

Is preoperative neutrophil-to-lymphocyte ratio a red flag which can predict high-risk pathological characteristics in renal cell carcinoma?

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Abstract

Introduction: Renal cell carcinoma (RCC) is known to invoke both immunological and inflammatory responses. While the neutrophils mediate the tumor-induced inflammatory response, the lymphocytes bring about the various immunological events associated with it. The neutrophil-to-lymphocyte ratio (NLR) is a simple indicator of this dual response. We investigated the association between preoperative NLR and histopathological prognostic variables of RCC intending to find out whether it can be of value as a red flag capable of alerting the clinician as to the biological character of the tumor under consideration.

Methods: Preoperative NLR and clinicopathological variables, namely histological subtype, nuclear grade, staging, lymphovascular invasion, capsular invasion, tumor necrosis, renal sinus invasion, and sarcomatoid differentiation of 60 patients who underwent radical or partial nephrectomy, were analyzed to detect the association between the two.

Results: We found that mean preoperative NLR was significantly higher in clear-cell carcinomas (3.25 ± 0.29) when compared with nonclear-cell carcinomas (2.25 ± 0.63). There was a linear trend of NLR rise as the stage of the disease advanced. A significant rise in preoperative NLR was noted in tumors with various high-risk histopathological features such as tumor size, capsular invasion, tumor necrosis, and sarcomatoid differentiation.

Conclusion: Preoperative measurement of NLR is a simple test which may provide an early clue of high-risk pathological features of renal cell cancer.

Keywords: Clear-cell carcinoma, neutrophil-lymphocyte ratio, radical/partial nephrectomy, renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of all adult cancers in India and 85% of all kidney tumors.^[1] Its incidence is increasing significantly in India as well

as globally.^[2] Up to 30% of patients present with the involvement of lymph nodes or metastatic disease at the initial diagnosis.^[3] Its prevalence is more in men and occurs predominantly in the sixth to eighth decade of life.^[4,5]

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The relationship between cancer and inflammation was proposed initially by Virchow in 1863, and subsequent studies have established this association.^[6,7] Patients with malignancy exhibit local and systemic inflammatory responses. These could be in the form of infiltration of the tumor by inflammatory cells or measurable parameters, namely acute-phase proteins such as C-reactive protein and albumin, erythrocyte sedimentation rate, and peripheral blood cell counts (neutrophils, lymphocytes, and platelets).^[7-9] The elevated inflammatory markers portend diminished quality of life in patients with advanced malignancy.^[8]

Neutrophils preside over ongoing inflammation in the host harboring the malignancy by releasing cytokines and various inflammatory mediators, while the lymphocytes represent a regulatory immune pathway against the tumor. Neutrophil-to-lymphocyte ratio (NLR) integrates information of these two distinct biological response pathways.^[10,11] Raised preoperative NLR was found to be associated with inferior outcomes in various malignancies such as those of the stomach, colon, and the rectum.^[12,13]

Based on the observation of extensive immune cell infiltration of the tumor as well as its responsiveness to immunotherapeutic modalities, RCC has been classified as an “immunogenic” tumor.^[14] The role of preoperative NLR in prognostication of RCC was demonstrated in various studies; however, the results of a few are conflicting.^[15,16] The current study aimed to assess the potential role of preoperative NLR in predicting high-risk pathological characteristics of RCC in preoperative setting.

METHODS

Study population and data collection

This was a retrospective study in which clinicopathological particulars of 60 patients who underwent radical/partial nephrectomy for RCC from January 2016 to December 2018 at our hospital were extracted from the database and analyzed. The clinical variables included were age, gender, absolute neutrophil count, and absolute lymphocyte count. Preoperative NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Pathological parameters such as histological subtype, nuclear grade, staging, lymphovascular invasion, capsular invasion, tumor necrosis, renal sinus involvement, and sarcomatoid differentiation were recorded. Those with inadequately documented data, benign renal tumor, and malignancies other than RCCs were excluded from the study. The relationship between preoperative NLR and various pathological parameters was analyzed. Preoperative NLR

was also correlated with the size of the renal mass (large versus small renal mass). Small renal mass was defined as the tumor size less than 4cm in maximal diameter.^[17] Nuclear grading by using the Fuhrman grading system is validated and accepted to be more reliable in clear-cell subtype of RCCs.^[18] Hence, we analyzed the relationship between preoperative NLR and nuclear grading only in clear-cell carcinomas. Further correlation of NLR with overall as well as cancer-free survival of the same cohort is being assessed at present. The results of the second part shall be reported on the completion of the study.

Statistical analysis

The data was analysed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM, Armonk, New York, USA). Normally distributed variables were compared across the groups and a grade using one-way ANOVA followed by *post hoc* Tukey’s multiple comparison test. Two group comparisons were done by students’ independent *t*-test and Mann–Whitney U-test. Categorical variables were analyzed by Chi-square and correlation was performed by Spearman’s test. All the results were expressed as mean \pm standard deviation/standard error of the mean, and $P < 0.05$ was considered to be significant.

RESULTS

From the 84 patients who underwent radical/partial nephrectomy during the study period, 60 cases ($n = 60$) were considered for the analysis after exclusion. The mean age of the study population was 57 ± 13 years. Forty-nine (82%) were male and 11 (18%) were female. The mean preoperative NLR was 3.1 ± 0.26 . Majority of the RCCs were clear-cell carcinomas ($n = 51, 85\%$). Other subtypes ($n = 9, 15\%$) were papillary type 1 ($n = 2$), papillary type 2 ($n = 4$), chromophobe ($n = 1$), and multilocular cystic clear-cell carcinoma ($n = 2$) [Table 1].

A linear trend of NLR rise was observed with advancing stage of the disease [Figure 1]. Significant elevation of preoperative NLR was noted in clear-cell carcinoma (3.25 ± 0.29) when compared with nonclear-cell carcinomas (2.25 ± 0.63) [Figure 2]. Preoperative NLR was raised in high-grade tumors (3.06 ± 0.34) compared to low-grade tumors (2.86 ± 0.5); however, it was statistically insignificant. When the size was taken into consideration, Spearman’s correlation test showed a significant positive ($r = 0.349, P < 0.01$) correlation between preoperative NLR and size of the tumor (small renal mass: 2.63 ± 0.47 versus large renal mass: 3.3 ± 0.32) [Table 2 and Graph 1]. Other pathological variables of great prognostic significance in which preoperative

Table 1: Clinicopathological characteristics of the study participants (n=60)

Characteristics	Mean values and proportions
Age (years), mean±SD	57±13
Gender, n (%)	
Male	49 (82)
Female	11 (18)
Neutrophils, mean±SD	63±11
Lymphocytes, mean±SD	26±10
NLR, mean±SE	3.1±0.26
Tumor size (cm), mean±SD	6.08±3
Small (<4) versus large (>4) renal mass, n (%)	18 (30):42 (70)
Stage, n (%)	
1	27 (45)
2	10 (16.6)
3	9 (15)
4	14 (23.4)
Histological type, n (%)	
Clear cell versus nonclear-cell carcinomas	51 (85):9 (15)
Nuclear grading (only for clear-cell carcinomas), n (%)	
Low:high	40 (78.5):11 (21.5)
Lymphovascular invasion (+/-)	12 (20):48 (80)
Capsular invasion (+/-)	23 (38.3):37 (61.7)
Renal sinus involvement (+/-)	10 (16.6):50 (83.4)
Tumor necrosis (+/-)	23 (38.3):37 (61.7)
Sarcomatoid differentiation (+/-)	4 (6.7):56 (93.3)

Descriptive statistics expressed as numbers, proportions and percentages. NLR: Neutrophil lymphocyte ratio, +: Presence, -: Absence, SD: Standard deviation, SE: Standard error

Table 2: Variation in preoperative neutrophil-to-lymphocyte ratio across various clinicopathological categories

Characteristics	NLR (mean±SEM)	P
Tumor size (cm)		
Small renal mass (<4)	2.63±0.47	0.12
Large renal mass (>4)	3.3±0.32	
Stage ^e		
1	2.41±0.39	0.01* [#]
2	2.91±0.43	
3	3.21±0.70	
4	4.48±2.08	
Histological type ^s		
Clear-cell carcinomas	3.25±0.29	0.03*
Nonclear-cell carcinomas	2.25±0.63	
Nuclear grading (only for clear-cell carcinomas)		
High	3.06±0.34	0.90
Low	2.86±0.5	
Lymphovascular invasion ^f		
Present	3.8±0.67	0.19
Absent	2.92±0.29	
Capsule ^e		
Involved	3.96±0.45	0.004*
Intact	2.56±0.3	
Renal sinus involvement ^e		
Positive	3.77±0.58	0.24
Negative	2.96±0.30	
Tumor necrosis		
Present	3.44±0.44	0.32
Absent	2.88±0.33	
Sarcomatoid differentiation		
Present	5±1.12	0.05
Absent	2.96±0.27	

[‡]ANOVA, post hoc by Tukey's test Significance was observed between stages 1 versus 3* and 1 versus 4* [§]Compared using independent t-test [¶]Other groups were compared by Mann-Whitney U-test. NLR: Neutrophil-to-lymphocyte ratio, SEM: Standard error of the mean

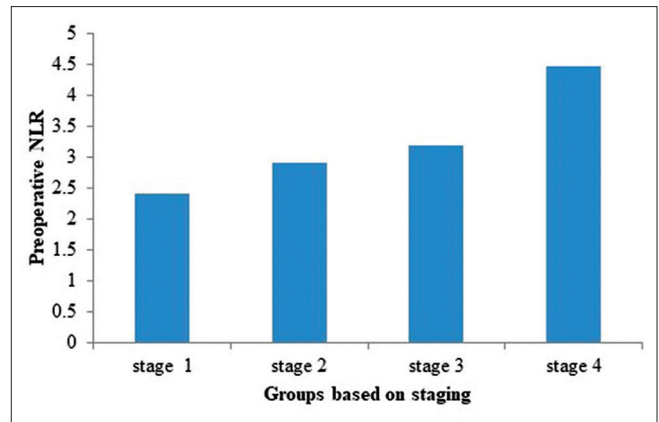


Figure 1: Preoperative neutrophil-lymphocyte ratio trend in various pathological stages

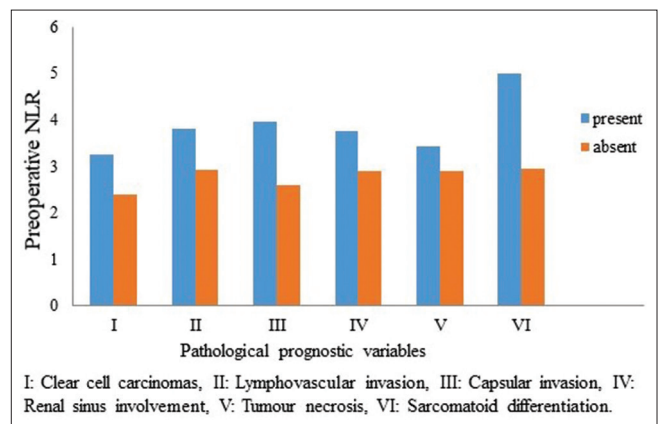
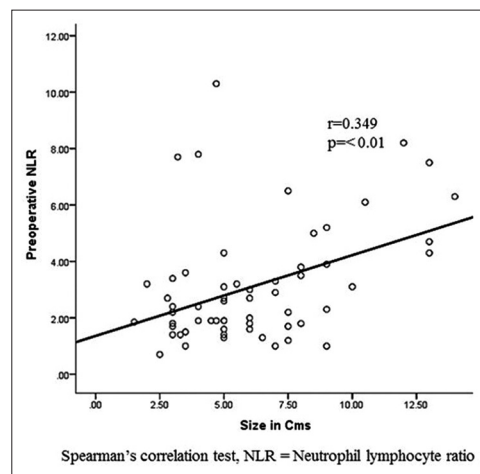


Figure 2: Preoperative neutrophil-lymphocyte ratio in various pathological prognostic features (presence vs. absence)



Graph 1: Correlation of preoperative neutrophil-to- lymphocyte ratio with the size of the tumor

NLR was significantly elevated were a capsular invasion, tumor necrosis, and sarcomatoid differentiation. An insignificant elevation of NLR was observed in patients with lymphovascular invasion and renal sinus involvement by the tumor [Table 2 and Figure 2].

DISCUSSION

The etiopathogenesis of cancer is classically described as the interplay between nature and nurture implying both inheritance and environment play important roles in tumorigenesis.^[19] Of the two, the environmental factors have been observed to induce some form of chronic inflammation.^[20] Besides tumorigenesis, the inflammatory milieu also aids in the proliferation and survival of malignant cells, subverts adaptive immune responses, and promotes angiogenesis and metastasis.^[21]

Neutrophils play a crucial role in inflammation-driven tumorigenesis. This was well-documented when neutrophils were shown to directly promote carcinogenesis in a mouse model of colitis.^[22] Tumor-associated neutrophils were also shown to support angiogenesis through the secretion of proangiogenic factors and promote tumor cell dissemination through metalloproteinases which can modify the extracellular membrane.^[23,24] On the other hand, there is increasing evidence supporting the role of lymphocytes in immune responses against cancer.^[25,26] Therefore, a low lymphocyte count may be indicative of an inadequate immunologic reaction to the tumor, and consequently, a defence cancer, resulting in a poor prognosis.^[9,27] These two major cell lines are expressed as NLR which represents the dual phenomena invoked by tumors.^[28]

Previous studies have shown that preoperative NLR provides independent prognostic information of the patients with various malignancies including RCC.^[12,13,29] Tumor staging and various histological features such as tumor grade, histological subtype, lymphovascular invasion, and tumor necrosis provide strong clues to prognosticate the natural course of RCC.^[29] While NLR can be measured preoperatively, the study of pathological characteristics depends on the availability of biopsy or surgical specimen of the tumor. Hence, the relationship between these two prognostic variables carries a prognostic potential as to the biological characteristics of a given tumor. We analyzed the possible association of NLR and the above-mentioned pathological prognostic factors to determine this predictive potential of NLR in anticipating adverse tumor characteristics preoperatively.

We observed a linear rise in the preoperative NLR with ascending stages of the tumor [Figure 1]. However, we did not find a statistically significant rise in preoperative NLR in high-grade tumors when compared to low-grade tumors. The conflicting relationship between preoperative NLR and grading has been made out in other studies

too. Otuncemur *et al.*^[30] compared the relationship of preoperative NLR with the renal tumor stage and grade. They found that preoperative NLR rise was statistically significant in the higher T-stage and grade. However, Arda *et al.*^[31] found no difference in preoperative NLR in different Fuhrman-graded cases.

Further, preoperative NLR was found to correlate significantly with the tumor size [Graph 1]. Preoperative NLR was low in small renal masses. Arda *et al.*^[31] observed a similar linear relationship between the tumor size and the NLR in nonmetastatic RCC. When pathological subtype was taken into consideration, we found a significant elevation of preoperative NLR in clear-cell carcinoma. It is well known that clear-cell carcinoma carries a worse prognosis than other subtypes of RCC even after stratification for stage and grade.^[32]

We also compared the preoperative NLR with other histopathological prognostic factors in which significant elevation was observed in patients with tumor necrosis, capsular invasion, and sarcomatoid differentiation [Figure 2]. However, preoperative NLR rise was found to be insignificant in cases of lymphovascular invasion and renal sinus involvement. In a large, multicenter cohort analysis conducted by Byun *et al.*,^[16] a significant preoperative NLR elevation was observed only in cases of tumor necrosis and sarcomatoid differentiation among the histopathological characteristics studied. Similar to this, Gu *et al.*^[33] found that preoperative NLR serves as a potential prognostic biomarker in patients with sarcomatoid RCC.

Even though there are many studies in the literature which have proven the prognostic value of preoperative NLR in terms of predicting the outcome, the relationship with various pathological prognostic factors in RCC exclusively has not been studied in detail.^[16,34] Our study is unique in this regard. From the observations of the current study, it appears that an elevated preoperative NLR is a red flag alerting the clinician as well as a pathologist of probable tumor aggressiveness. It has a potential utility as a caution to care provider to look for clinical as well as radiological signs of invasion preoperatively and also check for intraoperative evidence of subtle infiltration and nodal involvement.

NLR can be affected by systemic inflammatory conditions, but its association with various high risk pathological prognostic factors of RCC sets it apart as a parameter worth measuring.^[13] Hence, there is a need for an integrated scoring system/nomogram which uses a combination of various inflammatory prognostic markers or tumor-specific inflammatory marker to improve the

specificity. Intra- and interobserver discrepancies among pathologists while diagnosing various tumor attributes can affect the validity of the relationship of NLR with various tumor characteristics. This is true in the case of Furman grading.^[35] A histopathological study by a single uropathologist might decrease such discrepancies. In spite of these limitations, the association of elevated preoperative NLR with aggressive tumor characteristics suggests that this parameter has utility in preempting a biologically virulent tumor. Further correlation of NLR with overall as well as cancer-free survival of the same cohort is being studied. The results of the subsequent analysis might throw light on precise prognostication.

CONCLUSION

In patients with RCC, we found a significant elevation of preoperative NLR with various pathological variables which carry prognostic significance, namely clear-cell subtype, higher stage, larger tumor size, renal capsular invasion, and sarcomatoid differentiation. Preoperative measurement of NLR is a simple test to employ, and when high, the care provider should anticipate high-risk pathological characteristics of RCC. Besides the prognostic utility, our study also strengthens the link between RCC and inflammation.

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Conflicts of interest

There are no conflicts of interest.

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