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Prognostic role of the neutrophil–lymphocyte ratio in renal cell carcinoma: a meta-analysis

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ABSTRACT

Objective: Increasing evidence suggests that cancer-associated inflammation is associated with poor prognosis in patients with cancer. The role of the neutrophil–lymphocyte ratio (NLR) as a predictor in renal cell carcinoma (RCC) remains controversial. We conducted the meta-analysis to determine the association between NLR and clinical outcome of patients with RCC.

Methods and materials: Studies were identified from PubMed and EMBASE databases in March 2014. Meta-analysis was performed to generate combined HRs with 95% CIs for overall survival (OS) and recurrence-free/progress-free survival (RFS/PFS).

Results: 15 cohorts containing 3357 patients were included. Our analysis results indicated that elevated NLR predicted poorer OS (HR=1.82, 95% CI 1.51 to 2.19) and RFS/PFS (HR=2.18, 95% CI 1.75 to 2.71) in patients with RCC. These findings were robust when stratified by study region, sample size, therapeutic intervention, types of RCC and study quality. However, it differed significantly by assessment of the cut-off value defining 'elevated NLR' in RFS/PFS (p=0.004). The heterogeneity in our meta-analysis was mild to moderate.

Conclusions: Elevated NLR indicates a poorer prognosis for patients with RCC. NLR should be monitored in patients with RCC for rational risk stratification and treatment individualisation.

Strengths and limitations of this study

- Our study is the first systematic meta-analysis evaluating the relationship between elevated NLR and prognosis in patients with RCC. Our analysis provides substantial evidence that elevated NLR is significantly associated with poorer outcomes of patients with RCC. However, there were some limitations in our study.
- Firstly, the enrolled studies were retrospective cohort studies in which publication bias inevitably existed. We conducted a 'trim and fill' analysis to show that our conclusion was robust.
- Secondly, there was some heterogeneity in the included patient populations, so we confirmed the prognostic role of NLR in patients at different disease stages through subgroup analysis stratified by therapeutic intervention and types of RCC.
- Thirdly, we only searched limited databases (PubMed and EMBASE), which might weaken the estimating power of the pooled estimate.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2–3% of all malignant diseases in adults. It is the seventh most common cancer in men and the ninth in women worldwide.[1 2] The incidence of this cancer varies geographically and has increased over past decades owing to changes in the lifestyle and environment.[1] Despite a rapid development in surgical resection, immunotherapy and targeted therapy in RCC management, the long-term outcome is still not promising mainly due to common local recurrence, distal metastasis and limited drug response.[3] Hence, it is important to identify significant biomarkers, which can help clinicians to stratify patients in terms of prognosis and possibility of metastatic recurrence together with the tumour staging system, that is, the TNM staging system and Robson's staging system, and then set the most appropriate therapeutic strategy.

It is well recognised that the heterogeneity in clinical outcomes is determined by the oncological characteristics of the tumour itself and the host's response to the progressing malignancy.[4] Mechanisms involved in the interaction between cancer and inflammation were complicated. Inflammation impacts every single step of tumorigenesis, from tumour initiation to promotion and metastatic progression.[5] Recently, several serum biomarkers and haematological indices representative of inflammatory response, notably C reactive protein (CRP), fibrinogen, lymphocyte–monocyte ratio, neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio , have been demonstrated to be closely related to poor prognosis of patients with RCC.[6–9]

Generally speaking, lymphopenia well reflects impaired cell-mediated immunity, while neutrophilia represents a response to systematic inflammation.[5] So the NLR, defined as neutrophil counts divided by lymphocyte counts, is particularly noteworthy. Emerging evidences have shown that NLR gained its prognostic value in patients with colorectal cancer[10] and hepatocellular carcinoma.[11] Patients with RCC with elevated levels of pretreatment NLR may be more likely to gain a poorer clinical outcome.[12] However, the exact role of NLR in patients with RCC is not consistent in different studies due to the variance in study design, sample size and other factors. Some concluded a significant relationship between higher NLR and poorer prognosis, while others did not. Therefore, it is necessary to perform a meta-analysis to systematically and comprehensively understand the prognostic value of NLR in patients with RCC.

In this study, we aimed to assess the prognostic significance of high NLR for overall survival (OS) and recurrence-free (RFS)/progress-free survival (PFS) in patients with RCC by pooling outcomes from available data.

MATERIALS AND METHODS

Search strategy

A comprehensive literature search of the PubMed and EMBASE databases (up to March 2014) was conducted to identify relevant studies. The search strategy included terms for: "NLR" (eg, "neutrophil to lymphocyte ratio", "neutrophil lymphocyte ratio" and "neutrophil-lymphocyte ratio"), "RCC" (eg, "renal cancer", "renal carcinoma", "kidney cancer", clear cell carcinoma", "non-clear cell carcinoma", and "renal papillary carcinoma") and "prognosis" (eg, "recurrence", "survival" and "outcome"). Abstracts and information from conferences were collected independently. The reference list was also checked for additional articles. Only studies published in English were included.

Study inclusion criteria and definitions

Two independent authors (KH and LL) reviewed the retrieved studies and extracted data from each included study. Discrepancies were resolved by discussion. Studies included in our meta-analysis must meet the following criteria: (1) the diagnosis of RCC was based on the current clinical guidelines; (2) NLR was measured by serum-based methods before formal treatment; (3) studies reported HRs and 95% CIs for pretreatment NLR in OS and (or) RFS/PFS, or allowed for calculation from raw data contained in the article; (4) only primary data or data superseding earlier work were included, and articles were superior to conference abstracts.

NLR was defined as the serum absolute neutrophil count divided by lymphocyte count in peripheral blood.[8] OS was defined as the interval between medical treatment and death or last follow-up of patients. RFS (disease-free/metastasis-free survival, DFS/MFS) was measured from the date of curative treatment until the detection of tumour recurrence. PFS was calculated from the date of first treatment to radiologically or histologically confirmed disease progress. If all the patients in the individual study only received curative nephrectomy, the study was classified into the nephrectomy only subgroup, and the studies in which patients were mainly treated by non-surgical intervention were classified into the mixed therapies subgroup.

Data extraction

We extracted data including: (1) study information including name of first author, year of publication, study region, sample size, time of research; (2) patient characters including age, gender, follow-up period and treatment methods; (3) data about RCC including type, size, stage and distal metastasis; (4) NLR data and cut-off value of NLR; (5) survival data including OS and RFS/PFS.

Quality assessment of primary studies

Quality assessment of included studies was evaluated with the Newcastle-Ottawa quality assessment scale (NOS) range from 0 to 8 by two independent investigators (KH and LL). Studies with an NOS score $\geq$6 were assigned as high-quality studies. Studies from conference abstracts were defined as low-quality studies. Any inconsistencies were resolved by joint discussion.

Statistical analysis

HR greater than one indicated a poorer prognosis in patients with elevated NLR. Multivariate analysis for HR was superior to univariate analysis unless adjustment variables in multivariable analysis significantly interacted with the NLR level. As heterogeneity was detected among primary studies, meta-analysis was pooled using the random effects models with the DerSimonian Laird method.[13] Between-study heterogeneity was assessed using the Cochran Q test and I^2 statistic. The p value <0.10 was considered statistically significant for the Cochran Q test, I^2>50% indicating substantial heterogeneity between studies. Potential sources of heterogeneity were then investigated using subgroup analyses and meta-regression. All statistical tests were two sided and the significance level was set at 0.05. The possibility of publication bias was assessed using the Begg test and visual insection of a funnel plot.[14] We also performed the Duval and Tweedie non-parametric 'trim and fill' procedure to further assess the possible effect of publication bias in our meta-analysis.[15] All statistical manipulations were undertaken using the program STATA V.12.0 (Stata Corporation, College Station, Texas, USA).

RESULTS

Study characteristics

The initial search algorithm retrieved a total of 403 studies. After the title and abstract were reviewed, only 30 records were identified regarding the association of NLR and RCC (figure 1). After a full-text review, a total

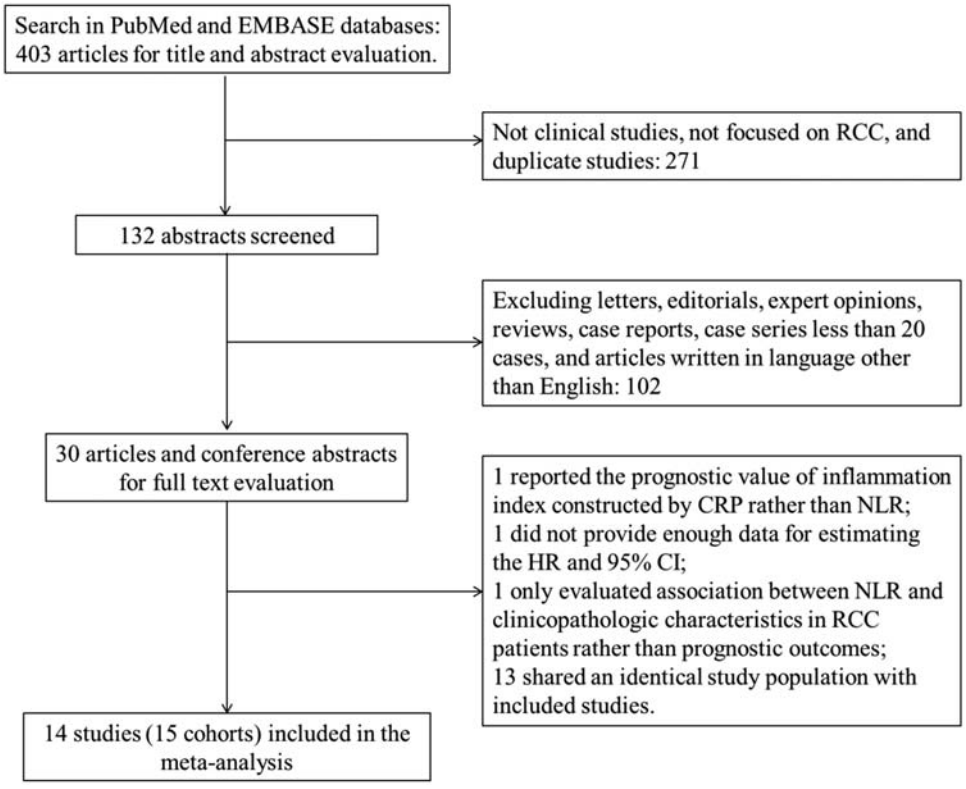

Figure 1 Flow chart of study selection process (CRP, C reactive protein; NLR, neutrophil–lymphocyte ratio; RCC, renal cell carcinoma).

of 14 retrospective studies[12 16–28] (15 cohorts) with 3357 RCCs were included in our meta-analysis. The study by Hatakeyama *et al*[28] reported the HR and 95% CI of two different cohorts separately. If the patients were overlapping or partially overlapping in several studies, only the study with the most complete data was included.

The basic features of the 14 studies were summarised in table 1. The median quality score of the involved studies was 6 (range 4–8). Eight studies were from western countries, including the USA, Italy, Belgium, Austria, Canada and Australia. The rest of the studies were from Turkey and Japan. Seven of these cohorts enrolled more than 200 patients and eight had less than 200 patients. Radical and partial nephrectomy as the only initial treatment for non-metastatic RCC was reported in four studies. Others were treated with mixed therapies, including nephrectomy, immunotherapy, targeted therapy and others. NLR was calculated using the white blood cell differentiated counts in all studies. In the study by Cetin *et al*,[21] some of the adjustment variables used in multivariate analysis was significantly associated with the NLR value, so HR and 95% CI from univariate analysis for PFS and OS were used in our meta-analysis.

NLR and OS in RCC

There were 13 cohorts presenting the data of pretreatment NLR and OS in patients with RCC. Elevated NLR was significantly associated with shorter OS (HR=1.82; 95% CI 1.51 to 2.19; p<0.001; figure 2), but there was evidence of moderate heterogeneity between studies (I^2=52.8%; p=0.013).

NLR and RFS/PFS in RCC

There were 10 cohorts presenting the data of pretreatment NLR and RFS/PFS in patients with RCC. A significant relationship between elevated pretreatment NLR and shorter RFS/PFS (HR=2.18; 95% CI 1.75 to 2.71; p<0.001; figure 3) with non-significant heterogeneity (I^2=25.0%; p=0.214) was detected according to our pooled estimates.

Subgroup analysis and meta-regression

To explore the heterogeneity, subgroup analysis and meta-regression were performed by study region (eastern vs western countries), sample size (≥200 vs <200), cut-off value defining 'elevated NLR' (>3 vs ≤3), therapeutic intervention (nephrectomy only vs mixed therapies), type of RCC (clear cell RCC vs non-clear cell RCC/NA; if the majority of patients were those with clear cell RCC in one study, the study was assigned to the clear cell RCC subgroup; NA: not applicable) and NOS score (≥6 vs <6). Subgroup analysis did not alter the prognostic role of NLR in OS or RFS/PFS substantially (table 2), except for stratified analysis[29] by cut-off

Table 1 Main characteristics of included studies in the meta-analysis

Study cohort	Year	Study region	Research time	Follow-up (month)	Treatment	M/F (n)	Age (years)	Tumour type	Distal metastasis (n)
De Martino *et al*[16]	2013	USA	1995–2012	Mean:49; IQR: (15–71)	Radical and partial nephrectomy	202/79	Mean: 63; IQR: (54–72)	Non-clear cell RCC	0
Ohno *et al*[17]	2012	Japan	1990–2008	Mean±SD: (75±54)	Radical and partial nephrectomy	186/64	Mean±SD: (61±12)	Clear cell RCC	0
Ohno *et al*[12]	2014	Japan	1990–2008	Mean (range): 20.6 (1–114)	Cytoreductive nephrectomy: Yes 48; No 25	61/12	Cytoreductive nephrectomy (median (range)): yes: 63 (38–79); No: 65 (34–88)	mRCC	73
Dirican *et al*[18]	2013	Turkey	2006–2011	Median:13.43; range: (1.97–40.91)	Nephrectomy, INF-α, sunitinib	17/6	Median (range): 59 (43–76)	Clear cell RCC:18; non-clear cell RCC: 5	23
Keizman *et al*[19]	2014	USA, Israel	2004–2013	NA	Sunitinib	186/92	Median: 63	mRCC	278
Santoni *et al*[20]	2013	Italy	2005–2013	Median:46.9; 95% CI (39.9 to 53.9)	Past nephrectomy: 91; second-line everolimus: 65; third-line everolimus: 32	70/27	Median:64; 95% CI (44 to 82)	mRCC	97
Cetin *et al*[21]	2013	Turkey	2008–2011	Median:15; range: (1–53)	First-line therapy with IFN-α; second-line therapy with VEGF targeted TKIs	76/24	Median (range): 58 (24–80)	mRCC: clear cell 73; non-clear cell 24; unknown 3	100: liver 17; bone 24; lung 65
Forget *et al*[22]	2013	Belgium	1993–2005	Median:74.5; IQR: (31–112)	Radical nephrectomy	71/156	Mean±SD: (63±12)	Clear cell 166; tubulopapillary 29; chromophobe 4; others 28	0
Pichler *et al*[23]	2013	Austria	2000–2010	Mean (range): 44 (0–130)	Curative radical or partial nephrectomy	Total: 678	Mean±SD: (63.7 ±11.9)	Clear cell RCC	0
Kobayashi *et al*[24]	2013	Japan	2008–2012	Median:12; range: (1.1–48.9)	Radical nephrectomy, cytokine therapy and sorafenib, sunitinib or mTORi	44/14	Median (range): 64 (53–81)	mRCC	26
Templeton *et al*[25]	2014	Canada	NA	NA	Targeted therapy	Total: 859	NA	RCC	NA
Fox *et al*[26]	2013	Australia	2002–2005	NA	As in EGF20001	268/94	Median (range): 62 (19–84)	mRCC	362
Huang *et al*[27]	2011	USA	2004–2011	Median: 35	Sunitinib	Total: 109	NA	mRCC	109
Hatakeyama *et al*[28]	2013	Japan	1995–2013	Surgery: 26; immunotherapy or IFN-α: 5	Radical nephrectomy with thrombectomy, immunotherapy or IFN-α	55/30	Mean±SD: (62±12)	RCC with tumour thrombus	14

Study cohort	NLR value	Cut-off	Elevated NLR (n)	Survival analysis	HR	Adjustment variables	NOS score
De Martino *et al*[16]	Median (IQR): 2.6 (1.9–3.6)	3.6	NA	RFS (DFS)	R (M)	Age, gender, ECOG performance score, pT stage, TNM group, grade, MVI, subtype, ANC, ALC	7
Ohno *et al*[17]	Mean±SD: 2.62±1.44	2.7	84	RFS	R (M)	Age, presentation, nephrectomy, tumour size, pT, grade, MVI, eastern Cooperative Oncology Group, neutrophil, lymphocytes	8
Ohno *et al*[12]	Mean±SD: 3.98±2.27	4	NA	OS	R (M)	Age, presentation mode, T stage, ECOG PS, Charlson comorbidity index, haemoglobin, LDH, corrected calcium, CRP, neutrophils, lymphocytes	5
Dirican *et al*[18]	NA	3	NA	OS, PFS	E (U)	/	4
Keizman *et al*[19]	NA	3	NA	OS, PFS	R (M)	Unclear	5
Santoni *et al*[20]	Median: 2.2	3	38	OS, PFS	R (M)	Gender, age, Motzer prognostic group, PFS on first-line therapy, neutrophilia	6
Cetin *et al*[21]	Median: 3.04	3.04	50	OS, PFS	R (U)	Age, tumour history, sex, haemoglobin level, red cell distribution width, albumin level, alkaline phosphatase level, PFS, site and number of metastatic organs, MSKCC score, dose reduction, second-line mTOR inhibitors	5
Forget *et al*[22]	Median (IQR): 3.01 (1.97–4.49)	5	52	OS, RFS	R (U)	Age, sex, node status, histological grade, stage	8
Pichler *et al*[23]	Mean±SD: 3.51±2.49	3.3	398	OS,RFS (MFS), CSS	R (M)	Age, gender, T stage, tumour grade, presence of tumour necrosis	7
Kobayashi *et al*[24]	Mean±SD: sorafenib: 4.25±3.01; sunitinib: 4.50±3.43; mTORi: 4.26±2.87	4.41	Sorafenib: 8; sunitinib: 23; mTORi: 16	OS, PFS	R (M) in OS, E (U) in PFS	Karnofsky PS, metastasis at presentation, number of metastases, prior nephrectomy, prior cytokine therapy, initial targeted agent, Heng's risk classification, pretreatment level of haemoglobin, platelet count, albumin, CRP, corrected calcium	5
Templeton *et al*[25]	Mean: 4.98; Median (95% CI) 3.51 (1.42 to 14.0)	2.5	622	OS	R (M), E (U)	6 international metastatic renal cell carcinoma database consortium (IMDC)	/
Fox *et al*[26]	NA	3	188	OS	R (M)	MSKCC and systemic inflammation markers	7
Huang *et al*[27]	NA	3	57	OS, PFS	R (U)	/	/
Hatakeyama *et al*[28]	Mean±SD: 3.1±1.5	NA	NA	OS	R (U, M)	Age, ECOG-performance status, gender, thrombus level, distant metastasis, underwent surgery, haemoglobin, serum albumin, eGFR, cholinesterase, serum sodium, correlated calcium, LDH, CRP, Charison comorbidity index, molecular targeted agents	5

HR obtained by reporting in text (R), or estimating (E).
ANC, absolute neutrophil count; ALC, absolute lymphocyte count; CSS; CRP, C reactive protein;
CSS, cancer-specific survival; DFS, disease free survival; ECOG, Eastern Cooperative Oncology Group; PS, ; EGF, epidermal growth factor; eGFR, estimated glomerular filtration rate; IFN-α, interferon α; LDH, lactate dehydrogenase; M/F, male, female; (M), the HR comes from multivariate analysis; MFS, metastasis free survival; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center; mTORi, inhibitor of the mammalian target of rapamycin; MVI, microvascular invasion; NA, not available; NLR, neutrophil–lymphocyte ratio; NOS, Newcastle-Ottawa Quality Scale; OS, overall survival; PFS, progress-free survival; PS, performance status; pT, primary tumour; RCC, renal cell carcinoma; RFS, recurrence-free survival; TNM, tumour, node, metastasis; TKIs, tyrosine-kinase inhibitor; (U), the HR comes from univariate analysis; VEGF, vascular endothelial growth factor.

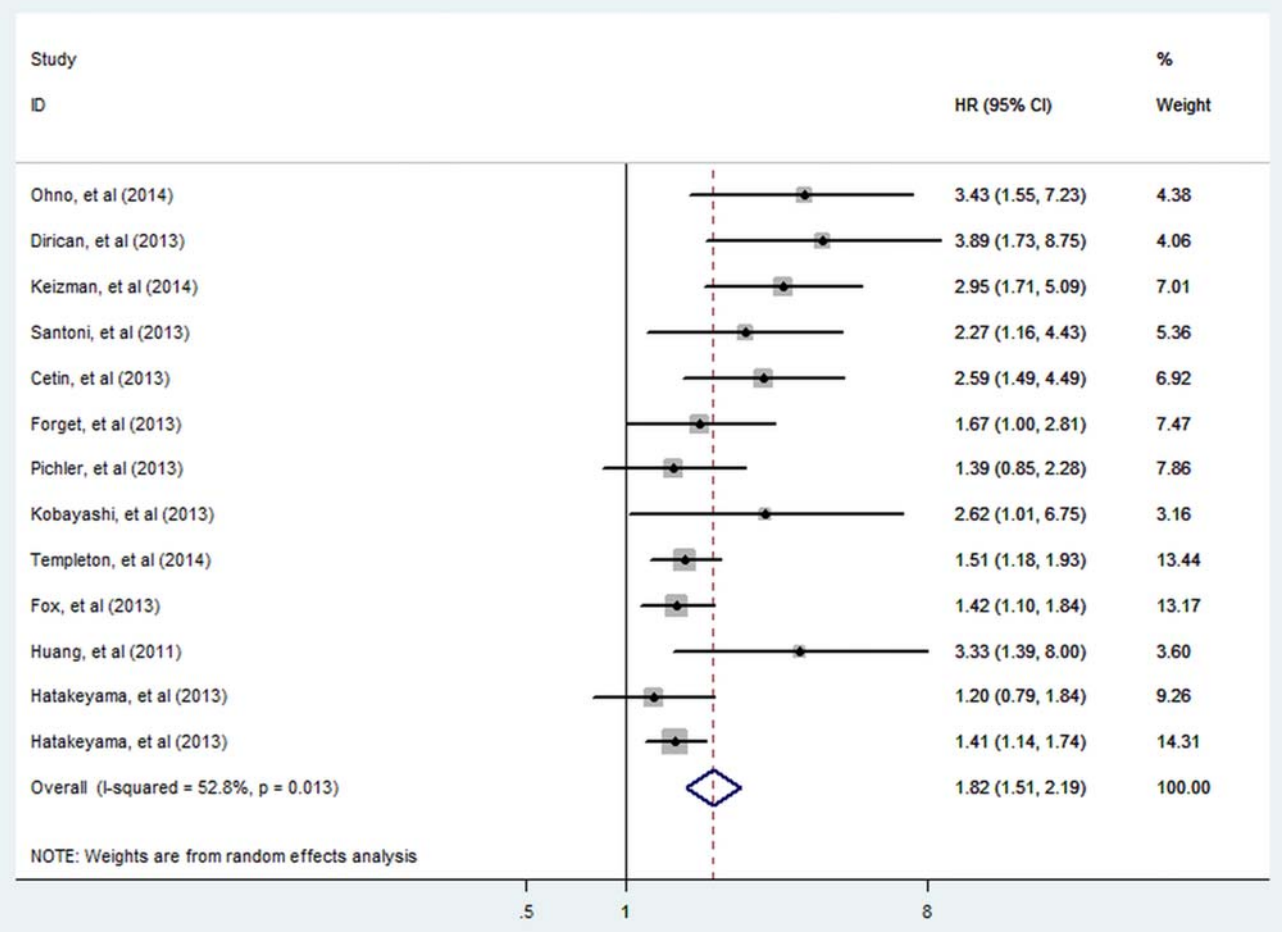

Figure 2 Meta-analysis of the association between elevated NLR and OS of RCC. Results are presented as individual and pooled HR and 95% CI (NLR, neutrophil-lymphocyte ratio; OS, overall survival; RCC, renal cell carcinoma).

of NLR in PFS/RFS. Meta-regression showed consistent results with subgroup analysis.

Sensitivity analyses

Each single cohort included in our meta-analysis was deleted every time to investigate the influence of individual data sets on the pooled HR. Results of sensitivity analyses indicated the robustness of our findings (data not shown).

Publication bias

Visual inspection of the Begg funnel plot revealed an asymmetry (p=0.001 in OS and p=0.003 in RFS/PFS; figure 4A), which raised the possibility of publication bias. As a result, we undertook sensitivity analysis using the trim and fill method, which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produced a symmetrical funnel plot (figure 4B). The pooled analysis incorporating the hypothetical studies continued to show a statistically significant association between elevated NLR and prognosis of patients with RCC (HR=1.54, 95% CI 1.25 to 1.88; p<0.001 in OS and HR=1.85, 95% CI 1.45 to 2.36; p<0.001 in RFS/PFS).

DISCUSSION

Since the TNM staging and Robson's staging system cannot estimate the outcomes of patients with RCC precisely or guide clinical practice appropriately, lots of patients in the same stage turned out to be quite different in prognosis. Therefore, the introduction of a new laboratory index as a supplementary item to the current RCC risk stratification system, which mainly focuses on the biological characteristics of the tumour itself, is really urgent for personalising the optimal treatment strategy.

As haematological tests are routinely conducted in patients with RCC before medical intervention, NLR acts as a simple, robust and convenient parameter of the inflammatory response. To the best of our knowledge, the present study is the first meta-analysis to systemically and comprehensively determine the exact relationship between elevated NLR and clinical outcomes of patients with RCC. We found that increased NLR has an unfavourable effect on OS and RFS/PFS in patients with

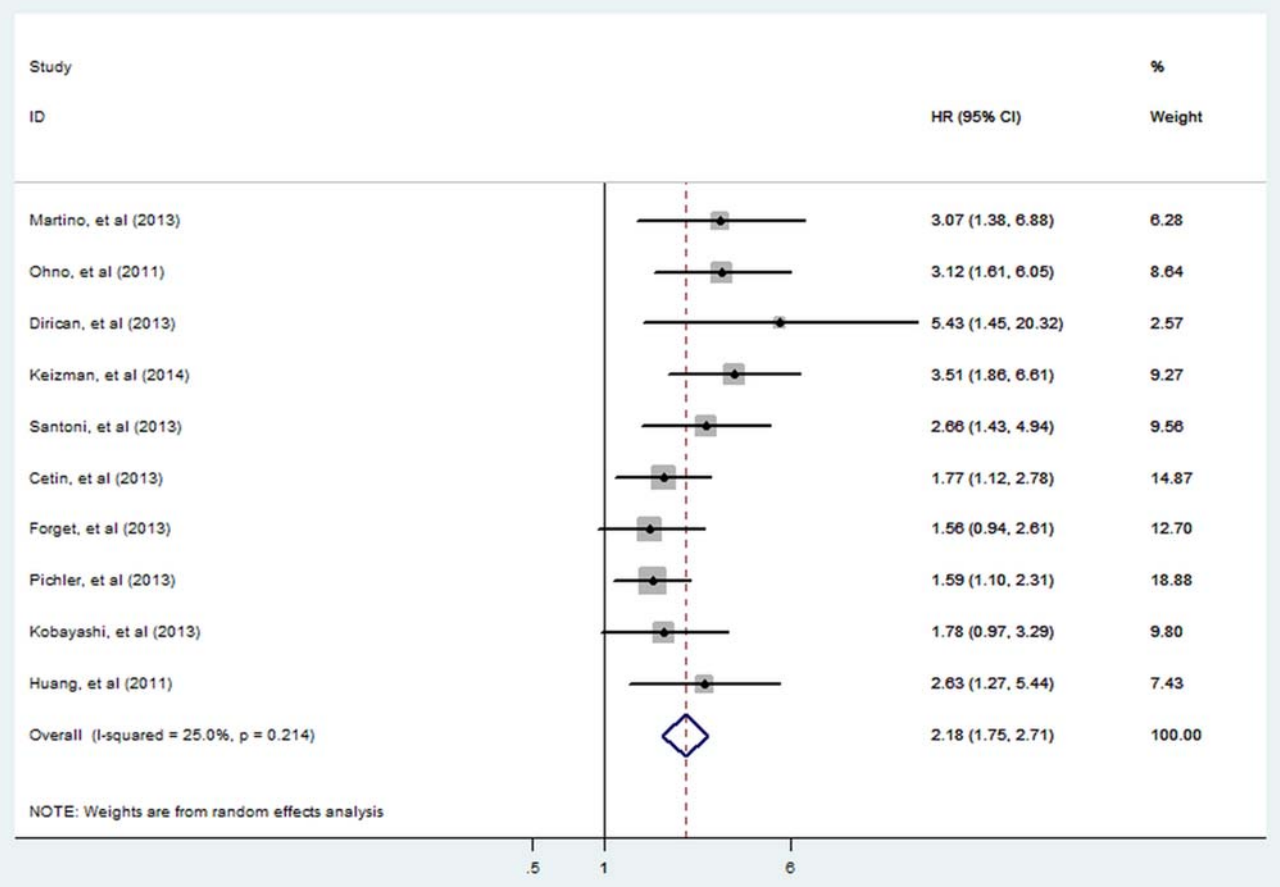

Figure 3 Meta-analysis of the association between elevated NLR and RFS/PFS of RCC. Results are presented as individual and pooled HR and 95% CI (NLR, neutrophil-lymphocyte ratio; RCC, renal cell carcinoma, RFS/PFS, recurrence-free/progress-free survival).

RCC. As there was heterogeneity existing among included studies, we also conducted subgroup analyses based on study region, sample size, cut-off value of NLR, therapeutic intervention, type of RCC and NOS score. No significant change was found according to subgroups. According to the results above, NLR is a promising prognostic biomarker to help physicians make appropriate treatment decisions and estimate clinical outcomes of patients with RCC.

We tried to figure out the source of heterogeneity observed among included studies by meta-regression and interaction revisited between subgroup estimates analyses. Although meta-regression did not find any possible reasons for heterogeneity in our meta-analysis for OS, sample size (p=0.132) and NOS score (p=0.083) according to results of interaction revisited between subgroup estimates may partially explain the interstudy heterogeneity. In the same way, we found that the NLR cut-off value (p=0.004) and tumour type (p=0.151) were responsible for the mild heterogeneity in RFS/PFS. It is inevitable that studies with a smaller sample size or lower NOS score are more likely to gain statistic heterogeneity. Authors of included studies defined the cut-off value of NLR, which best discriminated between good and poor survival, on the basis of different methods. A pooled analysis of studies with a cut-off value no more than 3 played a far more superior prognostic role in patients with RCC than studies with a cut-off value higher than 3. We suppose that some patients with poor outcomes were wrongly classified into the low-risk group if the cut-off was too large, which leads to an underestimate of the role of NLR in outcomes of patients with RCC. Although NLR is a sensitive prognostic indicator in retrospective researches, prospective clinical trials are still warranted to evaluate the exact value of NLR in predicting the prognosis of patients with RCC.

Although the funnel plot analysis showed some asymmetry in our meta-analysis suggesting the possibility of publication bias, the trim and fill sensitivity analysis did not change the general result, suggesting that the association of higher NLR value with a poorer prognosis of patients with RCC is not an artefact of unpublished negative studies.

In our analysis, subgroup defined as nephrectomy only also represented the patients' group with a clinically localised disease, while patients with metastatic disease were stratified to the mixed therapies subgroup. According to our results, elevated NLR was associated with both increased risk of future recurrence in localised disease and accelerated disease progression as well as

Table 2 Summary of subgroup analyses results

Analysis	N	References	Random effects model		Heterogeneity		Interaction revisited		Meta-regression
			HR (95% CI)	p Value	$I^{2\%}$	p Value	RHR (95% CI)	p Value	p Value
OS	12 (13)	12 18–28	1.82 (1.51 to 2.19)	<0.001	52.80				
Subgroup 1: study region									
Western countries	7	19 20 22 23 25–27	1.73 (1.39 to 2.14)	<0.001	39.80	0.126			
Eastern countries	5 (6)	12 18 21 24 28	2.06 (1.41 to 3.02)	<0.001	67.70	0.013	0.84 (0.54 to 1.30)	0.434	0.680
Subgroup 2: sample size									
≥200	5	19 22 23 25 26	1.60 (1.30 to 1.96)	<0.001	34.60	0.190			
<200	7 (8)	12 18 20 21 24 27 28	2.16 (1.55 to 3.01)	<0.001	62.80	0.013	0.74 (0.50 to 1.09)	0.132	0.305
Subgroup 3: cut-off value									
>3	5	12 21–24	2.04 (1.47 to 2.82)	<0.001	28.20	0.234			
≤3	6	18–20 25–27	2.07 (1.51 to 2.83)	<0.001	63.60	0.017	0.99 (0.63 to 1.55)	0.950	0.959
Subgroup 4: therapeutic intervention									
Nephrectomy only	2	22 23	1.52 (1.06 to 2.17)	0.022	0	0.615			
Mixed therapies	10 (11)	12 18–21 24–28	1.92 (1.54 to 2.38)	<0.001	60.10	0.005	0.79 (0.52 to 1.20)	0.275	0.424
Subgroup 5: NOS score									
≥6	4	20 22 23 26	1.51 (1.24 to 1.84)	<0.001	0	0.594			
<6	8 (9)	12 18 19 21 24 27 28	2.06 (1.51 to 2.70)	<0.001	65.10	0.003	0.73 (0.51 to 1.04)	0.083	0.313
Subgroup 6: tumour type									
Non-clear cell RCC/NA	7 (8)	12 19 20 24 25 27 28	1.87 (1.45 to 2.42)	<0.001	58.20	0.065			
Clear cell RCC	5	18 21–23 26	1.82 (1.32 to 2.50)	<0.001	53.70	0.067	1.03 (0.68 to 1.55)	0.891	0.859
PFS/RFS	10	16 17 18–24 27	2.18 (1.75 to 2.71)	<0.001	25				
Subgroup 1: study region									
Western countries	6	16 19 20 22 23 27	2.20 (1.64 to 2.96)	<0.001	35.70	0.169			
Eastern countries	4	17 18 21 24	2.23 (1.51 to 3.28)	<0.001	28.60	0.241	0.99 (0.61 to1.61)	0.957	0.958
Subgroup 2: sample size									
≥200	5	16 17 19 22 23	2.25 (1.56 to 3.24)	<0.001	51.30	0.084			
<200	5	18 20 21 24 27	2.15 (1.62 to 2.85)	<0.001	0	0.444	1.05 (0.66 to 1.66)	0.847	0.950
Subgroup 3: cut-off value									
>3	5	16 21–24	1.74 (1.39 to 2.17)	<0.001	0	0.675			
≤3	5	17 18–20 27	3.08 (2.24 to 4.24)	<0.001	0	0.867	0.56 (0.38 to 0.83)	0.004	0.020
Subgroup 4: therapeutic intervention									
Nephrectomy only	4	16 17 22 23	2.00 (1.40 to 2.85)	<0.001	39.90	0.172			
Mixed therapies	6	18–21 24 27	2.36 (1.79 to 3.12)	<0.001	11.40	0.342	0.85 (0.54 to 1.33)	0.472	0.404
Subgroup 5: NOS score									
≥6	5	16 17 20 22 23	2.08 (1.53 to 2.84)	<0.001	33.60	0.197			
<6	5	14 18 19 21 27	2.35 (1.67 to 3.32)	<0.001	26.50	0.245	0.89 (0.56 to 1.41)	0.605	0.622
Subgroup 6: tumour type									
Non-clear cell RCC/NA	5	16 19 20 24 27	2.62 (1.94 to 3.53)	<0.001	0	0.644			
Clear cell RCC	5	17 18 21–23	1.92 (1.42 to 2.59)	<0.001	34.10	0.194	1.36 (0.89 to 2.09)	0.151	0.112

Subgroup analyses for OS and RFS/PFS were performed by study region (eastern vs western countries), sample size (≥200 vs <200), cut-off value (>3 vs ≤3), therapeutic intervention (nephrectomy only vs mixed therapies), type of RCC (Clear cell RCC vs Non-clear cell RCC/NA) and NOS score (≥6 vs <6). Interactions revisited of estimates between subgroups and meta-regression were also applied to figure out heterogeneity among studies.
N, number of studies (cohorts); NOS, Newcastle-Ottawa Quality Scale; OS, Overall survival; PFS/RFS, progress-free/recurrence-free survival; RCC/NA, renal cell carcinoma not applicable; RHR, Ratio of HR.

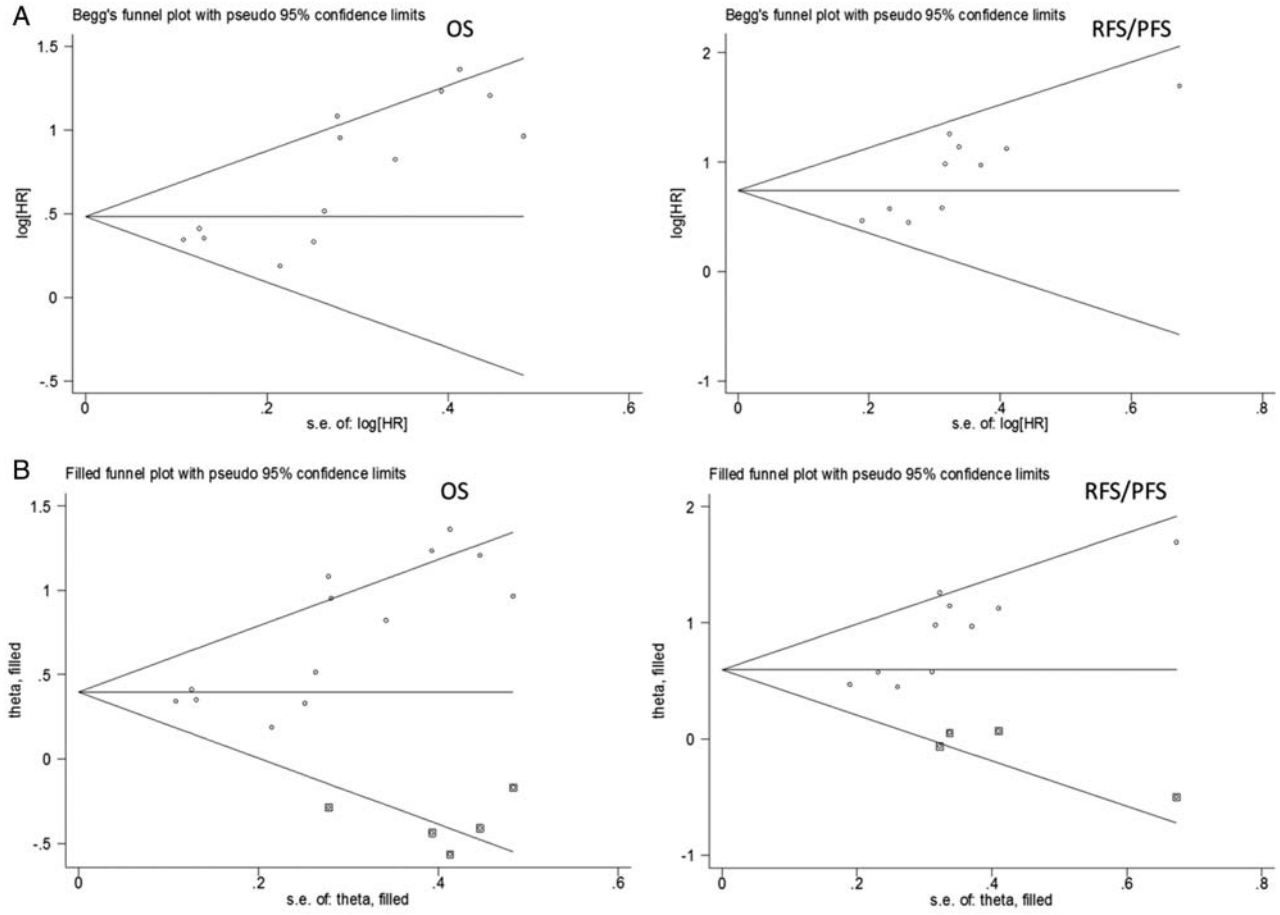

Figure 4 Funnel plots without and with trim and fill. The pseudo 95% CI is computed as part of the analysis that produces the funnel plot, and corresponds to the expected 95% CI for a given SE (OS, overall survival; RFS/PFS, recurrence-free/progress-free survival).

shortened OS in advanced disease. Therefore, we should take a more active attitude in treatment of patients with RCC, for example, consolidation and maintenance therapy, cytoreductive nephrectomy, especially in patients with elevated NLR before treatment.

Owing to limited data from available studies, we did not conduct pooled analysis on the correlation between elevated NLR and the clinicopathological parameters of RCC. As reported in several studies,[21 23 26] high NLR was closely correlated with more malignant tumour characteristics, as well as changed blood and biological indexes. Taking all these into consideration, there may be a significant association between NLR and pathological features and other known risk factors of RCC, but more clinical studies focusing on these relationships are still needed to help us better understand how NLR influences prognosis of patients with RCC.

There are other laboratory markers of systemic inflammation reaction besides NLR, such as CRP[30] and modified Glasgow prognostic score,[31 32] playing a prognostic role in patients with RCC. What is more, gene polymorphisms[33] and biological markers[34 35] are also suggested to be predictors of prognosis in patients with RCC. However, factoring in cost-effective analysis and accessibility, NLR stands out for its low-economic costs and wide availability even in primary hospitals. The results of our meta-analysis encourage the routine monitoring of NLR to predict recurrence, progress and survival outcomes in patients with RCC, irrespective of the detailed therapeutic intervention, stage and type of tumour and geographic region.

NLR is an inflammation marker. High NLR represents systemic and local inflammatory response to tumour, which provides a favourable microenvironment for tumour invasion and metastasis.[5] As traditional chemotherapy and immunotherapy are with limited benefit in metastatic RCC, treatment remains quite a challenge for clinicians. Now targeted therapy on vascular endothelial growth factor (VEGF) is generally recognised as the first choice for metastatic patients.[36] A major difficulty in developing anti-VEGF therapies is tumour intrinsic refractoriness and the emergence of treatment-induced resistance. Tumour-associated macrophages (TAMs) are identified to mediate refractoriness to anti-VEGF treatment recently.[37] TAMs promote systemic neutrophilia via secreting cytokines such as interleukin 6,[38] so high NLR is associated with high infiltration of TAMs.[39] However, tumours can produce immunosuppressive cytokines and

reduce cytotoxic T-lymphocyte infiltration.[40] Thus, NLR not only reflects system immune status but also a tumour microenvironment which favours tumour invasion and suppresses the host immune surveillance. Hence, NLR acts as an effective prognostic predictor for VEGF-targeted therapy in metastatic patients.

In conclusion, the present meta-analysis demonstrates that elevated NLR is closely associated with poorer prognostic outcome of patients with RCC in different stages. NLR is a widely available, robust and convenient predictor. It helps to figure out patients with high risk and not sensitive to targeted therapy for whom clinicians are urged to adjust the management accordingly. Further research on the best therapeutic schedule fitted with patients of high NLR is needed in the near future.

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