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MINIREVIEWS

Neutrophil-lymphocyte ratio in the management and prediction of outcomes in renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is one of the ten most common malignancies. The prognosis of RCC is poor when the disease is in advanced stages, with five-year survival of less than 10%. However current assessment approaches are limited in their ability to prognosticate and guide therapeutic decision-making. Cellular-mediated inflammatory response is increasingly being recognised to have an important role in carcinogenesis of RCC. Various inflammatory markers have been found to identify patients with RCC at high risk of recurrence and predict survival. Neutrophil-lymphocyte ratio (NLR) is a simple and inexpensive inflammatory marker that has been shown to be of value in the assessment of patients with RCC. An elevated pretreatment NLR has been found to be associated with reduced overall survival, recurrence-free survival and progress-free survival and risk of recurrence in localized RCC. In addition, lower pretreatment NLR has been demonstrated to be associated with better clinical response to systemic therapy including vascular endothelial growth factor inhibitors, among patients with metastatic RCC. However, NLR has not been found to differentiate whether small renal masses of less than 40 mm are benign or malignant. Further research is needed to determine the cut-offs for NLR to predict different clinical outcomes and how post-treatment NLR can be used. In addition, more work is also needed to evaluate combining NLR with other biomarkers in a model to predict patients' clinical outcome or response to treatment for RCC.

Key words: Neutrophil-lymphocyte ratio; Prognosis; Renal cell carcinoma; Survival

Core tip: Neutrophil-lymphocyte ratio (NLR) is a simple and inexpensive inflammatory marker that is useful in the assessment of patients with renal cell carcinoma (RCC). An elevated pretreatment NLR has been found to be associated with reduced overall, recurrence-free and progress-free survival as well as risk of recurrence

in localized RCC. In addition, a lower pretreatment NLR has been demonstrated to be associated with better clinical response to systemic therapy. NLR is a promising marker for risk stratification in RCC and guiding treatment choices.

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INTRODUCTION

Renal cell carcinoma (RCC) ranks as the third most common urological cancer but is associated with the highest mortality rate. The overall 5-year survival is 74% but decreases to 5%-10% in advanced stage RCC[1]. Approximately 30% of patients with RCC present initially with regional or distant metastases[1]. Of patients who have localized RCC treated with nephrectomy with curative intent, about 25% experience relapses in distant sites such as lymph nodes, lungs, liver, bone and brain[2].

RCC is a heterogenous group of cancers arising from nephrons, with different histopathological and molecular subtypes. Clear-cell is the most common subtype, making up about 70% of RCC[1]. Papillary RCC is the second most common subtype (10%). Other types of RCC include chromophobe (5%), collecting carcinoma, renal medullary carcinoma and carcinoma with translocation (each less than 1%).

In the past two decades, there is an increasing knowledge on prognostic factors of localized and metastatic RCC. Patient prognosis depends on multiple variables including patient-specific characteristics, histopathological features of the malignancy and response to treatment. Several predictive models have been developed by combining different prognostic features and are valuable tools for patient counselling, treatment decision-making and trial design. Two prognostic systems have been validated for RCC, namely The University of California, Los Angeles (UCLA) Integrated Staging System score for localized RCC and the Memorial Sloan Kettering Cancer Centre (MSKCC) score for metastatic RCC[3,4]. These systems take into the consideration the Eastern Cooperative Oncology Group status, serum calcium, hemoglobin, lactate dehydrogenase, Fuhrman grade and tumor size but none have included neutrophil-lymphocyte ratio (NLR).

Multiple potential biomarkers from plasma, neoplasm and host tissues have been investigated in metastatic RCC but all still await validation for clinical use[5]. Further research is needed to assess whether a combination of classical prognostic factors with molecular features and information from gene and protein expression profiling can increase the predictive accuracy of the current prognostic models.

The NLR is an important marker of inflammation and has been found to be an independent prognostic factor for several cancers such as colon, ovaries, pancreas, urothelium and kidneys[6]. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a complete blood examination with differentials. As NLR is an easily measured, reproducible and inexpensive marker of inflammation, consideration should be given to its clinical use in RCC. However, there is still much to learn about how NLR can be utilised in the evaluation of RCC.

The purpose of this review is to summarise current knowledge about the use of NLR in the management and prognostic evaluation of patients with RCC at various stages of the disease.

SEARCH STRATEGY AND SELECTION CRITERIA

We searched the PubMed and EMBASE databases (between 1 Jan 1990 and 30 Sep 2017) with the search terms: "NLR" ("neutrophil to lymphocyte ratio", "neutrophil lymphocyte ratio" and "neutrophil-lymphocyte ratio"), "RCC" ("renal cancer", "renal carcinoma" and "kidney cancer") and "prognosis" ("outcome", "survival" and "recurrence"). We mainly selected publications in the last 10 years, but did not exclude highly regarded and widely referenced older publications. We also searched the reference lists of articles identified by this search strategy, and selected those that were judged relevant. Only studies published in English were considered.

INFLAMMATION AND RCC

There is growing evidence to support an interactive mechanism between inflammation and malignancy. Inflammation can influence tumorigenesis in many ways, beginning with tumor initiation and progressing to tumor promotion and metastasis[7].

An elevated NLR indicates both local and systemic inflammatory response to tumor, which in turn facilitates tumor invasion and metastases[7]. Neutrophil may act as a malignancy-promoter, stimulating tumorigenesis, suppressing antineoplastic responses, participate in mechanisms for metastatic spread, effect angiogenesis, and promote leakage of malignant cells into the circulation, which all lead to promoting the progression of malignancy[8,9]. On the other hand, low lymphocyte counts is associated with tumor cells escaping from tumor-inflitrating lymphocytes[10].

Increase in inflammatory cytokines have been observed in the plasma of patients with elevated NLR (greater than 5)[11,12]. These cytokines are thought to have an important role in progression of malignancy[11,12]. For example, an increased NLR was associated with an elevation in interleukin-17 (IL-17) and increase

Table 1 Summary of key studies on the association of neutrophil-lymphocyte ratio and clinical outcomes of patients with renal cell carcinoma

References	Type of study	Study numbers (patient numbers)	Main findings
Hu *et al*[15]	Meta-analysis	15 (3357)	Elevated pretreatment NLR was significantly associated with reduced OS (HR: 1.82; 95%CI: 1.51-2.19; $P < 0.001$) and RFS/PFS (HR: 2.18; 95%CI: 1.75-2.71; $P < 0.001$) in RCC
Luo *et al*[16]	Meta-analysis	13 (3684)	Elevated pretreatment NLR was significantly associated with reduced OS (HR: 1.79; 95%CI: 1.51-2.00; $P < 0.00001$), RFS (HR: 1.97; 95%CI: 1.37-2.84; $P = 0.0003$) and PFS (HR: 1.85; 95%CI: 1.24-2.77; $P = 0.003$). However, NLR was not associated with CSS
Boissier *et al*[17]	Meta-analysis	15 (3512)	Higher pretreatment NLR was significantly associated with reduced OS in locally advanced or metastatic RCC (HR: 1.55; 95%CI: 1.36-1.76; $P < 0.00001$). In localized RCC, an elevated NLR was associated with reduced PFS
Na *et al*[23]	Meta-analysis	9 (1091)	In patients with metastatic RCC receiving tyrosine kinase inhibitors, elevated pretreatment NLR was associated with reduced OS (HR: 1.93; 95%CI: 1.35-2.77; $P = 0.0003$) and PFS (HR: 2.12; 95%CI: 1.42-3.17; $P = 0.0002$)
Grimes *et al*[18]	Systematic review	4 (2474)	All studies found an elevated NLR to be associated with a poorer prognosis in RCC. Elevated NLR were associated with a lower PFS, lower CSS (HR: 1.02, $P = 0.009$) and lower OS (HR: 1.02-1.6)

CI: Confidence interval; CSS: Cancer-specific survival; HR: Hazard ratio; NLR: Neutrophil-lymphocyte ratio; PFS: Progression-free survival; OS: Overall survival; RCC: Renal cell carcinoma; RFS: Recurrence-free survival.

in tumor-associated macrophages[11]. A high NLR is associated with increased infiltration of tumor-associated macrophages[13]. Infiltration of these macrophages have been identified to mediate reduced efficacy of anti-VEGF therapy[14].

NLR can be measured at different stages of RCC. In this review, pretreatment NLR refers to neutrophil and lymphocyte measurements in a pretreatment blood test, either before nephrectomy or any systemic therapy. Postnephrectomy NLR refers to this ratio being assessed after nephrectomy.

PRETREATMENT NLR AND OVERALL SURVIVAL

In a meta-analysis of 13 cohorts, elevated pretreatment NLR was significantly associated with shorter overall survival (OS) [hazard ratio (HR): 1.82; 95% confidence interval (CI): 1.51-2.19; $P < 0.001$] (Table 1)[15]. In this analysis, there was evidence of moderate heterogeneity between studies ($I^2 = 52.8\%$; $P = 0.013$). In subgroup analyses of studies involving clear cell RCC (5 studies), non-clear cell RCC (7 studies), nephrectomy only (2 studies) and mixed therapies (10 studies), elevated pretreatment NLR was also associated with a shorter OS[15]. In addition, the use of NLR cut-off values of above or less than 3 were both associated with shorter OS among patients with a higher NLR. Similar findings were also reported in another meta-analysis by Luo *et al*[16], involving patients with RCC.

In another meta-analysis of three studies, surprisingly, NLR was not significantly associated with OS in patients with localized RCC[17]. However, this result was probably limited by the inclusion of a smaller number of studies. When data of 7 studies evaluating NLR in locally advanced or metastatic RCC were pooled together, these studies showed a high NLR was associated independently with reduced OS (HR: 1.55; 95%CI: 1.36-1.76; $P < 0.00001$) (Table 1)[17]. In a systematic review, two studies demonstrated elevated NLR was associated with a lower OS in patients with localized RCC undergoing nephrectomy with curative intent (HR of 1.02 and 1.6 with *P*-value of 0.004 and 0.022, respectively)[18].

These studies consistently indicate that NLR has a role in predicting the OS of patients with RCC, with the evidence being more reproducible in people with metastatic disease.

PRETREATMENT NLR AND RECURRENCE-FREE OR PROGRESS-FREE SURVIVAL

Using data from 10 cohorts, one meta-analysis found that elevated NLR before treatment is associated with a shorter recurrence free survival (RFS) or progress-free survival (PFS) (HR: 2.18; 95%CI: 1.75-2.71; $P < 0.001$) (Table 1)[15]. No significant heterogeneity was detected in this pooled estimation ($I^2 = 25.0\%$; $P = 0.21$). In subgroup analyses of studies involving clear cell RCC (5 studies), non-clear cell RCC (5 studies), nephrectomy only (4 studies) and mixed therapies (6 studies), elevated pretreatment NLR was also associated with a shorter PFS/RFS[15]. In addition, the use of NLR cut-off values of above or less than 3 were both associated with lower PFS/RFS among patients with a higher NLR.

In another meta-analysis of 3 studies, metastatic or locally advanced RCC, elevated NLR was an independent factor associated with PFS (HR: 3.19; 95%CI: 2.23-4.57; $P < 0.00001$) (Table 1)[17]. No significant heterogeneity was observed in this analysis ($I^2 = 0\%$; $P = 0.78$). In a meta-analysis by Luo *et al*[16], a higher NLR was associated with a significantly lower RFS (HR: 1.97; 95%CI: 1.37-2.84; $P = 0.0003$) and PFS (HR: 1.85; 95%CI: 1.24-2.77; $P = 0.003$). However, significant high heterogeneity was found between these studies in the PFS analysis ($I^2 = 87\%$; $P < 0.00001$).

In a systematic review, two studies demonstrated that an elevated NLR was associated with a lower PFS in patients with localized RCC undergoing nephrectomy with curative intent[18]. In the same review, one study found that an elevated NLR was associated with a lower cancer-specific survival (HR: 1.02; $P = 0.009$).

PRETREATMENT NLR AND CANCER-SPECIFIC OR METASTASIS-FREE SURVIVAL

In a meta-analysis of four studies of patients with RCC, no significant difference in cancer-specific survival (CSS) between those with low and elevated NLR (HR: 1.38; 95%CI: 0.96-1.99; $P = 0.08$) (Table 1)[16]. However, there was significant heterogeneity in this analysis ($I^2 = 86\%$; $P < 0.0001$). In the same systematic review, the pooled results of two studies showed that patients with a lower NLR had a better metastasis-free survival (MFS) in RCC (HR: 1.60; 95%CI: 1.29-1.98; $P < 0.0001$)[16]. However, this finding was based only on two studies.

Only a small number of studies have evaluated the relationship between NLR and CSS or MFS in RCC. This is an area where more future studies need to focus on.

PRETREATMENT NLR AND RISK OF RECURRENCE IN LOCALIZED RCC

In a meta-analysis of 6 studies of patients with localized RCC, an elevated NLR on diagnosis was associated significantly with an increased risk of recurrence (HR: 1.63; 95%CI: 1.15-2.29; $P = 0.006$)[17]. All the patients in the included studies had either radical or partial nephrectomy. The threshold of NLR among these studies ranged between 2.7 and 5.0. However, a significantly high heterogeneity between studies was detected ($I^2 = 82\%$; $P < 0.0001$).

PRETREATMENT NLR AND CLINICOPATHOLOGICAL FEATURES OF RCC

In a study by de Martino *et al*[19], a NLR greater than 2.7 was significantly associated with metastatic lymph node involvement in non-clear cell RCC ($P = 0.04$). In the same study, a preoperative NLR of more than 2.7 was an independent risk factor for recurrence of RCC but not for OS. Therefore, a higher NLR is associated with a more aggressive presentation of RCC.

In a multi-centre cohort analysis involving 1284 patients with non-metastatic RCC, a higher NLR (cut-off of 3.7) was associated with larger tumors ($P < 0.001$), higher T stage ($P < 0.001$), sarcomatoid differentiation ($P = 0.004$) and tumor necrosis ($P < 0.001$). These findings support the observation that NLR is associated with poor prognostic features in RCC.

NLR AT DIFFERENT TIME-POINTS OF RCC

There is a paucity of studies evaluating the association between NLR and clinical outcomes in patients with RCC after having nephrectomy. Postnephrectomy NLR has been investigated in one study and was found to be associated with an increased risk of recurrence[20]. This study evaluated NLR in 250 people with RCC at three time-points: before nephrectomy, after nephrectomy and at the time of recurrence[20]. For patients who had recurrence, an increase of NLR above 2.7 was observed.

In a retrospective study of 1199 patients from the International Metastatic Renal Cell Carcinoma Database Consortium and 4350 patients from 12 prospective randomized trials, an early decline of NLR was associated with more favorable outcomes, while an increase was associated with poorer outcomes[21]. Compared with no change (decrease < 25% to increase < 25%), a rise in NLR at week 6 by 25%-50% and > 75% was associated with poor OS (HR: 1.55; 95%CI: 1.10-2.18 and HR: 2.31; 95%CI: 1.64-3.25, respectively), poor PFS (HR: 1.46; 95%CI: 1.04-2.03 and HR: 1.76; 95%CI: 1.23-2.52, respectively). However, this study was limited by its retrospective design.

NLR AND SYSTEMIC THERAPY FOR METASTATIC RCC

Cytotoxic chemotherapy and hormonal therapy have no clinical effect on metastatic RCC. Since 2005, other systemic therapies such as antiangiogenic drugs targeting the vascular endothelial growth factor (VEGF) and its receptors, mechanistic target of rapamycin (mTOR) inhibitors and immune checkpoint inhibitor, have been found to improve clinical outcomes of patients with metastatic RCC[22].

One meta-analysis of nine studies, with a total of 1091 participants, have evaluated the association between pretreatment NLR and OS or PFS for treatment of metastatic RCC with tyrosine kinase inhibitors[23]. The pooled analyses found that a high NLR was associated with a lower OS (HR: 1.93; 95%CI: 1.35-2.77; $P = 0.0003$) and PFS (HR: 2.12; 95%CI: 1.42-3.17; $P = 0.0002$). In both these analyses, a high level of heterogeneity between studies were observed ($I^2 = 82\%$; $P < 0.00001$ and $I^2 = 88\%$; $P = 0.0002$, respectively).

The effectiveness of antibodies against the programmed cell death protein (PD-1) receptor and its ligand 1 (PD-L1) in the treatment of metastatic RCC has highlighted the importance of the immune system[24]. Further work is needed to determine if NLR can help to identify patients who may benefit from such immunotherapy.

NLR IN SMALL RENAL MASSES

The widespread use of advanced abdominal and pelvic imaging has resulted in increasing findings of small,

incidental renal masses. About 13%-27% of abdominal imaging incidentally find a renal mass[25,26]. In general, a small renal mass is defined as a contrast-enhancing mass of 40 mm or less on abdominal imaging[26]. Of small renal masses, about 80% are cancerous and 20% are benign[27]. It is challenging to differentiate small benign renal masses from those which are malignant and determining the appropriate management approach[28].

One retrospective study evaluated the association between preoperative NLR and the tumor pathology of 1001 patients with small renal masses (40 mm or less) who underwent nephrectomy[29]. The study found no association between preoperative NLR and tumor pathology. Currently, there is no evidence that NLR is able to select the appropriate management options for small renal masses.

STUDY LIMITATIONS

Many of the published studies were retrospective and observational by study design, resulting in potential for selection bias. Although multivariate analyses were performed in most studies, there are probably confounding factors which were unaccounted for. Secondly, NLR is not only affected by malignancies but other conditions such as chronic infective and inflammatory disorders. Thirdly, many studies have not reported cancer-specific survival, which is an important cancer survival outcome. Fourthly, there is also heterogeneity between studies in relation to the TNM staging included in the analyses.

FUTURE DIRECTIONS

There are currently no established recommendations on how NLR can be used in the management and prognostication of RCC. Not all potential markers of inflammation such as NLR are related to the prognosis of RCC, nor are all types of RCC equally affected by inflammation. There is an emerging trend that NLR may reflect more advanced stages of malignancy or a marker of more rapid progression. Therefore, more research is needed to establish this association and its influence on management.

It is clinically important to realise that the cut-offs used for NLR are considerably heterogenous across all studies. In studies involving patients with RCC, the threshold used have ranged between 2.7 and 5. Using a cut-off of 3 has been proposed but more studies are needed to validate this threshold in predicting outcomes or guiding treatment[17].

In a study of patients with resected non-small cell lung carcinoma a combined score using NLR and other inflammatory markers was found to better predict the clinical outcomes[30]. Other blood-based biomarkers such as C-reactive protein, fibrinogen, platelet-lymphocyte ratio and lymphocyte-monocyte ratio have also been found to be associated with prognosis of RCC[31-34]. In the management of RCC, the ability to accurately predict response to treatment is immensely helpful to clinicians. Therefore, further work is required to formulate and validate combined scores incorporating NLR that can be used in predicting the outcomes of RCC treatment and therapeutic decision-making.

CONCLUSION

An elevated NLR has been associated with increased risk of future RCC recurrence in localised disease and more rapid disease progression as well as decreased OS in advanced disease. In metastatic RCC, an increased NLR is also an independent prognostic factor for response to systemic therapies and cytoreductive nephrectomy. NLR is an easily available and robust measurement that can be used to predict clinical outcomes and guide treatment in patients with RCC.

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