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Prognostic Significance of Preoperative C - Reactive Protein Elevation and Thrombocytosis in Patients with Non-Metastatic Renal Cell Carcinoma

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ABSTRACT

Aim: The aim of this study was to investigate the association of preoperative C-reactive protein (CRP) elevation and thrombocytosis with the prognosis of patients with non-metastatic renal cell carcinoma (RCC).

Materials and Methods: This was a retrospective review of the medical records of 43 patients (31 men and 12 women) with non-metastatic RCC who underwent a radical nephrectomy between August 2012 and August 2015 and for whom preoperative CRP and platelet data were available for analysis. Preoperative CRP elevation and thrombocytosis were compared with clinical and pathological variables.

Results: There were 10 patients with CRP elevation and 6 patients with thrombocytosis. The mean follow-up time was 28.3 months (range- 13-47 months). Six patients (13.9%) developed metastases and one patient died during the follow-up period. CRP elevation was significantly correlated with anemia (p=0.001), T stage (p=0.004), grade (p=0.025), and metastasis (p<0.001). Thrombocytosis was significantly correlated with anemia (p=0.003), T stage (p=0.002), and metastasis (p=0.001). The univariate analysis identified anemia, CRP elevation, thrombocytosis, tumor histology subtype, tumor size, T stage, and grade as significant prognostic factors associated with recurrence-free survival, whereas the multivariate analyses showed that CRP elevation (p=0.033) and tumor size (p=0.007) were independent prognostic factors.

Conclusions: Preoperative CRP elevation and thrombocytosis were associated with a poorer prognosis and a higher recurrence rate in patients with non-metastatic RCC. Moreover, preoperative CRP elevation appeared to be an independent predictor of tumor recurrence and prognosis. Preoperative thrombocytosis, however, was not an independent prognostic factor for tumor recurrence and prognosis.

Keywords: C-reactive protein, Prognosis, Renal cell carcinoma, Thrombocytosis

Introduction

Renal cell carcinoma (RCC) is the most common primary malignant neoplasm of the kidneyaggressive malignancy whose incidence of occurrence accounts for 2– 3% of cancers in adults. It is the second leading cause of death from urological cancers [1]. The incidence of RCC has been slowly increasing over the past decade.The size of tumors at presentation hasalsodecreased with more patients presenting with stage I disease. In an analysis of over 29,000 cases from the Surveillance, Epidemiology and End Results (SEER) database, this increased incidence has been associated with a steady decrease in the average size of tumors at presentation (6.7 versus 5.9 cm in 1988 and 2002, respectively)

Part of the increase in incidence may be explained by the greater number of asymptomatic tumors detected as a result of widespread use of noninvasive abdominal imaging. About30% of patients who presented with localized disease and undergo curative surgery, will eventually develop recurrence[2]. Hence, a means of identifying patients with poor prognosis, who may benefit from aggressive treatment, is greatly needed. The need for accurate prognostication became even more acute with the advent of targeted therapy for advanced RCC, and here too, new systems were devised. Of these, the International Metastatic RCC Database Consortium prognostic model has proven accurate and has recently been externally validated.

Although post-operative histopathological parameters are currently the most widelyused predictors to stratify patients, these variables might not be entirely reliable; further improvementin preoperative prognostication is warranted.Therefore biological markers,which can enhance outcome prediction, and help identify patients at greater risk, is required toprecisely guide clinical decisions.

A systemic inflammatory response has been shown to be a prognostic indicator for severaladvanced cancers. It is estimated that underlying infection and inflammatory responses are linked to 15% to 20% of all deaths from cancer worldwide [3].Although an elevated platelet count (PC) and thrombocytosis, a measure of systemic inflammatoryresponse, has been associated with poor RCC prognosis in several studies, variationsin results have precluded a consensus. Furthermore these studies combined all data together with no subgroup analysis and only looked at survival rates.

Hence this study was done to study the significance of preoperative elevation of CRP and thrombocytosisand its correlation with clinical and pathological variables.

Materials and Methods

This study was conducted at the Institute of Urology, Madras Medical College, Chennai between August 2012 and august 2015. The medical records of patients with non-metastatic RCC who underwent a radical nephrectomy for localized RCC between August 2012 and August 2015 and for whom preoperative CRP and platelet levels were available for analysis were retrospectively reviewed. Preoperatively, all patients were evaluated with a physical examination, routine hematology and biochemical analysis, and radiology studies, including abdominal computed tomography and chest X-ray. Baseline data collected on all patients included demographic variables, laboratory parameters, TNM stage, pathological features, and available follow-up and survival data. Those with metastasis,active infection(UTI) and myeloproliferative disorders were excluded.

The tumors were staged by using the 2002 TNM classification of the American Joint Committee on Cancer (AJCC) [4] and were graded according to Fuhrman's nuclear grading system [5]. All patients were evaluated postoperatively every 3 months for the first 2 years, every 6 months for the next 1 year and yearly thereafter.

CRP elevation was defined as a CRP level ≥0.8 mg/dl, and thrombocytosis was defined as a platelet count ≥380,000/µl in men and ≥370,000/µl in women according to the normal reference range in our hospital. Disease recurrence was defined as local failure in the tumor bed or regional lymph nodes or distant metastasis.

Statistical Analysis

The chi-square test or Fisher's exact test was used to analyze the correlation between preoperative CRP elevation or thrombocytosis and the clinical and pathological variables, including age, gender, anemia, histology subtype, tumor size, T stage, nuclear grade, and metastasis during follow-up. Kaplan –Meier plots were used to graphically illustrate the survival. Univariate and multivariate analyses were performed by using the log-rank test or the Cox proportional hazards regression model. For all tests, $p<0.05$ was considered to indicate statistically significant differences.

Results

Patient characteristics are shown in Table 1.The majority (72.0%) were men and their age ranged from 10 to 77 years (mean- 62.6). 5 patients were anemic. The meantumor size was 5.12 cm (range-3-14cm). Regional lymph node dissection was performed in 8 patients who showed suspicious lymph node metastasis on computed tomography. However, none had a pathological diagnosis of lymph node metastasis.Clear cell histology was the most common histological type which was present in 38 cases (88.37%). 10(23.25%) patients had CRP elevation and 6 (13.9%) had thrombocytosis. Among patients with CRP elevation, 8 patients (80%) showed CRP normalization after surgery. The normalization occurred within 3 months of the radical nephrectomy. The mean follow-up period was 28.3 months (13-47 months). 6 Patients (13.9%) developed metastases and one patients died during the follow-up period.

Table1: clinicopathologic data

Characteristics	No. of Patients
AGE <60 >60	27(62.8) 16(37.2)
Gender Male Female	31(72.1) 12(27.9)
Anemia No Yes	38(88.37) 5(11.62)
Histology Conventional Papillary Chromophobe Collecting duct	38(88.37) 2(4.65) 2(4.65) 1(2.32)
Tumour size <7 cm >7 cm	33(76.74) 10(23.2)
Grade 1/2/3/4	16/8/19/0(37.2/18.6/45.23/0)
Metastasis No/Yes	37/6(86/13.9)

Table2: Relationship between preoperative CRP and clinicopathologic variables

Variables	CRP <0.8 mg/dl	CRP >0.8 mg/dl	P- value
	(n=33)	(n=10)	
Age (yr) <60 >60	 20 13	 7 3	0.389
Gender Male Female	 23 10	 8 2	0.970
Anemia No Yes	 32 1	 6 4	0.001
Histology Conventional Non-Conventional	 31 2	 7 3	0.209
Tumor Size (cm) <7 >7	 27 6	 6 4	0.053
T Stage Low (T1+T2) High (T3+T4)	 27 6	 8 2	0.004
Grade Low (G1+G2) High (G3+G4)	 22 11	 2 8	0.025
Metastasis at follow-up No Yes	 30 3	 7 3	<0.001

Preoperative CRP elevation was significantly correlated with anemia (p=0.001), T stage (p=0.004), grade (p=0.025), and metastasis (p<0.001), but not with age, gender, tumor histology subtype, or tumor size (Table 2). Preoperative thrombocytosis was significantly correlated with anemia (p=0.003), T stage (p=0.002), and metastasis (p=0.001), but not with age, gender, tumor histology subtype, tumor size, or grade (Table 3). No significant correlation was found between preoperative CRP levels and platelet counts when analyzed by using Pearson's correlation coefficient (r=0.132, p=0.079).

Table 3: Relationship between preoperative platelet count and clinicopathological variables

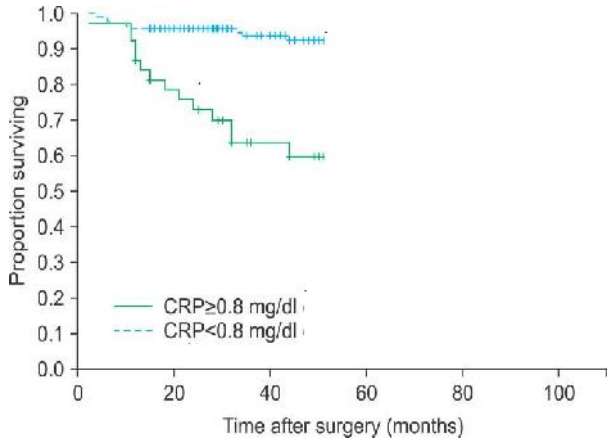
Variables	Without Thrombocytosis	With Thrombocytosis	p - value
	(n=37)	(n=6)	
Age (yr) <60 >60	 23 14	 4 2	0.748
Gender Male Female	 28 9	 3 3	0.070
Anemia No Yes	 34 3	 4 2	0.003
Histology Conventional Non-Conventional	 33 4	 5 1	1.000
Tumor Size (cm) <7 >7	 29 8	 4 2	0.128
T Stage Low (T1+T2) High (T3+T4)	 29 8	 5 1	0.002
Grade Low (G1+G2) High (G3+G4)	 22 15	 2 4	0.340
Metastasis at follow-up No Yes	 34 3	 3 3	0.001

Kaplan-Meier recurrence-free survival curves according to CRP level showed that the survival rate of patients with CRP elevation (CRP≥0.8 mg/dl) was significantly lower than that of patients with normal CRP levels (p<0.001) (Fig. 1). The univariate analysis identified anemia, CRP elevation, thrombocytosis, tumor histology subtype, tumor size, T stage, and grade as significant prognostic factors for recurrence-free survival, whereas the multivariate analysis showed that CRP elevation (p=0.033) and tumor size (p=0.007) were independent prognostic factors (Table 4).

Table 4 : Univariate and multivariate analysis of recurrence- free survival

	Univariate	Multivariate	
	P – value	Hazards ratio (95% CI)	P - value
Age (<60 vs. >60 yr)	0.262	1.332 (0.468-3.791)	0.591
Gender (male vs. female)	0.715	1.351 (0.512-3.561)	0.543
Anemia (No vs. Yes)	<0.001	1.132 (0.265-4.843)	0.867
CRP (<0.8 vs. >0.8 mg/dl)	<0.001	3.123 (1.099+8.872)	0.033
Thrombocytosis (No vs. Yes)	<0.001	2.845 (0.673-12.022)	0.155
Histology (Conventional vs. Non-conventional)	0.032	2.714 (0.889-8.284)	0.079
Tumor size (<7 vs. >7)	<0.001	4.181 (1.478-11.828)	0.007
T stage (T1+T2 vs. T3+T4)	<0.001	2.574 (0.766-8.647)	0.126
Grade (G1+G2 vs. G3+G4)	0.009	1.438 (0.489-4.234)	0.509

Figure 1 : Kaplan-Meier recurrence-free survival curves



Discussion

As biomarkers in fluids offer the opportunity for more objective and reproducible measurement prior to tumour surgery, the use of CRP and thrombocytosis as a well-standardized parameter worldwide, should not be underestimated. Rather than tumour tissue-based factors, it can easily be implemented as a prognostic factor in addition to tumour stage and grade, to more accurately stratify patients with RCC.

CRP is an acute phase reactant that is produced exclusively by hepatocytes in response to cytokines such as interleukin (IL)-6, which are known mediators of ongoing inflammatory processes[6]. The relationship between cancer and CRP elevation is explained by overproduction of IL-6 by tumor cells. Hepatic production of CRP is induced by cytokines such as IL-1, tumor necrosis factor (TNF), and primarily IL-6, which is frequently overproduced by the tumor cells themselves. Experimental studies on RCC cell lines and expression studies of renal surgical specimens have shown that at least some renal tumors produce IL-6, which functions as an autocrine growth factor of the RCC [7]

Lamb et al. showed that the tumour cell expression of IL-6 was not significantly associated with circulating CRP levels hypothesizing that the main source of IL-6 causing an elevated CRP level is not the tumour itself. In contrast, in 2005 Jabs et al. published a study with 40 patients suggesting that the CRP expression by the tumour itself is directly associated with the circulating CRP concentration indicating an autonomous production of CRP in the tumor and normal kidney tissue.

The presence of a systemic inflammatory response might be associated with aggressive RCC behavior. The prognostic value of CRP levels has been reported in many recent studies of cancers, including those of the esophagus, ovaries, and colon [8]. However, the mechanism by which a systemic inflammatory response affects cancer-specific survival in patients with RCC is unclear.

Hwang et al studied the relationship between CRP and survival in patients with RCC who underwent a radical nephrectomy. They reported a statistically insignificant difference in the survival rates of patients with and without CRP elevation and concluded that CRP was not a significant prognostic factor for RCC when compared with tumor stage, grade, tumor size, and cell type.

Lamb et al. indicated that the presence of a preoperative systemic inflammatory response measured in an elevated CRP level might be an independent negative predictor for relapse-free survival in patients with localized RCC after curative surgery. However, Lamb and co-workers evaluated 60 patients with localized clear cell RCC, only, and used a CRP level of >10 mg/l as cut off point.

Johnson et al. evaluated the influence of intratumoral CRP on overall survival in 95 patients with localized clear cell RCC using immunohistochemical analysis. The tumours were categorized into low, intermediate, and high CRP staining intensity. Mean overall survival was significantly longer in the low (44.2 months) and intermediate (40.5 months) risk (i.e. CRP) group compared to the group of tumours expressing high amounts of CRP (31.6 months; $p = 0.002$ and $p = 0.067$). Applying multivariate analysis, patients with high intratumoural CRP levels experienced a 12-fold increased risk of overall mortality compared to patients with low CRP expressing tumours. Further theypresented a study suggesting a CRP-based prognostic classification of patients with localized RCC. The authors recommended tostratify patients according to the CRP cut-off values 4.0 and 10.0 mg/l.

An elevated circulating CRP concentration had also been suggested to be a poor prognostic factor in patients with metastatic RCC [9]. Masuda et al. published a retrospective study including patients with advanced RCC which identified the CRP-level as a prognostic factor independent of tumour stage and grade.Ito et al. [9] were able to demonstrate in a cohort of 178 patients that a CRP elevation >10 mg/l might be an independent predictor for recurrence and prognosis in both localized and metastatic RCC.

Karakiewicz et al [10] were able to show in a group of 313 patients that the incorporation of the CRP value into the UISS scoring systems for patients with localized RCC might improve its prognostic significance. Furthermore, Iimura et al. introduced the TNM-C Score, a prediction model including C-reactive protein in patients treated with nephrectomy for clear cell RCC. In a cohort of 249 patients - and 290 for external validation - they were able to show that the model is a useful tool to predict cancer specific survival . However, to our knowledge, the incorporation of CRP in a prognostic model is not yet an established tool used in clinical routine.

Fujikawa et al. suggested that a decrease in serum CRP is an indicator to response to cytoreductive nephrectomy and immunotherapy. Ito et al,komai et al ,casamassima et al[9,11,12] also demonstrated that CRP is an independent predictor of survival post nephrectomy.

In the present study, preoperative CRP elevation was associated with a poorer prognosis and a higher recurrence rate in patients with non-metastatic RCC. We corroborated these findings within a cohort of south indian patients where we confirmed the independent predictor status of CRP. Our study is consistent with the findings of earlier reports showing that a high CRP level is associated with poor survival in localized RCC.

Thrombocytosis has been implicated as an adverse prognostic factor in a number of malignancies including RCC. The exact cause of the secondary thrombocytosis is unclear, but it appears that circulating cytokines and growth factors play an important role [13]. Of these, interleukin (IL)-6 appears to be the most potent stimulator of megakaryocyte progenitors, and a raised level has been demonstrated in the majority of patients with malignancy-associated thrombocytosis. Other cytokines that have been implicated include macrophage-colony stimulating factor, thrombopoietin, and IL-11. Platelets have also been implicated in tumor growth as they can secrete large concentrations of vascular endothelial growth factor (VEGF) that is crucial for tumor angiogenesis, while also stimulating megakaryocyte maturation at the bone marrow level. Activated platelets also secrete thrombopoietin, which reinforces platelet formation in the bone marrow. Platelets and their secretory product thrombospondin have also been implicated in tumor metastasis. The proposed mechanisms include allowing adhesion of tumor cells to the vascular endothelium, penetration through the endothelial barrier, and preventing malignant cells from being cleared from the circulation [14].

Karakiewicz et al[10] analyzed 1828 patients with RCC by univariable, multivariable, and predictive accuracy analyses with regard to RCC-specific mortality. In that study, they showed that the addition of thrombocytosis to the base model (age, tumor size, TNM stage, ECOG-performance status, Fuhrman grade, and histology subtype) increased the predictive accuracy by only 0.3% (from 85.3% to 85.6%); these changes in predictive accuracy were not statistically significant. Consequently, they concluded that patients who presented with thrombocytosis did not have poorer prognosis than did their counterparts who did not exhibit these apparently unfavorable characteristics, as long as the effects of the TNM stage, histology, tumor grade, and ECOG-performance status were considered. However, many investigators have reported that thrombocytosis is related to a poor prognosis in patients with RCC.

Over the past decade, a few studies have studied the prognostic significance of thrombocytosis in RCC. In the largest study so far Bensalah*et al*.[15] reported that a platelet count > 450,000/cuml positively correlated with worsening T stage, Fuhrman grade, tumor size, lymph node status, and distant metastasis in 804 patients with RCC. Patients with thrombocytosis also had a significantly worse 5-year survival on both

univariate and multivariate analyses. This impact on prognosis was seen for both localized and metastatic disease. Inoue *et al*.[16] also showed a positive correlation between thrombocytosis and tumor size and stage. In their study, thrombocytosis was associated with a worse prognosis, but when adjusted for stage or tumor size, this was limited to pT1-2 tumors. In the study by Cho *et al*., thrombocytosis significantly correlated with tumor size and metastasis. It was a predictor of recurrence-free survival on univariate but not multivariate analysis. Patel *et al*.[17] reported a retrospective study on 237 patients who underwent radical nephrectomy for clinically localized disease. They concluded that an increase in platelet count of >20% following radical nephrectomy could reliably predict recurrence and cancer-free survival.

In the present study, we showed that preoperative thrombocytosis was significantly correlated with anemia, T stage, and metastasis. In addition, thrombocytosis was a significant prognostic factor associated with recurrence- free survival in the univariate analysis. Therefore, thrombocytosis was associated with a poorer prognosis and a higher recurrence rate in patients with non-metastatic RCC; these findings are consistent with those of previous studies. Ito et al showed that preoperative CRP levels and platelet counts had a significant correlation and suggested that this was because the reactive thrombocytosis and CRP elevation in RCC were both caused by the production of inflammatory cytokines such as IL-6.

As in the study by Ito et al, we analyzed the relationship between preoperative CRP and platelet count. However, we did not find a statistically significant association between preoperative CRP and platelet count (r=0.132, p=0.079). Therefore, the exact relationship between preoperative CRP and platelet count remains to be determined. A limitation of this study is that several variables could not be considered in the current analysis. Nonetheless, all available variables were included, and our findings indicate that several known prognostic factors were valuable as prognostic factors. However, T stage and grade were not significant in the multivariate analysis. The reason for this result was, to some extent, too many patients in stage T1 rather than other T stages and a small number of patients with grade 4 compared with other grades according to the early detection of RCC nowadays.

In this study, we could reveal that elevated CRP levels and thrombocytosis were significantly associated with tumour stage, grade, and a poor cancer specific and overall survival in patients undergoing resection for RCC. These results confirmed the association of circulating CRP levels and platelet counts with the tumour stage and its impact on the prognosis of patients with RCC.

Conclusion

RCC is an aggressive malignancy accounting for 3% adult cancers. The incidence of localized early tumors is on the rise due to increasing use of imaging modalities. Though most patients presume to undergo a curative surgery,many recur.This has brought in the need to identify markers that can predict the aggressiveness of the tumour apart from histopathology and staging.

The success of targeted therapy has also opened up the possibilities of neoadjuvant and adjuvant therapy for locally advanced RCC. Research in this area is underway and various randomized trials are ongoing to determine the efficacy of these drugs in the adjuvant setting.

The fact that preoperative CRP and thrombocytosis correlates well with adverse prognosis, even in patients with clinically nonmetastatic disease, may possibly be used toselect patients who would benefit from further treatment.Its routine use could allow better risk stratification and surveillance for patients with kidney cancer.

Our study is limited by its retrospective nature,the relatively short follow-up of patients and that several variables could not be considered in the current analysis

While there is no doubt that a combination of factors will be most reliable in prognostication, the platelet count and CRP values alone is a simple investigation that can give the clinician an indicator of the gravity of disease, and we believe that further prospective studies could help better establish its exact role.

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