Original research article

A Hospital based Prospective Assessment of the Prognostic Potential of FAR of Patients with Renal Cancer

Dr. Rana Pratap Singh[1], Dr. Arshad Jamal[2], Dr.Nikhil Ranjan[3]

[1]Assistant Professor, Department of Urology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

[2]Associate Professor, Department of Urology, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

[3]Assistant Professor , Department of Urology, IGIMS, Patna Bihar, India

Corresponding Author: Dr. Arshad Jamal

Abstract

Aim: We investigated whether FAR had a potential value in evaluating the prognosis of patients with non-metastatic kidney cancer or not.

Methods: The present study was conducted in the department of Urology, Rajendra Institute of medical sciences (RIMS), Ranchi, Jharkhand, India and 50 patients with renal cancer who underwent radical nephrectomy were included in the study.

Results: Of the 50 patients included in the study, 36 (72%) were male and 14 (28%) were female. Of the 50 individuals in our control group, 44 (88%) were male and 6 (12%) were female. The mean age in the patient group was 58.86 (min 34-max 82) and the mean age in the control group was 59.05 (min 32-max 81). There were 43 (86%) patients with grade 1–2 and 7 (14%) patients with grade 3–4 according to Furhman Grade (FG). The distribution by tumor size was similar to the distribution set by FG. According to TNM staging, the number of patients with T1-2 was 43 (86%) and the number of patients with T3-4 was 7 (14%). Median score (min–max) NLR, PLR, HRR, LMR, SLL and FAR in all patient groups were 6.10 (1.17–25.37), 165.0650 (41.30–708.33), 0.9450 (0.44–1.38), 2.4100(0.42–32.87), 1,271,030(102,030–7,203,240) and 0.08000(0.007/0.286) respectively. In the control group, the Median score (min–max) of NLR, PLR, HRR, LMR, SLL and FAR were 1.4500 (0.34–4.69), 93.6250 (67.00–270.23), 1.0250 (0.57–1.35), 2.3000 (1.00–8.09), 505,975.00 (234,546– 1,428,000) and 0.05450 (0.010– 0.117) respectively.

Conclusion: Recently, the prognostic significance of FAR in various cancers has been investigated. In non-metastatic RCC patients, there is a need for indices which have prognostic importance to determine a cut-off during follow-up; to better categorize patients according to grade and tumor size; to reach early treatment and not to impair patients' quality of life.

Keywords: Renal cell cancer, Fibrinogen to albumin ratio, Biomarkers, Prognostic factor

INTRODUCTION

Renal cell carcinoma (RCC) represents 2-3% of malignancies worldwide.[1] Although, 70% of patients who present with localized disease are amenable to curative treatment with radical or partial nephrectomy, 20-40% of these cases will develop metastatic disease.[2,3] Surgical management is the treatment of choice and has evolved deeply in the past decade.[4] At

present, patients usually present with localized RCC that can be cured with either partial or radical nephrectomy. After Nephrectomy, patients will be scheduled for follow up with imaging to diagnose local recurrence or metastatic disease. Currently, there is no consensus guideline for the optimal time for follow up which should be individualized on patients risk factors.[5,6]

There are no valid postoperative risks stratification for non-metastatic RCC patients for this purpose, the clinical outcome of treatment is varied even in patients who are classified into the same TMN staging group, and received similar treatment.[7] It is necessary to find other prognosis factors that can accurately assess patient outcomes. Increasing evidence supports the association of the systemic inflammatory response and progression of malignancy. Hence, measurement of inflammatory response markers, such as elevated C-reactive protein levels, platelet count, neutrophil, hypoalbuminemia, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), allows the prediction of patients' survival in many cancers and guides the choice of adjuvant treatment in each patient.[8,9]

The initiation, development, invasion, and metastasis of a tumor are always accompanied by inflammation and immune response, which have a complex interaction with the tumor microenvironment.[10,11] Recently, hematological inflammatory markers that are easily and quickly measured in the clinic, such as red cell distribution width (RDW), monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR), are drawing increased attention because they could be prognostic or predictive factors for numerous cancers.[12] Fibrinogen and albumin are frequently measured tests in clinical practice. Fibrinogen is both an indicator in the coagulation cascade and an acute phase protein that increases in systemic inflammation.[13] Albumin is a negative acute phase protein that decreases in systemic inflammation.[14]

This study aimed to evaluate the prognostic value of a preoperative FAR in patients RCC and to compare it with established systemic inflammation markers, including NLR, LMR, PLR, hemoglobin-RDW(Red Cell Distribution Width) ratio (HRR) and SII.

METHODS

The present study was conducted in the department of Urology, Rajendra Institute of medical sciences (RIMS), Ranchi, Jharkhand, India and 50 patients with renal cancer who underwent radical nephrectomy were included in the study.

All cases were confirmed with a postoperative pathology report. None of the patients had a history of other types of malignant tumor, lymph node metastasis or distant metastasis, cardiovascular, thrombotic, liver failure or infection diseases. We also included 50 healthy individuals as the control group in our study. The individuals included in the control group were older than 18 years. In addition, these people had no diagnosis of acute infection, acute renal failure, liver failure, chronic disease or cancer throughout the study. During the follow-up of this study, the patients or their relatives were informed about the content of this study in detail and oral and written informed consent were provided.

Pathological and clinical data of all patients were obtained completely from the hospital's medical records. All blood test results, including serum fibrinogen and albumin levels, white blood cell count, and platelet count, were obtained within 2 weeks before surgery. Inflammatory indices were calculated using the following formulas: FAR = total fibrinogen/ total albumin; NLR = neutrophil count/lymphocyte count; LMR = lymphocyte count/

monocyte count; PLR = platelet count/lymphocyte count; SII = platelet count × NLR; HRR = hemoglobin count/RDW count.[15]

The patients were followed up every 3 months in the first 3 years and every 6 months thereafter. Patients were followed up with blood examination, biochemical tests, chest and abdominal CT (Computed Tomography). OS was calculated from the date of diagnosis to the date of death due to disease, and disease-free survival (DFS) was calculated from the date of diagnosis to the date of tumor recurrence.

Statistical analysis

SPSS 24.0 software was used to analyze the data. The normal distribution of the data, arithmetic mean, ± standard deviation, and median minimum/maximum values were analyzed by Shappiro wilk test. Student T test was used for the analysis of 2 groups with normal distribution, and Mann–Whitney U test was used for the analysis of 2 groups without normal distribution. Kaplan–Meier and Log-rank tests were used to evaluate survival. The best cut off value of the FAR was obtained using ROC curve analysis, and patients were divided into high- and low-FAR groups. The correlation between the preoperative FAR and clinic-pathological features was analyzed with Log-rank test. $P < 0.05$ was accepted for statistical significance.

RESULTS

Table 1: Comparison of clinicopathological data of different FAR groups

Features	Total (%)	Preoperative FAR		P value
		≤ 0.114 (n = 35)	> 0.114 (n = 15)	
Age				
≤ 65 years	35 (70)	21 (60)	14 (40)	0.938
>65 years	15 (30)	14 (93.34)	1 (6.66)	
Gender				
Male	36 (72)	25 (69.44)	11 (30.55)	0.750
Female	14 (28)	10 (71.42)	4 (28.58)	
Fuhrman grade				
I–II	43 (86)	40 (93.02)	3 (6.97)	< 0.0001
III-IV	7 (14)	1 (14.2)	6 (85.8)	
Pathological T stage				
pT1–2	43 (86)	40 (93.02)	3 (6.97)	< 0.0001
Pt3–4	7 (14)	1 (14.2)	6 (85.8)	
Histology				
Clear cell carcinoma	50 (100)	36 (72)	14 (28)	< 0.0001
Non clear cell carcinoma	0	0	0	
Case survıval				
Exitus	5 (10)	0	5 (100)	< 0.0001
Alive	45 (90)	35 (77.77)	10 (22.23)	

Of the 50 patients included in the study, 36 (72%) were male and 14 (28%) were female. Of the 50 individuals in our control group, 44 (88%) were male and 6 (12%) were female. The mean age in the patient group was 58.86 (min 34-max 82) and the mean age in the control group was 59.05 (min 32-max 81). Patients younger than 18 years of age were not included in the study. The patient group was selected from patients who had radical nephrectomy in the urology department. Of the 50 patients, 5 died during the 24-month follow-up period. The average DFS was 34 months and the OS was 34 months as of the period of analysis. When

the OS and DFS rates were compared with the Log Rank test, there was no significant difference between male and female patients ($p > 0.05$). All of the patients had undergone radical nephrectomy and their histological subtype was reported as clear cell carcinoma based on pathological findings. There were 43 (86%) patients with grade 1–2 and 7 (14%) patients with grade 3–4 according to Furhman Grade (FG). The distribution by tumor size was similar to the distribution set by FG. According to TNM staging, the number of patients with T1-2 was 43 (86%) and the number of patients with T3-4 was 7 (14%).

Table 2: Mean and median values of hematological parameters in patient and control groups

Group	Age	NLR	PLR	Hgb/RDW	LMR	SII	FAR
Control							
N	50	50	50	50	50	50	50
Mean	59.05	1.58	106.96	1.00	2.84	526,446.8	0.555
Std. Deviation	9.32	0.92	41.41	0.187	1.32	233,046.0	0.026
Median	60.0	1.45	93.62	1.02	2.30	505,975.0	0.054
Minimum	32	0.34	67.0	0.57	1.00	234,546	0.010
Maximum	81	4.69	270.23	1.35	8.09	1,428,000	0.117
Patient							
N	50	50	50	50	50	50	50
Mean	58.86	7.88	194.98	0.92	3.74	1,731,262	0.097
Std. Deviation	11.53	6.27	118.73	0.203	5.64	1,469,844	0.054
Median	59.0	6.1	165.07	0.94	2.41	1,271,030	0.08
Minimum	34	1.17	41.30	0.44	0.42	102,030	0.007
Maximum	82	25.37	708.33	1.38	32.87	7,203,240	0.286
Total							
N	100	100	100	100	100	100	100
Mean	58.93	5.63	163.54	0.94	3.42	1,300,971	0.082
Std. Deviation	10.75	5.88	106.84	0.20	4.59	1,318,051	0.0504
Median	59.0	2.94	130.32	0.97	2.34	676,058.5	0.071
Minimum	32	0.34	41.30	0.44	0.42	102,030	0.007
Maximum	82	25.37	708.33	1.38	32.87	7,203,240	0.286

Median score (min–max) NLR, PLR, HRR, LMR, SLL and FAR in all patient groups were 6.10 (1.17–25.37), 165.0650 (41.30–708.33), 0.9450 (0.44–1.38), 2.4100(0.42–32.87), 1,271,030(102,030–7,203,240) and 0.08000(0.007/0.286) respectively. In the control group, the Median score (min–max) of NLR, PLR, HRR, LMR, SLL and FAR were 1.4500 (0.34–4.69), 93.6250 (67.00–270.23), 1.0250 (0.57–1.35), 2.3000 (1.00–8.09), 505,975.00 (234,546– 1,428,000) and 0.05450 (0.010– 0.117) respectively. NLR, PLR, HRR, SLL and FAR ratios between the patient and control groups were found to be significantly higher in the patient group when compared with the Mann–Whitney U test $p < 0.001$.

The patients were divided into 2 groups as Grade 1–2 and Grade 3–4. When the NLR, PLR, HRR, LMR, SLL and FAR values of these two groups were compared with Mann–Whitney-U and Wilcoxon tests, PLR and FAR values were significantly higher in the Grade 3–4 group ($p < 0.05$). In addition, the patients were divided into two groups as T1-2 and T3-4. At the same time, PLR and FAR rates were significantly higher in T3-T4 patients ($p < 0.05$).

DISCUSSION

FAR, which reflects the ratio of fibrinogen to albumin, has been a candidate to be a good prognostic factor in many cancers in recent years. In this regard, studies have been conducted on many cancers such as esophageal cancer[16], hepatocellular carcinoma[17], breast cancer[18], renal cell carcinoma[19] and prostate cancer.[20] Nuclear grade, pathological stage, and pathological tumor type are commonly used indices to evaluate the prognosis of patients with RCC.[21] However, the effect of inflammation on tumor biology has been the subject of research for centuries. In general, inflammation is believed to affect every stage of tumor development, from tumor formation to metastases.[22] Pre- and post-operative inflammation indicators can predict the prognosis of the tumor, and these markers can guide the clinician in the treatment and follow-up of the disease.

Systemic inflammation and coagulation are closely associated with tumor development.[23] Fibrinogen can be directly involved in cell angiogenesis, proliferation and distribution. It can do this by directly participating in the interaction between vascular endothelial growth factor, transforming growth factor-B, platelet-derived growth factor and fibroblast growth factor.[24-26] Albumıne which has been shown to decrease in inflammation is a negative acute phase reactant.[14] Inflammation and tumor formation and development reduce albumin levels, and as albumin decreases, the immune system may weaken and tumor development may accelerate.[27] We did not include patients with infectious disease, liver disease, known coagulation disorder and heart disease when choosing our patient group since albumin also decreases independently of the tumor in case of liver failure and infection.

In the present study, patients were divided into grades 1–2 and 3–4. In addition, according to the pathological tumor size, 2 separate groups were formed as T1-2 and T3-4. On the other hand, we also had a control group of 50 healthy individuals. When the NLR, PLR, HRR, SLL, FAR ratios between the patient group and the control group were compared with the Mann–Whitney U test, a significant increase was found in the patient group ($p < 0.001$). There was no additional disease in the healthy control group and the patient group and we found that FAR and other inflammatory blood indices were higher in the patient group. In different studies, these indices have been interpreted as useful prognostic factors in RCC.[28,29]

The number of patients with grade 3–4 in the patient group was 11 and the number of patients with grade 1–2 was 61. PLR and FAR rates were significantly higher in the grade 3–4 patient group ($p < 0.05$). Likewise, when the T1-2 and T3-4 groups were compared, the PLR and FAR ratios were found to be significantly higher in the T3-4 group ($p < 0.05$). It was assumed that the same results emerged due to the fact that patients with T3-4 and patients with grade 3–4 were in the same group.

In a study conducted by Jun Liu et al., similar results were obtained, and in this study, FAR and OS were compared among patients with grade 3–4 patients, but it was observed that FAR could not distinguish patients with worse OS. It was believed that this might result from the smaller number of grade 3–4 patient groups, as in our study. However, the prognostic effect of FAR was found to be more significant in the grade 1–2 subgroup. In other words, a patient with grade 1–2 with high FAR was believed to have worse OS, and it was recommended that these patients be followed more closely.[19] Since the number of patients was lower in our study, no significant relationship was found between FAR and OS in the subgroup analysis. Ki-Tae Hwang et al. conducted a study on 793 patients with breast cancer and found that FAR was significantly higher in patients with stage 3–4, tumor size > 2 cm, and lymph node positive, and its prognostic importance was emphasized in these patients.[18] In this study, it

was reported that the importance of FAR could not be determined clearly in subgroup analyses and further research was required on this subject.

CONCLUSION

Recently, the prognostic significance of FAR in various cancers has been investigated. In non-metastatic RCC patients, there is a need for indices which have prognostic importance to determine a cut-off during follow-up; to better categorize patients according to grade and tumor size; to reach early treatment and not to impair patients' quality of life. Therefore, studies on FAR are very important. We believe that the present study will contribute to the studies conducted in order to determine the prognostic importance of FAR in RCC.

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