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Clinical significance of pretreatment De Ritis ratio in renal cell carcinoma

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ABSTRACT

Aims: This study aimed to investigate the relationship between pretreatment De Ritis ratio and Fuhrman nuclear grade and tumor stage in renal cell carcinoma (RCC).

Methods: The data of 288 patients treated for RCC were analyzed. The De Ritis ratio was evaluated in patients classified by Fuhrman nuclear grade and tumor stage. The De Ritis ratio between groups was compared using Levene's test.

Results: A total of 145 patients (50.3%) were women female. Their mean age, aspartate aminotransferase, alanine aminotransferase values, and De Ritis ratio were as follows, respectively: 60.32±12.65 years, 20.55±11.54 IU/L, 17.4±10.87 IU/L, and 1.34±0.75. The De Ritis ratio was 1.12±0.44 in the low stage group and 2.01±1.05 in the high stage group. According to the Fuhrman nuclear grading, the De Ritis ratio was 1.15±0.43 in the low grade group and 1.70±1.14 in the high grade group. There was a statistically significant difference between the groups ($p<0.001$).

Conclusion: The present study showed high preoperative De Ritis ratio is significantly correlated with high tumor stage and Fuhrman nuclear grade in RCC.

Keywords: De Ritis ratio, transaminases, renal cell carcinoma, furhman grade

INTRODUCTION

Renal tumors constitute approximately 3% of all malignancies seen in adulthood. It is the third most common urogenital malignancy following prostate and bladder cancers. According to histopathological analyses, 80-85% of all renal tumors were composed of renal cell carcinomas (RCC).[1] RCCs are more frequently observed in industrial societies and many factors such as obesity, hypertension, and smoking are blamed in the etiology. It is 1.5 times more common in males than in females, with a significant increase in the incidence of diagnosis in the 6th and 7th decades of life. Clinical presentation of RCC patients shows variation.[2] Only 6-10% of diagnosed cases present with the classic triad of RCC: gross hematuria, side pain, and a palpable abdominal mass.[3] Surgical resection is the only curative treatment option. 1/3 of the patients are metastatic at the time of diagnosis and another 1/3 may develop metastasis after treatment.[4]

In parallel with the developments in the field of uroradiology and the increased awareness of the patients, the number of RCC cases diagnosed has increased significantly over the years. Current literature suggests that RCC incidence has increased by 2-4% worldwide over the last decade.[5] The increased knowledge of RCC cases has led to different approaches regarding the clinical impression of the disease. In this context, promising improvements in prognosis have been observed. For example, the timing of cytoreductive nephrectomy in RCC has been recognized and proved to be indisputable. In addition, pharmacological agents, such as immunotherapy and targeted therapy, have entered clinical practice.[6] However, despite all these developments, RCC remains the most mortal urologic malignancy.[1] Therefore, the molecular biological character of RCC is important in developing an optimal treatment strategy against recurrent diseases and determining follow-up protocols. For this reason, it is very important to investigate prognostic markers in RCC patients.[7]

Alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) are liver enzymes commonly used in clinical laboratory tests.[8] The De Ritis ratio, calculated by dividing AST by ALT, was first described by Fernando De Ritis in 1957 as a diagnostic marker for viral hepatitis.[8,9] It is also used as an independent predictor of patient survival in chronic liver diseases.[10] On the other hand, intensive research has been carried out recently to show that the ratio of De Ritis will change in various malignancies according to the differences in the functions of these two enzymes in tissue distribution and energy metabolism.[7] In this context, previous clinical studies have reported that De Ritis ratio may be prognostic factors in urological tumors such as kidney, prostate, and bladder.[11-13]

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This retrospective study aimed to investigate the relationship of the preoperative De Ritis ratio with Fuhrman nuclear grade and tumor stage in patients who underwent partial or radical nephrectomy and were diagnosed with RCC based on histopathological examination

METHODS

Medical record of patients who underwent partial or radical nephrectomy in our clinic between January 2011 and May 2023 were analyzed retrospectively. A total of 288 patients patients, who received the diagnosis of RCC based on histopathological investigation were included. The Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.07.2023, Decision No: 23-KAEK-162) approved this study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients' ages, genders, ALT and AST levels were noted preoperatively. Pathological T stage, histological subtypes, Fuhrman nuclear grade of tissue samples were analyzed.[1,14-16] Surgical specimens were assessed for tumor grades and stage using the Fuhrman system and 2018 TNM classification respectively.[14] The De Ritis ratio, calculated by dividing AST by ALT.[8]

According to Fuhrman nuclear grade, Grade 1 and 2 patients were defined as low grade and the others as high grade. Similarly, stage 1 and stage 2 patients were classified as low stage and others as high stage. Fuhrman grade is not used in chromophobe RCC, renal medullary carcinoma and unclassified type of RCC due to the aggressive nature of these subgroups.

We excluded patients with a history of hepatitis, chronic liver disease alcoholism, heart failure, drug use that may impair liver enzymes, and any other cancer that may affect the AST/ALT ratio.

Statistical Analysis

Descriptive statistical work-up was conducted fort he study in order to give insight on general characteristics. Data on continuous variables were given as arithmetic mean and standart devision. As for inter-group comparisons of variables indicated with messurements, a t-test was used for independent samples to study inter-group differences. ROC (receiver operating characteristics) curve analysis was applied to determine the cut-off values of the variables, and the area under the Roc curve (AUC) was also evaluated. Levene's test was used to check whether data pertaining to continuous variables matched with normal distribution or not. A p-value of less than 0.05 was considered statistically significant. Calculations were made with available statistical software (IBM SPSS 22, SPSS Inc., an IBM Co., Somers, NY).

RESULTS

A total of 288 patients included in the study, 145 patients (50.3%) were female. The mean age was 60.32±12.65. Ninety nine patients (34.3%) underwent partial nephrectomy, and 189 patients (65.7%) underwent radical nephrectomy. A total of 151 patients (52.43%) were operated on the left side and 137 patients (47.57%) 62 patients (50.4%) on the right side. Seventy one patients (24.65%) had high-grade tumors (T3 or T4), and 217 (75.35%) had low-grade tumors (T1 or T2). In the Fuhrman nuclear grading, 218 patients (82.6%) had low-grade tumors, and 46 patients (17.4%) had high-grade tumors. Surgical specimens were evaluated according to histological subtypes: RCC in 216 patients (75%), papillary in 48 (16.67%), chromophobe in fourteen (4.86%), renal medullary carcinoma in six (2.08%), and an unclassified type of RCC in four (1.39%).

In the classification according to tumor stage, the AST/ALT ratio was 1.12±0.44 and 2.01±1.05 in the low and high-stage groups, respectively (Table). The relationship between low and high tumors was evaluated by ROC analysis. The NLR cut-off value was 0.873, with significant difference between the two groups (p<0.001) (Figure 1). The AST/ALT ratio for low- and high-grade tumors was 1.15±0.43 and 1.70±1.14, respectively. According to the ROC analysis of both groups, the cut-off value was 0.848, which was statistically significant (p<0.001) (Figure 2).

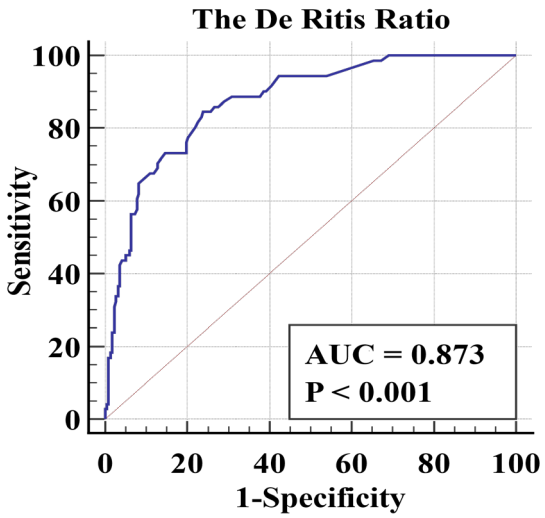

Figure 1. The result of ROC analysis for tumor stage
Area under the Roc curve:0.873, %95 confidence interval:0.829-0.909, significance level p<0.001*, associated criterion:1.25

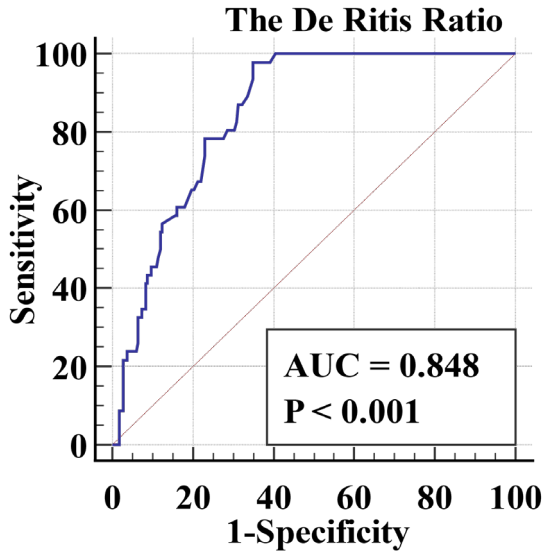

Figure 2. The result of ROC analysis for Fuhrman nuclear grade
Area under the Roc curve:0.848, %95 confidence interval: 0.799-0.889, significance level p<0.001*, associated criterion: 1.17

Table. De Ritis Ratio ratio according to tumor parameters				
		n	Mean±SD	p
Tumor stage	Low stage (T1+2)	217	1.12±0.44	<0.001*
	High stage (T3+4)	71	2.01±1.05	
Nuclear grade	Low grade (grade 1+2)	218	1.15±0.43	<0.001*
	High grade (grade 3+4)	46	1.70±1.14	
Indepence samples T test, *: p value is significant less than 0.05				

DISCUSSION

RCC is a highly complex disease in terms of histological subgroups, clinical course, and response to treatment. The prognosis is poor in patients diagnosed at the metastatic stage or who develop recurrence after receiving treatment for the local disease. The expected survival in patients presenting with metastasis varies between 6-10 months, with a 2-year survival rate of 10-20%. Local recurrence after radical nephrectomy is rare and ranges from 0.8% to 4% in various series.[17] A better understanding of the molecular biology of RCC, angiogenesis, and related signaling pathways has broadened horizons in the treatment strategies of the disease in recent years. Although there have been significant improvements in the use of targeted agents recently, there is ongoing scientific research on the use of these agents for adjuvant and neoadjuvant purposes. These improvements make it very important to predict the prognosis and response to the treatment chosen for RCC patients. However, clinicians are faced with great difficulties in predicting prognosis as the natural course of RCC is complex and varies from patient to patient.[18,19] TNM staging adapted for all solid tumors is the most important prognostic marker for RCC. In fact, many different prognostic markers have been analyzed in previous studies in the literature.[1] Anatomic prognostic factors include tumor size, venous invasion, capsule invasion, microvascular invasion, lymphovascular invasion, renal sinus fat invasion, perinefric fat invasion, adrenal involvement, lymph node, and distant metastasis. Histologic subgroup, sarcomatoid/rhabdoid transformation, nuclear grade, tumor necrosis, microvascular invasion, and collecting system invasion are evaluated for histopathological prognostic parameters. As for clinical factors, the patient's performance status, the presence of localized symptoms, cachexia, anemia, and thrombocytosis are analyzed.[18,20] In addition, a number of molecular markers have recently been shown to be important prognostic factors. The most prominent ones are carbonic anhydrase 9, hypoxia-inducing factor-1 alpha (HIF-1 alpha), VHL tumor suppressor protein, vascular endothelial growth factor (VEGF), apoptosis regulators (Bcl-2, p53), cell cycle regulators (p27 and Phosphatase-tensin homolog (PTEN), cell adhesion molecules (CD44, EpCam, Eph A2), C-reaktive Protein (CRP), and osteopontin.[18,21] However, due to the lack of standardization as well as the time-consuming and expensive nature of the as says none has been suitable for clinical practice.[11] In this context, the medical disciplines has long been in a search for using biochemical parameters for prediction of postoperative period. De Ritis ratio is one of them.

The relationship between the De Ritis ratio and cancer is based on different hypotheses.[22] Rapidly proliferating tumors convert glucose into lactate in an aerobic environment, although the amount of adenosine triphosphate obtained from one glucose molecule is very small. This feature of cancer cells is called the Warburg effect. Decreasing Ph affects the tumor microenvironment, influencing cancer progression, metastasis, and local invasion.[13] However, lactate elevation plays an essential role in the continuation of glycolysis, and cytosolic nicotinamide adenine dinucleotide hydride/nicotinamide adenine dinucleotide (NADH/NAD) is critical in glucose transport. AST is one of the important components of the malate-aspartate shuttle pathway that allows NADH/NAD conversion.[9,13] In addition, AST is generally produced in different tissue types such as kidney, heart, gastric mucosa, adipose tissue, skeletal muscle, and brain, while ALT is considered more liver-specific. Accordingly, a more serious increase in AST level is observed in tissue damage secondary to oxidative stress.[8,9,12]

The relationship between kidney cancer and De Ritis rate has been studied in detail in recent years. The case series of 698 cases by Bezan et al.[11] reported that the AST/ALT ratio was evaluated preoperatively as an independent prognostic factor in patients with non-metastatic RCC. In another study examining patients with non-metastatic RCC, Canat et al.[7] reported that an increased preoperative AST/ALT ratio was significantly associated with renal pelvis involvement, renal capsule infiltration and renal vein invasion. Ishihara et al.[10] stated that the preoperative AST/ALT ratio is an indicator for cancer-specific survival and overall survival in patients with metastatic RCC who underwent radical nephrectomy. Similarly, Laukhtina et al.[23] observed that a high preoperative De Ritis ratio was closely associated with liver metastasis in their studies evaluating metastatic RCC patients treated with cytoreductive nephrectomy. Lee et al.'s[24] large-series studies including 2965 cases reported that RCC patients with high AST/ALT ratios had significantly worse overall and cancer-specific survival outcomes. A retrospective study by Ikeda et al.[25] observed that the AST/ALT ratio was significantly associated with cancer-specific survival after radical nephrectomy in patients with RCC associated with end-stage renal disease. Kang et al.[26] reported that a high De Ritis ratio is correlated with adverse survival outcomes after first-line tyrosine kinase inhibitor therapy in patients with metastatic RCC. Our study observed that preoperatively increased AST/ALT ratio in patients with RCC was associated with higher postoperative tumor stage and Fuhrman grade. In another study, Batur et al.[27] could not find a significant value for the De Ritis ratio as a predictive parameter in non-metastatic clear cell RCC prognosis. In a similar study, Janisch et al.[28] examined 220 metastatic RCC patients treated with tyrosine kinase inhibitors and could not detect an independent association between the De Ritis rate and survival.

Limitations

The main limitation of our study is that it was conducted retrospectively, with a single center and a limited number of cases.

CONCLUSION

According to the data obtained in our study, preoperatively increased De Ritis ratio is closely associated with high tumor stage and Fuhrman grade. We think multicenter, randomized, and controlled studies are needed to use these data in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Tokat Gaziosmanpaşa University Faculty of Medicine Clinical Researches Ethics Committee (Date: 13.07.2023, Decision No: 23-KAEK-162).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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