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

Kaimin Hu,¹ Lixia Lou,² Juan Ye,² Suzhan Zhang¹

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.

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.¹ 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.⁴ 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 systemic inflammation. 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. Patients with RCC with elevated levels of pretreatment NLR may be more likely to gain a poorer clinical outcome. 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. 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 ≥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. Between-study heterogeneity was assessed using the Cochran Q test and I² statistic. The p value <0.10 was considered statistically significant for the Cochran Q test, I²>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 insenction of a funnel plot. 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. 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 405 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
of 14 retrospective studies\textsuperscript{12, 16–28} (15 cohorts) with 3357 RCCs were included in our meta-analysis. The study by Hatakeyama \textit{et al.}\textsuperscript{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 \textit{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 \textit{et al.}\textsuperscript{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; \textit{p}<0.001; \textit{figure 2}), but there was evidence of moderate heterogeneity between studies ($I^2=52.8\%$; \textit{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; \textit{p}<0.001; \textit{figure 3}) with non-significant heterogeneity ($I^2=25.0\%$; \textit{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 ($\geq 200$ vs $<200$), cut-off value defining ‘elevated NLR’ ($>3$ vs $\leq 3$), 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 ($\geq 6$ vs $<6$). Subgroup analysis did not alter the prognostic role of NLR in OS or RFS/PFS substantially (\textit{table 2}), except for stratified analysis\textsuperscript{29} by cut-off...
<table>
<thead>
<tr>
<th>Study cohort</th>
<th>Year</th>
<th>Study region</th>
<th>Research time</th>
<th>Follow-up (month)</th>
<th>Treatment</th>
<th>M/F (n)</th>
<th>Age (years)</th>
<th>Tumour type</th>
<th>Distal metastasis (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohno et al</td>
<td>2012</td>
<td>Japan</td>
<td>1990–2008</td>
<td>Mean±SD: (78±54)</td>
<td>Radical and partial nephrectomy</td>
<td>186/64</td>
<td>Mean±SD: (61±12)</td>
<td>Clear cell RCC</td>
<td>0</td>
</tr>
<tr>
<td>Ohno et al</td>
<td>2014</td>
<td>Japan</td>
<td>1990–2008</td>
<td>Mean (range): 20.6 (1–114)</td>
<td>Cytoreductive nephrectomy: Yes 48; No 25</td>
<td>61/12</td>
<td>Cytoreductive nephrectomy (median (range)): yes: 63 (38–79); No: 65 (34–88)</td>
<td>mRCC</td>
<td>73</td>
</tr>
<tr>
<td>Dirican et al</td>
<td>2013</td>
<td>Turkey</td>
<td>2006–2011</td>
<td>Median:13.43; range: (1.97–40.91)</td>
<td>Nephrectomy, INF-α, sunitinib</td>
<td>17/6</td>
<td>Median (range): 59 (43–76)</td>
<td>Clear cell RCC; non-clear cell RCC: 5</td>
<td>23</td>
</tr>
<tr>
<td>Keizman et al</td>
<td>2014</td>
<td>USA, Israel</td>
<td>2004–2013</td>
<td>NA</td>
<td>Sunitinib</td>
<td>186/92</td>
<td>Median: 63</td>
<td>mRCC</td>
<td>278</td>
</tr>
<tr>
<td>Santoni et al</td>
<td>2013</td>
<td>Italy</td>
<td>2005–2013</td>
<td>Median:46.9; 95% CI (39.9 to 53.9)</td>
<td>Past nephrectomy: 91; second-line everolimus: 65; third-line everolimus: 32</td>
<td>70/27</td>
<td>Median:64; 95% CI (44 to 82)</td>
<td>mRCC</td>
<td>97</td>
</tr>
<tr>
<td>Cetin et al</td>
<td>2013</td>
<td>Turkey</td>
<td>2008–2011</td>
<td>Median:15; range: (1–53)</td>
<td>First-line therapy with IFN-α, second-line therapy with VEGF targeted TKIs</td>
<td>76/24</td>
<td>Median (range): 58 (24–80)</td>
<td>mRCC: clear cell 73; non-clear cell 24; unknown 3</td>
<td>100: liver 17; bone 24; lung 65</td>
</tr>
<tr>
<td>Forget et al</td>
<td>2013</td>
<td>Belgium</td>
<td>1993–2005</td>
<td>Median:74.5; IQR: (31–112)</td>
<td>Radical nephrectomy</td>
<td>71/156</td>
<td>Mean±SD: (63±12)</td>
<td>Clear cell 166; tubulopapillary 29; chromophobe 4; others 28</td>
<td>0</td>
</tr>
<tr>
<td>Pichler et al</td>
<td>2013</td>
<td>Austria</td>
<td>2000–2010</td>
<td>Median (range): 44 (0–130)</td>
<td>Curative radical or partial nephrectomy</td>
<td>Total: 678/44/14</td>
<td>Mean±SD: (63.7±11.9)</td>
<td>Clear cell RCC</td>
<td>0</td>
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<tr>
<td>Kobayashi et al</td>
<td>2013</td>
<td>Japan</td>
<td>2008–2012</td>
<td>Median:12; range: (1.1–48.9)</td>
<td>Radical nephrectomy, cytokine therapy and sorafenib, sunitinib or mTORi</td>
<td>44/14</td>
<td>Median (range): 64 (53–81)</td>
<td>mRCC</td>
<td>26</td>
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<tr>
<td>Templeton et al</td>
<td>2014</td>
<td>Canada</td>
<td>NA</td>
<td>NA</td>
<td>Targeted therapy</td>
<td>Total: 859/268/94</td>
<td>Median (range): 62 (19–84)</td>
<td>mRCC</td>
<td>362</td>
</tr>
<tr>
<td>Fox et al</td>
<td>2013</td>
<td>Australia</td>
<td>2002–2005</td>
<td>NA</td>
<td>As in EGF20001</td>
<td>109/55/30</td>
<td>Mean±SD: (62±12)</td>
<td>mRCC</td>
<td>109</td>
</tr>
<tr>
<td>Huang et al</td>
<td>2011</td>
<td>USA</td>
<td>2004–2011</td>
<td>Median: 35</td>
<td>Sunitinib</td>
<td>Total: 109</td>
<td>Mean±SD: (62±12)</td>
<td>RCC with tumour thrombus</td>
<td>14</td>
</tr>
<tr>
<td>Hatakeyama et al</td>
<td>2013</td>
<td>Japan</td>
<td>1995–2013</td>
<td>Surgery: 26; immunotherapy or IFN-α: 5</td>
<td>Radical nephrectomy with thrombectomy, immunotherapy or IFN-α</td>
<td>Total: 109</td>
<td>Mean±SD: (62±12)</td>
<td>RCC with tumour thrombus</td>
<td>14</td>
</tr>
<tr>
<td>Study cohort</td>
<td>NLR value</td>
<td>Cut-off</td>
<td>Elevated NLR (n)</td>
<td>Survival analysis</td>
<td>HR</td>
<td>Adjustment variables</td>
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<tr>
<td>De Martino et al</td>
<td>Median (IQR): 2.6 (1.9–3.6)</td>
<td>3.6</td>
<td>NA</td>
<td>RFS (DFS)</td>
<td>R (M)</td>
<td>Age, gender, ECOG performance score, pT stage, TNM group, grade, MVI, subtype, ANC, ALC</td>
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<td></td>
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<tr>
<td>Ohno et al</td>
<td>Mean±SD: 2.62±1.44</td>
<td>2.7</td>
<td>84</td>
<td>RFS</td>
<td>R (M)</td>
<td>Age, presentation, nephrectomy, tumour size, pT, grade, MVI, eastern Cooperative Oncology Group, neutrophil, lymphocytes</td>
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<tr>
<td>Ohno et al</td>
<td>Mean±SD: 3.98±2.27</td>
<td>4</td>
<td>NA</td>
<td>OS</td>
<td>R (M)</td>
<td>Age, presentation mode, T stage, ECOG PS, Charlson comorbidity index, haemoglobin, LDH, corrected calcium, CRP, neutrophils, lymphocytes</td>
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<tr>
<td>Dirican et al</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>OS, PFS</td>
<td>E (U)</td>
<td>Age, sex, motzer prognostic group, PFS on first-line therapy, neutrophilia</td>
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<tr>
<td>Keizman et al</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>OS, PFS</td>
<td>R (M)</td>
<td>Gender, age, stage, presence of tumour necrosis</td>
<td></td>
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<tr>
<td>Santoni et al</td>
<td>Median: 2.2</td>
<td>3</td>
<td>38</td>
<td>OS, PFS</td>
<td>R (M)</td>
<td>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</td>
<td></td>
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<tr>
<td>Cetin et al</td>
<td>Median: 3.04</td>
<td>3.04</td>
<td>50</td>
<td>OS, PFS</td>
<td>R (U)</td>
<td>Age, sex, node status, histological grade, stage</td>
<td></td>
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<tr>
<td>Forget et al</td>
<td>Median (IQR): 3.01 (1.97–4.49)</td>
<td>5</td>
<td>52</td>
<td>OS, RFS</td>
<td>R (U)</td>
<td>Age, gender, T stage, tumour grade, presence of tumour necrosis</td>
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<tr>
<td>Pichler et al</td>
<td>Mean±SD: 3.51±2.49</td>
<td>3.3</td>
<td>398</td>
<td>OS, RFS (MFS), CSS</td>
<td>R (M)</td>
<td>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, 6 international metastatic renal cell carcinoma database consortium (IMDC)</td>
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<tr>
<td>Kobayashi et al</td>
<td>Mean±SD: sorafenib:4.25±3.01; sunitinib: 4.50±3.43; mTORi: 4.26±2.87</td>
<td>4.41</td>
<td>Sorafenib: 8; sunitinib: 23; mTORi: 16</td>
<td>OS, PFS</td>
<td>R (M) in OS, E (U) in PFS</td>
<td>Age, gender, T stage, tumour grade, presence of tumour necrosis</td>
<td></td>
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<tr>
<td>Templeton et al</td>
<td>Mean: 4.98; Median (95% CI): 3.51 (1.42 to 14.0)</td>
<td>2.5</td>
<td>622</td>
<td>OS</td>
<td>R (M), E (U)</td>
<td>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, 6 international metastatic renal cell carcinoma database consortium (IMDC)</td>
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<tr>
<td>Fox et al</td>
<td>NA</td>
<td>3</td>
<td>188</td>
<td>OS</td>
<td>R (M)</td>
<td>MSKCC and systemic inflammation markers</td>
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<tr>
<td>Huang et al</td>
<td>NA</td>
<td>3</td>
<td>57</td>
<td>OS, PFS</td>
<td>R (U)</td>
<td>Age, ECOG-performance status, gender, thrombus level, distant metastasis, underwent surgery, haemoglobin, serum albumin, eGFR, cholinesterase, serum sodium, correlated calcium, LDH, CRP, Charlson comorbidity index, molecular targeted agents</td>
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<tr>
<td>Hatakeyama et al</td>
<td>Mean±SD: 3.1±1.5</td>
<td>NA</td>
<td>NA</td>
<td>OS</td>
<td>R (U, M)</td>
<td>Age, ECOG-performance status, gender, thrombus level, distant metastasis, underwent surgery, haemoglobin, serum albumin, eGFR, cholinesterase, serum sodium, correlated calcium, LDH, CRP, Charlson comorbidity index, molecular targeted agents</td>
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<td></td>
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</tbody>
</table>

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, progression-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.
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 RCC.
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 underestimation 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

<table>
<thead>
<tr>
<th>Analysis</th>
<th>N</th>
<th>References</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>Heterogeneity</th>
<th>Interaction revisited</th>
<th>Meta-regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>12 (13)</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.82 (1.51 to 2.19)</td>
<td>&lt;0.001</td>
<td>0.84 (0.54 to 1.30)</td>
<td>0.434</td>
<td>0.680</td>
</tr>
<tr>
<td>Subgroup 1: study region</td>
<td>Western countries</td>
<td>7</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.73 (1.39 to 2.14)</td>
<td>&lt;0.001</td>
<td>0.98 (0.61 to 1.57)</td>
<td>0.924</td>
</tr>
<tr>
<td>Subgroup 2: sample size</td>
<td>≥200</td>
<td>6</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.60 (1.30 to 1.96)</td>
<td>&lt;0.001</td>
<td>0.84 (0.54 to 1.30)</td>
<td>0.434</td>
</tr>
<tr>
<td>Subgroup 3: cut-off value</td>
<td>≥3</td>
<td>6</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.92 (1.54 to 2.38)</td>
<td>&lt;0.001</td>
<td>0.89 (0.57 to 1.39)</td>
<td>0.633</td>
</tr>
<tr>
<td>Subgroup 4: therapeutic intervention</td>
<td>Nephrectomy only</td>
<td>5</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.60 (1.30 to 1.96)</td>
<td>&lt;0.001</td>
<td>0.84 (0.54 to 1.30)</td>
<td>0.434</td>
</tr>
<tr>
<td>Subgroup 5: NOS score</td>
<td>≥65</td>
<td>5</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.51 (1.24 to 1.84)</td>
<td>&lt;0.001</td>
<td>0.96 (0.61 to 1.57)</td>
<td>0.924</td>
</tr>
<tr>
<td>Subgroup 6: tumour type</td>
<td>Non-clear cell RCC/NA</td>
<td>5</td>
<td>19 20 22 23 24 25 26 27</td>
<td>1.87 (1.45 to 2.42)</td>
<td>&lt;0.001</td>
<td>0.84 (0.54 to 1.30)</td>
<td>0.633</td>
</tr>
</tbody>
</table>

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 (≥65 vs <65). 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, Progression-free survival; RFS, Recurrence-free survival; RCC-NOS, renal cell carcinoma not applicable; RHR, Ratio of HR.
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, 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 and modified Glasgow prognostic score, playing a prognostic role in patients with RCC. What is more, gene polymorphisms and biological markers 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. 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. 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. TAMs promote systemic neutrophilia via secreting cytokines such as interleukin 6, so high NLR is associated with high infiltration of TAMs. However, tumours can produce immunosuppressive cytokines and

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).
reduce cytotoxic T-lymphocyte infiltration. Thus, NLR not only reflects systemic 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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Prognostic role of the neutrophil–lymphocyte ratio in renal cell carcinoma: a meta-analysis

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