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Original Research Article

The role of hematological parameters in predicting tumor grade and stage in renal cell carcinoma patients undergoing nephrectomy

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ABSTRACT

Background: The aim of this study is to evaluate the role of hematological parameters in predicting Fuhrman grade and tumor stage in renal cell carcinoma patients undergoing nephrectomy.
Methods: All patients newly admitted in the Department of Genitourinary Surgery in Kozhikode Medical College with a diagnosis of renal cell carcinoma from 01 August 2020 to 31 July 2021 were included after taking informed consent and considering the inclusion and exclusion criteria.
Results: Hematological parameters such as red blood cell distribution width (RDW), haemoglobin to platelet ratio (HPR), procalcitonin (PCT) and platelet to lymphocyte ratio (PLR) when correlated with the grade of cases, RDW and PLR were seen increased in high grade tumours. RDW and PLR showed statistically significant correlation with a p value of <0.001 for RDW and 0.02 for PLR. An RDW above 14.2 and PLR more than 140.69 is likely to be predictive of high Fuhrman grade. ROC curve was plotted and the mean RDW, PLR, PCT cut-off values of the patients for FG and T stage were 12.8%, 130.7, 0.24% and 13.8%, 166.01, 0.19% respectively. RDW, PLR, PCT, HPR were analyzed for any correlation for predicting whether the tumor be limited to kidney or extending outside kidney. Only RDW showed a statistically significant result with p value 0.02 and it suggests that RDW above 14.52 is suggestive of a tumor limited to kidney.
Conclusions: We conclude that when hematological parameters such as RDW and PLR were correlated with grade of the tumor and RDW with the stage of the tumor. HPR and PCT didn't show significant relation with grade of tumor.

Keywords: Hematological parameters, Renal cell carcinoma, PCT, PLR, RDW, HPR

INTRODUCTION

Accounting for approximately 2% of global cancer diagnoses and projected to burden upon the global demographic outspread and public health finances, renal cell carcinoma (RCC) continues to be one of the most portentous neoplasms, perturbing medical professionals worldwide. A 2018 GLOBOCAN study estimates 403,000 annual diagnoses of neoplasms of the kidney, thereby accounting for 2.2% of all cancer diagnoses. With approximately 254,500 of RCC cases diagnosed in males and 148,800 in females, men are at a relative risk of about 1.7 compared to women.[1] This is mainly attributed to the most important modifiable risk factor, smoking. The unmodifiable risk factors for renal cell carcinoma include race, age, and sex, whereas, the modifiable risk factors include smoking, alcoholism, obesity, hypertension, and occupational exposure. However, the evaluation of RCC risk factors may be biased by case counts of incidental cancer detection during diagnoses performed for other reasons. This is suspected to have increased the probability of misconstrued associations between RCC and some specific cofactors.[2]

The systemic immune-inflammation index (SII), being a function of blood counts of neutrophils, lymphocytes, and platelets, has long been recognized as a prognostic factor for mortality and an indicator for various malignancies.

Though conclusive evidence associating an increased SII with a risk for developing cancer in generally healthy individuals remains elusive, studies have found higher SIIs at baseline associated with a 30% higher risk of developing a solid cancer.[3]

The physiological changes that manifest as malignancy develops often include inflammatory responses and interaction with the tumour microenvironment.[3] Such inflammatory microenvironments are known to induce evasion from immune responses and promote tumour progression. Neutrophils and lymphocytes are considered the primary components of the tumour-related stroma. Apart from being associated with local inflammation and immune responses, they also reflect the balance between pro-tumour and anti-tumour status.

Pathophysiological markers that are characteristic of certain malignancies may leave notable trails. An elevated platelet count can be considered as a reliable metric for the severity of inflammation in cancer vide its indirect relation to pro-inflammatory mediators.[4]

Platelet to lymphocyte ratio (PLR) is an inflammatory marker which has gained prognostic value in a number of malignant diseases, including RCC. PLR has also been reported to be linked to poor outcomes in different malignant tumours. RBC distribution width (RDW) measures variation in red blood cell size and is now considered as a marker of inflammation and unfavourable prognostic factor in malignancies. It is a negative predictor of overall and cancer-specific survival.[5] Reduced haemoglobin to platelet ratio (HPR) seems to be linked to poor outcomes in urothelial cancer.

Identification of prognosis predictors could have clinical significance influencing therapeutic decisions and follow-up arrangements. Preoperative biomarkers could aid in effectively predicting oncologic outcomes, considering that most prognosis predictors are assessed postoperatively. The hematological parameters of inflammation are easily available with the modern instrumental solutions such as hematological analyzer. This makes the hematological parameters a promising marker for the prognosis and risk stratification of various malignancies. Hence proceeding with this study which evaluates the role of hematological parameters in predicting Fuhrman grade and tumor stage in RCC.

METHODS

This is a prospective cohort study done in 76 patients admitted in the Department of Urology in Government Medical College Kozhikode with a diagnosis of renal cell carcinoma for radical/partial nephrectomy from 01 August 2020 to 31 July 2021.

The present study got approval from Institutional Review Board of Kozhikode Medical College (Approval number GMCKKD/RP2020/IEC/497). Patients with non RCC malignant mass, benign mass, metastatic RCC and who didn't undergo surgical treatment were not included in the study. Each participant was interviewed with a structured questionnaire. Information obtained about the patients included the bio-data as well as past medical and surgical history. This includes age, sex, symptoms, history of any previous illness or addictions.

Detailed clinical examination of the patient and radiological investigations for staging the tumour was done. Tumor staging was performed in accordance with the 2009 tumor node metastasis (TNM classification (7th edition) approved by Union for International Cancer Control (UICC).[6] Size of the tumour was also collected from radiological investigation. Relevant laboratory investigations were done and RDW.

MPV, PLT, PCT, PLR, HPR values of patients were obtained preoperatively. Nephrectomy specimens were sent for histopathology and their results with Fuhrmans grading was recorded.

The patients were divided into two groups based on their FG: low (I–II) and high (III–IV) and their T stages were similarly grouped as limited to kidney (pT1–pT2) and not limited to kidney (pT3–pT4). The RDW, PLR, HPR, PCT values were compared in terms of their role in predicting pathologically low or high FG, their relationship with T stages limited and not limited to the kidney, as well as their sensitivity, specificity, and negative predictive values (NPV) and positive predictive values (PPV) percentages.

Inclusion criteria

Patients with newly-identified RCC who underwent radical or partial nephrectomy and pathologically diagnosed as RCC without under-listed exclusion criteria and who gave their consent to take part in the study were included.

Exclusion criteria

Patients who had non-RCC malignant masses, masses that did not correspond to known RCC types, masses with benign pathology, patients who had distant metastases at the time of diagnosis, patients who did not undergo surgical treatment, patients who had autoimmune diseases and other malignancies besides RCC, and patients who had incomplete data were excluded.

RESULTS

76 patients participated in this study, of which 53 (69.7%) were males and 23 (30.3%) females. Mean age of patients participated in this study was 57.96 for males and 55.69 for females. Detection of renal mass was incidental in 34 cases (44.7%), while 23 patients (30.3%) presented with hematuria, 16 patients (21.1%) with loin pain and 3 patients (3.9%) with fever. 56.6 % of patients had renal mass on left side while 43.4% had on right side. 30 patients

(39.5%) were hypertensive, while 28 patients (36.8%) were diabetic. 46.1% of patients included in the study were smokers, while 32.9% patients were alcoholics. The mean hemoglobin of patients included in the study was 12.90. Mean neutrophil count was 5888.48, mean lymphocyte count was 2296.51 and platelet count 279618.42 (Table 1).

Table 1: Demographic profile of patients.

Variables	N (%)
Number of patients	76
Gender	
Male	53 (69.7)
Female	23 (30.3)
Age, mean (SD)	
Males	57.96 (10.28)
Females	55.69 (12.09)
Presentation type	
Incidental	34 (44.7)
Hematuria	23 (30.3)
Loin pain	16 (21.1)
Fever	3 (3.9)
Laterality	
Right	33 (43.4)
Left	43 (56.6)
Medical history	
Hypertension	30 (39.5)
Diabetes	28 (36.8)
Habits	
Smoking	35 (46.1)
Alcohol	25 (32.9)
Hematological parameters, mean (SD)	
Hemoglobin	12.9 (2.04)
Neutrophil	5888.48 (1452.32)
Lymphocyte	2296.51 (766.51)
Platelet	279618.42 (79628.63)
T stage	
Limited to kidney (T1-T2)	63 (82.9)
Not limited to kidney (T3-T4)	13 (17.1)
Fuhrman grade	
Low grade (I-II)	40 (52.6)
High grade (III-IV)	36 (47.4)

The correlation between the hematological parameters and Fuhrman grade was analysed using independent t test (Table 2). Regarding RDW, the low mean was 12.73 and high mean 14.42, and a p value of <0.001 which is highly significant. Platelet lymphocyte ratio correlation also showed a statistically significant p value of 0.02 with a low mean of 107.93 and high mean of 140.69.

The RDW (>14.42) and PLR (>140.69) were determined to be statistically significant predictors of a pathologically high FG. Meanwhile PCT and HPR didn't show any statistical significance.

Analysis was done to assess relation between the local stage of tumor and hematological parameters, which revealed a significant p value of 0.02 for RDW. The relationships of RDW (>14.52) value with a pathological T stage limited to the kidney revealed statistically significant correlation, but not with PCT, PLR or HPR (Table 3).

Chi square test was done to look for any association between smoking and alcoholism with Fuhrmans grade. There is no statistically significant association according to this study. 44 out of 76 patients (57.9%) had T1 tumor, 21 patients (27.6%) T2, 9 patients (11.8%) T3 and only 2.6 % had T4 disease. Disease was limited to kidney in 63 out of 76 patients.72.4% of patients (55 out of 76) were in Fuhrman grade 2 and 3 group. Fuhrman grade 4 was the least (9.2%).

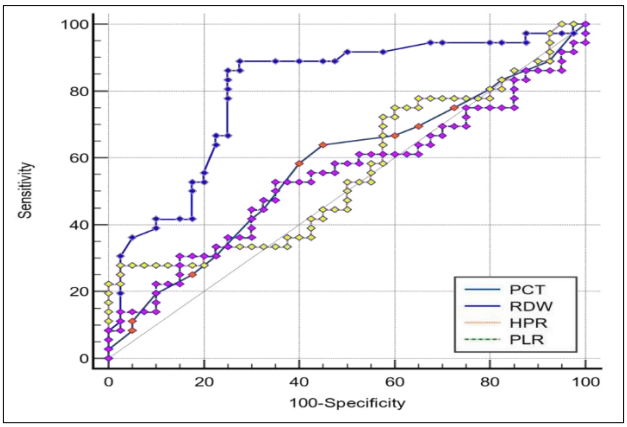

Figure 1: Results of ROC curve of PCT, RDW, PLR, HPR to predict grade.

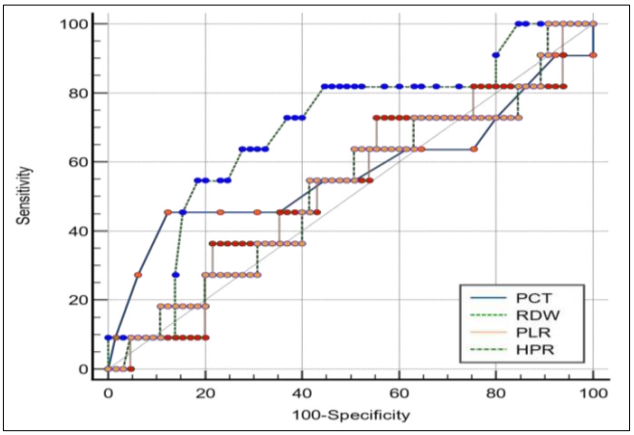

Figure 2: Results of ROC curve of PCT, RDW, PLR, HPR to predict tumor stage.

When ROC curve was plotted against the grade of tumor with hematological parameters (Figure 1), RDW was showing 88.8 percent sensitivity and 72.5 percent specificity in diagnosing high grade tumor with a AUC of 0.8 and p value of 0.001.

PLR was showing 72.8 percent sensitivity and 85 percent specificity in diagnosing high grade tumor with a AUC of 0.7 and p value of 0.03 (Table 4). When ROC curve was plotted against the stage of tumor with hematological parameters (Figure 2), RDW was showing 72.7 percent sensitivity and 61.5 percent specificity in diagnosing a tumor confined to kidney with a AUC of 0.7 and p value of 0.03 (Table 5).

Table 2: The relationship between PCT, RDW, PLR, HPR and Fuhrman grade.

Variables	Low mean (SD)	High mean (SD)	T value	P value
PCT	0.24 (0.04)	0.25 (0.04)	-1.02	0.31
RDW	12.73 (1.36)	14.42 (1.38)	5.34	<0.001**
PLR	107.93 (44.79)	140.69 (61.47)	1.04	0.02*
HPR	0.005 (0.001)	0.005 (0.002)	1.74	0.08

Independent t test

Table 3: The relationship between PCT, RDW, PLR, HPR and T stage.

Variables	Kidney (T1T2) mean (SD)	Outside kidney (T3T4) mean (SD)	T value	P value
PCT	0.25 (0.04)	0.24 (0.06)	0.77	0.44
RDW	13.36 (1.58)	14.52 (1.47)	-2.27	0.02*
PLR	134.04 (52.97)	133.61 (58.33)	0.02	0.98
HPR	0.005 (0.001)	0.004 (0.001)	0.27	0.78

Independent t test, *p value <0.05 is statistically significant; ** <0.001 is statistically highly significant

Table 4: Results of ROC curve of PCT, RDW, PLR, HPR to predict grade.

Fuhrman grade	AUC	Confidence interval U	L	Cut off	Youden index	Sensitivity	Specificity	+LR	-LR	PPV	NPV	P
PCT	0.57	0.45	0.68	0.24	0.18	63.9	55.0	1.42	0.66	56.1	62.9	0.29
RDW	0.80	0.69	0.88	12.8	0.61	88.8	72.5	3.23	0.15	74.4	87.9	0.001*
PLR	0.71	0.52	0.82	130.7	0.31	72.8	85	1.51	0.73	67.6	80.5	0.03*
HPR	0.55	0.43	0.67	0.0065	0.25	27.8	97.5	5.56	0.76	83.3	59.4	0.41

AUC=Area under the curve, PPV=positive predictive values, NPV=negative predictive values, +LR=positive likelihood ratio, -LR=negative likelihood ratio

Table 5: Results of ROC curve of PCT, RDW, PLR, HPR to predict tumor stage.

Fuhrman grade	AUC	Confidence interval U	L	Cut off	Youden index	Sensitivity	Specificity	+LR	-LR	PPV	NPV	P
PCT	0.57	0.45	0.68	0.19	0.33	45.5	87.7	3.7	0.6	38.5	90.5	0.56
RDW	0.7	0.57	0.79	13.8	0.37	72.7	61.5	1.9	0.4	24.2	93	0.03*
PLR	0.53	0.41	0.64	166.01	0.17	81.8	24.6	1.1	0.7	15.5	88.9	0.76
HPR	0.52	0.41	0.63	0.00450	0.13	54.55	58.46	1.3	0.8	18.2	88.4	0.82

DISCUSSION

There were of total 76 persons involved in the study out of which 53 were males and 23 were females. The mean age of males participated in this study was 57.96 with a standard deviation of 10.28 and for females it was 55.69 with a standard deviation of 12.09. Douglas et al in their study showed only 4.7% of their study population were less than 40 years.[7]

Peired et al in their study mentioned that incidence of RCC is more in males than in females.[8] In our study 30.3% of cases were females that is 23/76 and 69.7% were males that is 53/76 of cases which is in accordance with previous study.

44% of the cases were detected incidentally, rest 56% presented with hematuria, abdominal pain or fever which corresponds to the results of previous study. Vasudev et al in their study showed that majority (60%) of patients were

diagnosed incidentally. 87% of patients with stage Ia and 36% with stage III or IV disease presented incidentally. Visible haematuria was reported in 23% of patients and was commonly associated with advanced disease.[9]

We assessed the hematological parameters of seventy-six cases. RDW, PLR, PCT, HPR were analyzed for any correlation for predicting Fuhrman grade. RDW and PLR showed statistically significant correlation with a p value of <0.001 for RDW and 0.02 for PLR (Table 1). An RDW above 14.2 and PLR more than 140.69 is likely to be predictive of high Fuhrman grade. ROC curve was plotted (Figures 1 and 2) and the mean RDW and PLR cut-off values of the patients for FG and T stage were 12.8%, 130.7 and 13.8%, 166.01, respectively (Tables 3 and 4). Kisa et al in 2019 showed that the RDW (>15.65) and NLR (>3.65) were determined to be statistically significant predictors of a pathologically high FG, whereas the PCT (>0.28) value was not a statistically significant predictor of high FG.[10]

RDW, PLR, PCT, HPR were analyzed for any correlation for predicting whether the tumor be limited to kidney or extending outside kidney. Only RDW showed a statistically significant result with p value 0.02 and it suggests that RDW above 14.52 is suggestive of a tumor limited to kidney (Table 2). Yuk et al in their study showed that the patients with a high PLR had worse clinical characteristics in terms of advanced clinical stage (p<0.001) and rate of lymph node invasion. But our result is not in accordance with the result of this study.[11]

According to Kisa et al, the relationships of RDW (>14.35), NLR (>2.69) and PCT (>0.28) values with a pathological T stage limited to the kidney revealed statistically significant correlations. But in our study that relationship was established only with RDW (>14.52).

When comparing the smoking and alcoholism status and T stage and Fuhrman grade, there was no significant relation observed between them.

57.9 of cases were in T1 stage and 27.6% in T2 stage. According to Qin et al, 55.6% patients presented in T1 stage in their study.[12] This is in accordance with the results of our study.

Our study assessed the clinical significance of inflammation-related parameters derived from peripheral blood in RCC, including RDW, HPR, PLR, and PCT. There were significant increases in RDW, and PLR between low grade and high grade. Our present data showed that patients with RCC were different from healthy person in inflammatory condition and patients with different stages had different inflammatory states. From these results, we can infer that an inflammatory response continuously progresses in patients as disease advances. In addition, RDW and PLR were found to be independent predictors of grade of tumour, while PCT and HPR were not.

The prognostic value of pretreatment PLR in renal cancer patients has less been examined than NLR and RDW. According to Huszno et al, higher PLR (p=0.0002) was an independent negative prognostic factor for PFS together with higher Fuhrman grade (p=0.001), higher neutrophil level (p=0.001), and lower lymphocyte level.[13] According to our study, high PLR values increased the likelihood of the presence of a high grade tumor.

The association between PLR and Fuhrman grade is a less studied area, while there are enough studies for RDW, NLR and grade of tumor. The real importance of this study comes in case of small renal masses, which is a very frequently encountered and seemingly difficult scenario to choose the management option. In cases where these small renal masses are managed conservatively with active surveillance, the use of these hematological parameters in predicting grade of tumor helps in prognostication. The absence of a specific tumor marker for RCC and decreased chance of getting a successful biopsy report to grade the tumor makes the hematological parameters a valuable option, and it helps in deciding whether to continue follow-up or to proceed with surgery.

The occurrence, development, and prognosis of neoplasm involve multiple factors, including inflammation and host immunity response. The link between inflammation and cancer can be taken together, the levels of monocyte, neutrophil, and platelet reflect inflammatory states that act as evil in tumor microenvironment of patients with cancer and lymphocyte levels indicate an antitumor response. PLR, HPR, NLR, MLR are parameters that take both inflammatory cells and lymphocytes into account, so their variation in renal cancer patients reflects a state of inflammatory responses and antitumor immune responses in cancer progression.

There are some limitations in this study. The sample size in our study is small and the proportion of advanced RCC is low as well, which may lead to incorrect results in evaluating the significance of the parameters, as the hematological ratios such as HPR and PLR are more useful and indicative of tumour characteristics in advanced RCC. The hematological parameters evaluated in this paper are transient and susceptible to many factors and we cannot eliminate all of potential factors that impact these parameters. Finally, RDW, PCT, HPR and PLR are all based on machine automatic count, which makes it difficult to validate the correctness of our data. Therefore, the studies below are required to confirm our observations: a large-scale prospective study with repetitive measurements data that considers as many as possible confounding factors, a set of validated study like flow cytometry with cell markers compared with machine reading data. Despite these important limitations, our study presents the possible role of RDW and PLR in clinical practice of RCC.

CONCLUSION

In our study we analysed the hematological parameters of RCC patients and assessed its role in predicting Fuhrman grade and tumor stage and found that high values of PLR and RDW increases the likelihood of high Fuhrman grade, in other words it can predict the chance of high Fuhrman grade in a patient preoperatively. Also, a high RDW increases the chance of a tumor being confined to kidney only. NLR and PLR, which are easily calculated, readily accessible and inexpensive, could be simple-to-use predictors of Fuhrman grade and might be used to manage the disease accordingly. It is essentially useful in cases of small masses for active surveillance or advanced inoperable mass, these parameters can predict the grade of disease.

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