospective. In observational studies, selection bias is impossible to avoid, although a multivariate analysis can control the confounding factors to a certain extent. Second, the NLR could be affected by different conditions, especially undetected diseases such as chronic infection, chronic disease, and autoimmune disorders, such as rheumatic disease. Third, we noted that the majority of the included studies did not report cancer-specific survival, which is an essential outcome for cancer survival analysis. Fourth, the reciprocal correlation between the NLR and other systemic inflammatory response markers should be noted, which

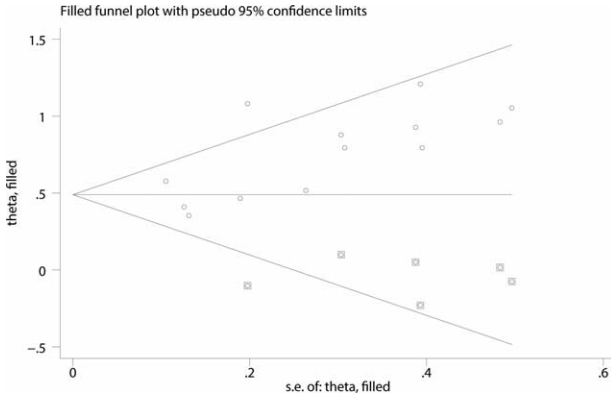

FIGURE 7. Trim and fill method for overall survival of renal cell carcinoma.

probably result in high co-linearity in a multivariate analysis and affect the parameter estimation of the Cox model. For instance, we may realize that CRP or the platelet lymphocyte ratio was correlated with NLR. Report bias was also observed while reading the full texts. Several studies did not present the univariate or multivariate HR for lack of significance; additionally, stepwise regression that would eliminate the nonsignificant factors was used, and only the significant factors were included.

CONCLUSIONS

Our meta-analysis summarized the published literature of the prognostic value of the NLR, and the pooled results suggested that the NLR was an effective prognostic predictor. Patients with a high NLR were deemed to have a poor prognosis.

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