

# Correlation of prognostic inflammatory markers with renal tumour characteristics- a prospective study

## Abstract

**Purpose:** Renal cell carcinoma (RCC) accounts for about 3% of all malignancies. There is increasing evidence of systemic inflammation in cancer development and progression and RCC is no exception. C-reactive protein (CRP), Neutrophil-Lymphocyte ratio (NLR) and Serum Lactate Dehydrogenase (LDH) level are systemic inflammatory markers associated with poor prognosis in many cancer types. With this background in mind, we carried out a prospective study to find out any association between the inflammatory markers and renal tumour characteristics like histology, tumour size, presence of necrosis and calcification.

**Method:** A prospective study was conducted February 2011 to September 2015. Sixty four patients with localised RCC who fulfilled our inclusion criteria were taken up for the study. Preoperative CRP, LDH and NLR were measured. All the patients fulfilling the inclusion criteria were subjected to partial or radical nephrectomy and the specimen were sent for histopathological examination. The histology and tumour characteristics like tumour size, presence of necrosis and calcification were then correlated with the above mentioned prognostic variables of RCC.

**Results:** A statistically significant association was found between raised preoperative CRP level and NLR with the papillary variety of RCC ( $p=0.018$ ,  $OR=6.6$  and  $p=0.04$ ,  $OR=5$  respectively). Further, a statistically significant correlation was also found between elevated levels of CRP and NLR with the presence of necrosis, ( $p=0.04$ ,  $OR=3.29$  and  $p=0.01$ ,  $OR=5.8$  respectively) while elevated levels of LDH was significantly associated with an enlarged tumour size ( $>7\text{cm}$ ) ( $p=0.04$ ,  $OR=0.10$ ). No correlation was seen between any of the inflammatory markers with the presence of calcification in RCC.

**Conclusion:** Ours is a landmark study correlating inflammatory markers with various renal tumour histological characteristics. Whether these markers of systemic inflammation play any role in the incitation of these renal tumours as observed in our study is yet to be known.

**Keywords:** renal cell carcinoma, c-reactive protein, neutrophil-lymphocyte ratio, serum lactate dehydrogenase

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**Abbreviations:** RCC, renal cell carcinoma; CRP, c-reactive protein; NLR, neutrophil-lymphocyte ratio; LDH, serum lactate dehydrogenase; TNM, tumour-node-metastasis; NSAIDs, non steroidal anti-inflammatory drugs; PNET, primitive neuroectodermal tumour

## Introduction

Renal cell carcinoma (RCC) is one of the most common solid neoplasm of urinary tract accounting for about 3% of all malignancies in adult.<sup>1</sup> Although majority of the patients present with localised disease, approximately 30% of patients are diagnosed with metastasis<sup>2</sup> and another 30% of patients develop metastasis after radical nephrectomy.<sup>3</sup> Although various genetic aberration has been implicated as the causative agents of RCC little is known regarding the role of inflammation in pathogenesis of RCC. In the year 1863, Virchow first stated that cancers may occur at the sites of chronic inflammation. Since then various studies have described chronic inflammation as a trigger of the process of carcinogenesis and predisposing factor for

the development of cancer.<sup>4-6</sup> Chronic activation of bacterial, viral and parasitic infections are responsible for the development of tumors in the bladder, liver and different regions of the body, including the head and neck region and RCC is no exception.<sup>7,8</sup>

Recently, the markers of inflammation like C-reactive protein (CRP), neutrophil lymphocyte ratio (NLR) and Serum lactate dehydrogenase (LDH) are being extensively studied in solid tumours and in most of the studies it has been established that markers of inflammation bears a prognostic information in most of the carcinoma including RCC.<sup>9-11</sup> However, it is still not known whether alteration in serum levels of these markers of inflammation is influenced by tumour related factors of RCC like histological variety, tumour size, presence of necrosis and calcification. The present study was aimed to ascertain the correlation, if any, between CRP, NLR and LDH and the above mentioned tumour related factors. These findings might provide valuable information regarding the association of inflammatory markers with histological variety of RCC.

## Materials and methods

The present study was conducted from February 2012 to December 2015. All patients with localised RCC attending the Urology outpatient department were taken up for the study, after obtaining informed consent. Ethical committee clearance was obtained prior to commencement of the study. The extent of the tumour was assessed on the basis of clinical findings, computed tomography scan or magnetic resonance imaging. Tumour stage was determined according to UICC TNM staging of malignant tumours. Laboratory data including CRP, S. LDH, neutrophil count, lymphocyte count level were assessed apart from the other routine investigations. Cut off value of serum CRP, NLR and LDH were defined as  $\leq 5\text{mg/L}$ ,  $< 2.7$  and  $< 450\text{ IU/L}$  respectively.<sup>12-14</sup> we excluded patients with metastatic RCC, infective renal pathology, patients with diabetes mellitus or any acute and chronic inflammatory disease. Patients with history of prior drug intake like NSAIDs, steroids and any other anti-inflammatory drugs were also excluded from our study. Any disease affecting bone and joints were also excluded from our study.

All the patients fulfilling the inclusion criteria were subjected to either partial or radical nephrectomy. The extirpated tumour specimens were sent for histopathological examination. Data were described as mean $\pm$ SD and 95% confidence interval; and  $p < 0.05$  was considered statistically significant. Fisher's exact test was used to determine if there is any significant correlation between tumour histology and prognostic inflammatory markers like CRP, LDH and NLR as well as other tumour related factors like tumour size, necrosis and calcification.

## Results

The total numbers of patients in our study was 64. Five patients with metastatic disease, 11 patients with urinary tract infection and 12 patients with diabetes mellitus were excluded from our study

of the subjects enrolled in the study, 47(64%) were males, while 27(36%) were females. Their ages ranged from 17-70years with a mean $\pm$ SD age of  $54\pm 6$ years. Of the total study population, thirty five (55%) patients had right sided tumours and 29 (45%) patients had left sided tumours. Of the total 64 cases of RCC, the highest number of cases belonged to the clear cell variety (53.12%) followed by papillary carcinoma (26.56%), chromophobe carcinoma (9.37%), primitive neuro ectodermal tumour (PNET) (1.56%), Wilms' tumour (3.12%), multilocular cystic renal cell carcinoma (1.56%), squamous cell carcinoma (1.56%), leiomyosarcoma (1.56%) and oncocytoma (1.56%) (Table 1).

Comparison of CRP level, LDH level and NLR was done among the various histological types of RCC. A statistically significant association was seen between papillary variety of RCC and elevated CRP level (Fisher's exact test,  $p=0.018$ , OR=6.6) (Table 2). Also the association between papillary variety of RCC and NLR was found to be statistically significant (Fisher's exact test,  $p=0.04$ , OR=5) (Table 3). However, no statistically significant association was seen between the other varieties of RCC with elevated CRP level and NLR (Table 2, 3). Also, we did not found any statistically significant association between LDH level and various histological types of RCC (Table 4).

In addition, a comparison between the various inflammatory markers and the presence and absence of necrosis and calcification was done. A statistically significant correlation was found between elevated CRP and NLR levels ( $p=0.04$ , OR=3.29 and  $p=0.01$ , OR=5.8 respectively) and the presence of necrosis in various RCC types. However, no significant correlation was found between the presence necrosis and LDH (Table 5). Moreover, no significant correlation was found between the presence of tumour calcification and the various inflammatory markers. On the other hand, a statistically significant correlation was seen between elevated levels of LDH and that of tumours  $> 7\text{cm}$  size ( $p=0.04$ , OR=0.10). However, no such correlation was found between tumour size and CRP and NLR (Table 5).

**Table 1** Histopathological types of renal cell carcinoma in the study population

Histopathology	No. of patients	Percentage (%)
Clear Cell Carcinoma	34	53.12
Papillary Carcinoma	17	26.56
Chromophobe Carcinoma	6	9.37
Primitive Neuroectodermal Tumour	1	1.56
Wilms' Tumour	2	3.12
Multilocular Cystic Renal Cell Carcinoma	1	1.56
Squamous Cell Carcinoma	1	1.56
Leiomyosarcoma	1	1.56
Oncocytoma	1	1.56
Total	64	100%

**Table 2** Comparison of C-reactive protein level with histopathology of renal cell carcinoma in the study population

Histopathology	Elevated CRP	Non elevated CRP	Total	p value	Odds ratio
Clear Cell Carcinoma	18	16	34	0.59	0.66
Papillary Carcinoma	15	2	17	0.018	6.6
Chromophobe Carcinoma	3	3	6	1	0.9
Primitive Neuroectodermal Tumour	1	0	1	0.53	0.44
Wilms' Tumour	1	1	2	0.53	0.44
Multilocular Cystic Renal Cell Carcinoma	0	1	1	0.31	0.75
Squamous Cell	0	1	1	1	1.4
Leiomyosarcoma	1	0	1	1	1.4
Oncocytoma	1	0	1	1	1.4
Total	40	24	64		

**Table 3** Comparison of Neutrophil-Lymphocyte ratio level with histopathology of renal cell carcinoma in the study population

Histopathology	Total	Elevated NLR	Non Elevated NLR	p value	Odds ratio
Clear Cell Carcinoma	35	27	8	1	0.88
Papillary Carcinoma	16	12	4	0.04	5
Chromophobe Carcinoma	6	6	0	0.32	4.2
Primitive Neuroectodermal Tumour	1	1	0	0.39	0.27
Wilms' Tumour	2	1	1	0.39	0.27
Multilocular Cystic Renal Cell Carcinoma	1	1	0	0.39	0.27
Squamous Cell	1	0	1	0.22	0.9
Leiomyosarcoma	1	1	0	1	0.88
Oncocytoma	1	1	0	0.39	0.27
Total	64	50	14		

**Table 4** Comparison of Serum Lactate Dehydrogenase level with histopathology of renal cell carcinoma in the study population

Histopathology	Total	Elevated LDH	Non Elevated LDH	p value	Odds ratio
Clear Cell Carcinoma	34	32	2	1	0.79
Papillary Carcinoma	17	15	2	1	1.36
Chromophobe Carcinoma	6	5	1	0.4	0.37
Primitive Neuroectodermal Tumour	1	1	0	1	0.28
Wilms' Tumour	2	2	0	1	0.48
Multilocular Cystic Renal Cell Carcinoma	1	1	0	1	0.28
Squamous Cell	1	1	0	1	0.28
Leiomyosarcoma	1	1	0	1	0.28
Oncocytoma	1	1	0	1	0.28
Total	64	59	5		

**Table 5** Comparison between the inflammatory markers and tumour necrosis, tumour size and calcification

	No. of tumours with necrosis	Tumour Size >7cm	No. of tumours with calcification
Elevated CRP	23(36%)[p=0.04]	23(36%)[p=0.30]	22(34%)[p=0.44]
Elevated LDH	35(55%)[p=0.64]	42(66%)[p=0.04]	34(53%)[p=0.65]
Elevated NLR	35(55%)[p=0.01]	28(44%)[p=0.55]	31(48%)p=1.00]

CRP, c-reactive protein; NLR, neutrophil-lymphocyte ratio; LDH, serum lactate dehydrogenase

## Discussion

Renal cell carcinoma is primarily a disease of the elderly age group; the typical age of presentation being the 6<sup>th</sup> and 7<sup>th</sup> decades of life, with a male: female ratio of 3:2. In the present study, the mean age of presentation in males was 55±6years whereas in case of females it was 40±8years. The earlier trend of presentation can be attributed to the increasing use of imaging modalities for the evaluation of a variety of abdominal complaints resulting in the increased proportion of incidentally discovered renal tumours.<sup>15</sup> Most of the tumours in our study were located on the right side (55%) and extensive search of literature did not reveal any explanation regarding the predominant side distribution of renal tumours. Clear cell variety of RCC is the most predominant variety accounting for 70-80% of all RCC, followed by papillary RCC.<sup>16</sup> However, in our study, cases of clear cell RCC comprised of 53.12% of the study population, followed by papillary RCC (26.56%) (Table 1). This may be largely due to the fact that patients with localised tumour only were included in this study and clear cell variety is more aggressive than others and usually has metastatic disease at initial presentation.

Cancer-related inflammation is considered to be the seventh hallmark of cancer. Inflammatory cells and mediators are essential components of the tumour microenvironment. The association between inflammation and cancer is a well established phenomenon, illustrated by various epidemiologic and clinical studies.<sup>17,18</sup> Cousens LM described that various inflammatory cells and a variety of mediators like cytokines and enzymes establish an inflammatory microenvironment leading to cancer development.<sup>19</sup> C-reactive protein, first described in 1930, is widely used as a sensitive, but nonspecific marker of systemic inflammation.<sup>20</sup> C reactive protein is one of the significant factors in predicting survival in patients with RCC, thereby is an informative biomarker that reflects disease progression. In our study, CRP level was seen to be elevated in 40 cases (62.5%), with a statistically significant rise in papillary variety of RCC (p=0.018) (Table 2), indicating that there might be a possible role of elevated CRP in the incitation of papillary RCC.

Neutrophil Lymphocyte Ratio is an easily measurable parameter of systemic inflammation and stress.<sup>6</sup> The NLR, derived from the quotient of the absolute neutrophil count and the absolute lymphocyte count, can be used as an important and independent prognostic tool for patient outcome in a variety of tumours.<sup>21,22</sup> Studies have shown that NLR is associated with tumour size and is independent indicator of survival in patients with renal cell carcinoma.<sup>17</sup> In our study, NLR was elevated in 50 patients (83.33%) with statistically significant rise in papillary variety RCC (p=0.04) (Table 3), validating the role of inflammation in the occurrence of papillary variety of RCC.

Serum lactate dehydrogenase, a cellular enzyme, is increased following tissue breakdown. Serum LDH has previously been reported mainly as a diagnostic and prognostic marker of a variety of solid tumours, including RCC.<sup>23-28</sup> Hala Girgis et al.,<sup>29</sup> found in

their study a higher expression of LDH in advanced clinical stage and histological grade of clear cell RCC. In our study, serum lactate dehydrogenase was elevated in 59 cases (92.19%). Preoperative LDH level was not statistically significant with various histological variety of RCC (Table 4).

RCC tumours showing necrosis are not uncommon. Tumour necrosis is associated with larger tumours, higher grade, and higher proliferative activity in RCC, and thereby is an essential indirect indicator of biologically aggressive tumour behaviour, as described by Lam JS. In our study, statistically significant correlation was found between elevated CRP and NLR levels and the presence of necrosis in various RCC types (p=0.04, OR=3.29 and p=0.01, OR=5.8 respectively), indicating the possible role of elevated CRP and NLR as markers of aggressiveness of renal tumours. However, there was no significant correlation seen between elevated LDH and presence of necrosis in RCC (p=0.64, OR=2.19) (Table 5).<sup>30</sup>

Computerized tomography demonstrates calcification in up to 31% of RCCs, with an increasing incidence of calcification noted with increasing size. Haddad et al.,<sup>31</sup> found calcification in renal tumours is independent of tumour grade and does not affect in prognosis. Kreiger et al.,<sup>32</sup> also in their studies showed that calcification in RCC are independent of their prognosis. In our study, there was no significant correlation was found between the presence of tumour calcification and the various inflammatory markers like CRP, NLR and LDH (p=0.44, p=1.00, p=0.65 respectively) (Table 5).

Guðmundsson E et al.<sup>33</sup> in their study described an almost linear relationship between size and synchronous metastasis for tumours ≤7cm. They also found patients with 1- to 2-cm RCCs, 2% had locally aggressive growth, which increasing to 34% for 6- to 7-cm RCCs. In our study, there was statistically significant correlation seen between elevated levels of LDH and that of tumours >7cm size (p=0.04, OR=0.10) (Table 5). Hala Girgis et al, in their study, found that LDH level is proportional to the size of renal tumours and hence is associated with a poor survival rate.<sup>29</sup> However, no such correlation was found between tumour size and the other markers of inflammation. (CRP, p=0.30; NLR, p=0.55 respectively).

## Conclusion

Various pathologic and biochemical parameters can be used as a predictive means to validate the histological variety of RCC as well as disease progression. Whether markers of systemic inflammation play a role in the incitation of renal tumours as observed in our study is yet to be known. In this regard, a multicentric study with large group of population will definitely establish their relation in the development of RCC.

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## Conflict of interest

Author declares that there is no conflict of interest.

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