European Journal of Therapeutics

DOI: 10.54614/eurjther.2022.0038

Original Article

Effectiveness of De Ritis (AST/ALT) Ratio in Predicting Biochemical Recurrence in Patients Underwent Radical Prostatectomy for Localized Prostate Cancer

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ABSTRACT

Objective: Several studies have shown that the De Ritis (aspartate aminotransferase/alanine aminotransferase) ratio is a prognostic biochemical biomarker in many cancers, including urological cancers. Biochemical recurrence is a well-known indicator of the biological aggressiveness of the tumor. In our study, we aimed to evaluate the predictability of the De Ritis ratio for biochemical recurrence in patients who underwent radical prostatectomy due to localized prostate cancer.

Methods: This study included 198 patients who underwent radical prostatectomy for localized prostate cancer between 2008 and 2015 in our clinic. Preoperative data of the patients included age, prostate-specific antigen level, post-biopsy Gleason score, De Ritis ratio, neutrophil/lymphocyte ratio, and platelet count. Among the postoperative data, the Gleason score, extracapsular invasion, positive surgical margin, seminal vesicle invasion, perineural invasion, lymph node invasion, and pathological tumor stage data were evaluated retrospectively. The relationship of these parameters was examined in patients who developed biochemical recurrence during the follow-up period.

Results: The mean follow-up period of the patients was 56.7 ± 23.6 months and biochemical recurrence occurred in 10.1% of all patients. In the receiver-operating characteristic analysis, the cut-off value for biochemical recurrence was 1.184, and the patients with a ratio below this value were grouped as the low De Ritis group and the patients with higher rates were grouped as the high De Ritis group. According to multivariate logistic regression analysis, high De Ritis ratio, Gleason score >8 of radical prostatectomy specimen, positive surgical margin, and the presence of seminal vesicle invasion were detected as independent risk factors for biochemical recurrence after radical prostatectomy.

Conclusion: De Ritis ratio is an independent risk factor for predicting biochemical recurrence in patients who underwent radical prostatectomy due to localized prostate cancer.

Keywords: Biochemical recurrence, De Ritis ratio, prostate cancer

INTRODUCTION

Prostate cancer is the second most common cancer in men after lung cancer and represents 15% of all cancer cases.[1] Radical prostatectomy and radiotherapy are the first options for the treatment of localized prostate cancer, and definitive treatment can be provided with both treatment methods. Unfortunately, biochemical recurrence (BCR) can be seen after radical prostatectomy, which is one of these treatment methods, and its frequency varies between 19% and 35% in a 10-year follow-up.[2] A great number of studies in the current literature have examined the factors that are associated with the risk of BCR after radical prostatectomy with interest. Fundamentally, high Gleason score, advanced stage tumor, and high basal serum prostate-specific antigen (PSA) levels are among the factors that are associated with BCR.[3]

The ratio of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), known as the De Ritis rate, was mainly utilized as an indicator for liver function.[4] Studies have implied that this ratio is an important prognostic factor for colorectal cancer, lung cancer, breast cancer, and pancreatic cancer, as well as urological cancers such as bladder cancer, upper urinary tract cancer, and testicular cancer.[5,6] Since the presence of active proliferation, active oxidative stress, and increased aerobic glycolysis in cancer cells causes this rate to increase, it can be thought that this ratio may indicate the biological behavior of cancer.[5]

In our study, we aimed to evaluate the predictability of the preoperative De Ritis ratio of patients who underwent radical prostatectomy due to localized prostate cancer and BCR recurrence in a 10-year follow-up.

Cite this article as: Taştemur S, Şenel S, Kasap Y, Odabaş O. Effectiveness of de ritis (AST/ALT) ratio in predicting biochemical recurrence in patients underwent radical prostatectomy for localized prostate cancer. *Eur J Ther.* 2022;28(1):8–13.

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Received: March 31, 2021 **Accepted:** May 18, 2021

METHODS

This study was performed in accordance with the principles of Helsinki Declaration and Ethics committee approval was received for this study from the ethics committee of Ankara City Hospital No.1 Clinical Research Ethics Committee (Date: March 24, 2021, Decision No: E2-21-303).

The data of 244 patients who underwent radical prostatectomy for prostate cancer in our clinic between 2008 and 2015 were retrospectively analyzed. All of the middle-high-risk patients included in our study were scanned for metastases with whole-body bone scintigraphy and abdominopelvic computed tomography, and patients with metastases were not included in the study. Forty-six patients with known liver disease, insufficient data, not being followed up, who underwent neoadjuvant hormone therapy, and who passed away during follow-up were excluded from the study.

This study included 198 patients. The diagnosis of prostate cancer in all patients was made by a transrectal ultrasound-guided biopsy performed due to elevated PSA levels and/or abnormal rectal examination. The life expectancy of the patients was over 10 years. All patients diagnosed with localized prostate cancer as a result of the biopsy were operated on by open retropubic radical prostatectomy procedure and extended pelvic lymph node dissection was performed in all patients.

The preoperative data of the patients, which are age, serum PSA level, transrectal ultrasound-guided biopsy's Gleason score, preoperative De Ritis ratio, neutrophil/lymphocyte ratio (NLR), and platelet count, were evaluated 1-2 days before the operation. Postoperative surgical material was examined and the data of Gleason score, extracapsular invasion, surgical margin positivity, seminal vesicle invasion, perineural invasion, lymph node positivity, and pathological tumor stage (according to the American United Cancer Committee Tumor, Node, Metastasis classification) were evaluated. In the follow-up of patients after radical prostatectomy, serum PSA levels were tested every 3-6 months. A serum PSA level of >0.2 ng/mL in 2 consecutive measurements was defined as BCR.

Statistical Analysis

The coding and statistical analysis of the data were executed on the computer, accessing the Statistical Package for the Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) package program. While descriptive statistics data for continuous variables were expressed with the average, categorical variables were expressed in terms of frequency and percentage. Mann–Whitney *U* test, Chi-square test, and Fisher's exact test were used to evaluate continuous and categorical variables. Receiver-operating characteristic (ROC) analysis was used to determine the estimated value of the De Ritis ratio that can be used to predict BCR. Univariate and multivariate logistic regression analyses were used to evaluate independent risk factors for BCR. A *P*-value of <.05 was considered statistically significant for all analyses.

Main Points

After radical prostatectomy for localized prostate cancer, the following points were observed:

- De Ritis ratio cut-off value to predict the biochemical recurrence was 1.184.
- High De Ritis ratio was detected as an independent risk factor for biochemical recurrence.
- Gleason score >8 of radical prostatectomy specimen, positive surgical margin, and the presence of seminal vesicle invasion are other risk factors for biochemical recurrence.

RESULTS

The mean follow-up period of the patients was 56.7 ± 23.6 months. Biochemical recurrence occurred in 21 patients (10.1%). The ROC analysis was performed using the Youden index (Figure 1), the De Ritis ratio cut-off value was found to be 1.184 to predict the BCR. The patients with a ratio below this value were grouped as the low De Ritis group and the patients above it as the high De Ritis group.

According to the streaming, the relationship between the De Ritis ratio and the clinical and pathological characteristics of the patients is shown in Table 1.

Among the patient groups divided according to low and high rates of De Ritis, there was no statistically significant difference between age, preoperative serum PSA level, Gleason score of ultrasound-guided transrectal biopsy, Gleason score of radical prostatectomy specimen, extracapsular invasion, surgical margin positivity, the presence of seminal vesicle invasion, the

Figure 1. Evaluation of De Ritis ratio by ROC analysis in predicting biochemical recurrence. The cut-off point is 1.184 (AUC = 0.673, *P* = .01, 95% CI (0.557-0.789)). AUC, area under curve; ROC, receiver-operating characteristic.

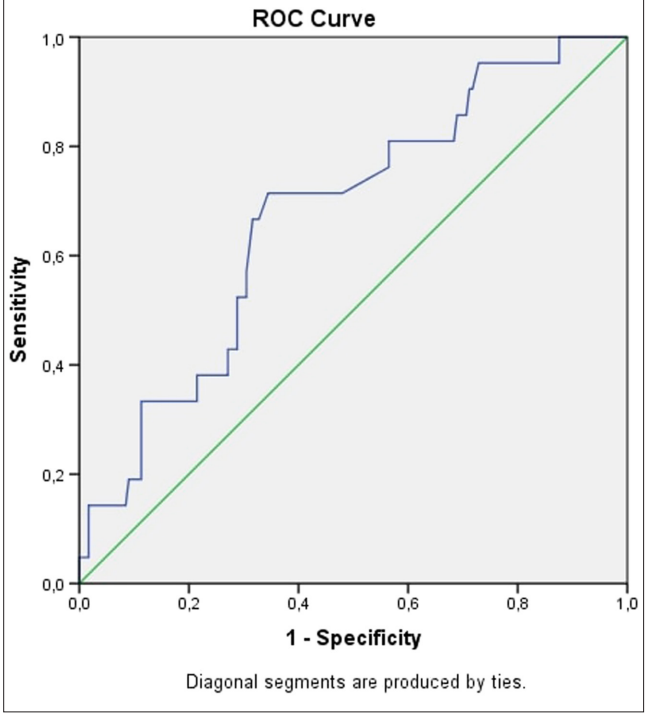

Table 1. Clinical and Pathological Characteristics of Patient Groups Separated According to De Ritis Rate

	De Ritis Ratio			
Parameters	**Total (n = 198)**	**Low (n = 128, 64.7%)**	**High (n = 70, 35.3%)**	***P***
Age, mean ± SD	62.8 ± 6.7	62.3 ± 6.8	63.6 ± 6.5	.208*
PSA, mean ± SD	10.5 ± 7.1	10.1 ± 7.1	11.2 ± 7.2	.101*
PSA, n (%)				
<10 ng/mL	130 (65.7)	90 (70.3)	40 (57.1)	.062**
≥10 ng/mL	68 (34.3)	38 (29.7)	30 (42.9)	
Post-biopsy Gleason Score, n (%)				
6	141 (71.2)	92 (71.9)	49 (70)	.622**
7	28 (14.2)	16 (12.5)	12 (17.1)	
≥ 8	29 (14.6)	20 (15.6)	9 (12.9)	
Postoperative Gleason score, n (%)				
6	113 (57.1)	77 (60.1)	36 (51.4)	.493**
7	57 (28.8)	34 (26.6)	23 (32.9)	
≥ 8	28 (14.1)	17 (13.3)	11 (15.7)	
Extracapsular invasion, n (%)				
No	159 (80.3)	105 (%82)	54 (77.1)	.408**
Yes	39 (19.7)	23 (%18)	16 (22.9)	
Surgical margin, n (%)				
No	133 (67.2)	87 (68)	46 (65.7)	.747**
Yes	65 (32.8)	41 (32)	24 (34.3)	
Seminal vesicle invasion, n (%)				
No	171 (86.4)	110 (85.9)	61 (87.1)	.813**
Yes	27 (13.6)	18 (14.1)	9 (12.9)	
Neurovascular invasion, n (%)				
No	60 (30.3)	32 (25)	26 (37.1)	.053**
Yes	138 (69.7)	96 (75)	44 (62.9)	
Lymph node invasion, n (%)				
No	186 (93.9)	120 (93.8)	66 (94.3)	.574***
Yes	12 (6.1)	8 (6.2)	4 (5.7)	
Pathological tumor stage, n (%)				
T2a	44 (22.2)	28 (24.5)	16 (22.9)	.987**
T2b	34 (17.2)	22 (16.3)	12 (17.1)	
T2c	71 (35.9)	47 (40.8)	24 (34.3)	
T3	49 (24.7)	31 (18.4)	18 (25.7)	
NLR, mean ± SD	2.5±1.3	2.6±1.4	2.4±1.1	.469*

*Mann-Whitney *U* test; **Chi-square test; ***Fisher's exact test.
PSA, prostate-specific antigen; SD, standard deviation; NLR, neutrophil/lymphocyte ratio.

Table 2. Identifying Risk Factors for Biochemical Recurrence

	Univariate		Multivariate	
Parameters	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
De Ritis ratio (high)	4.321 (1.653–11.298)	**.003**	5.84 (1.889–18.054)	**.002**
Age (continue)	0.986 (0.923–1.053)	.673		
PSA (≥10)	1.865 (0.749–4.643)	.18		
Post–biopsy Gleason score (≥ 8)	3.523 (1.281–9.684)	**.015**	0.691 (0.096–4.983)	.714
Postoperative Gleason score (≥8)	8.03 (2.998–21.511)	**<.001**	11.882 (3.229–43.726)	**<.001**
Extracapsular invasion (yes)	1.314 (0.45–3.838)	.617		
Surgical margin (positive)	4.941 (1.885–12.954)	**.001**	4.409 (1.364–14.255)	**.013**
Seminal vesicle invasion (yes)	1.575 (0.487–5.096)	**.448**	5.938 (1.013–34.792)	**.048**
Neurovascular invasion (yes)	4.2 (0.942–18.728)	.06		
Lymph node invasion (yes)	1.758 (0.358–8.626)	.487		
Pathological tumor stage (T3)	2.041 (0.791–5.265)	.14		
NLR (continue)	0.972 (0.676–1.395)	.879		
Platelets (continue)	1.001 (0.994–1.007)	.782		

PSA, prostate–specific antigen; NLR, neutrophil/lymphocyte ratio.

presence of perineural invasion, lymph node positivity, pathological tumor stage, and NLR detected ($P > .05$).

According to the multivariate logistic regression analysis performed to establish the risk factors for BCR, high De Ritis rate (OR = 5.84; 95% CI = 1.889-18.054; $P = .002$), Gleason score >8 after radical prostatectomy (OR =11.882; 95% CI = 3.229-43.726; $P < .001$), surgical margin positivity (OR = 4.409; 95% CI = 1.364-14.255; $P = .013$), and the presence of seminal vesicle invasion (OR = 5.938; 95% CI = 1.013-34.792; $P = .048$) were determined as independent risk factors (Table 2).

DISCUSSION

In our study, the high rate of De Ritis was found to be an independent risk factor for BCR in patients who underwent radical prostatectomy for localized prostate cancer. However, it has been shown that there is no relationship between the clinical and pathological features of the patients. Aspartate aminotransferase and ALT are among the most used serum biomarkers in our daily practice. It can be used to predict BCR as an easily accessible, fast, and inexpensive way.[7]

Aspartate transaminase and ALT are mainly used as important parameters in the diagnosis of liver-specific diseases and in their follow-up after treatment.[8] Generally, ALT is specific to the liver, while AST is expressed from different tissues such as brain, muscle, and kidney.[9] The De Ritis rate is defined as the ratio of the activities of AST and ALT in serum.[10] Throughout the years, it has been considered that this rate may change by various mechanisms in malignancies. Among these mechanisms, AST, which is also expressed from organs other than ALT, is more in cancer cells with high proliferation.[11] Yet again, Warburg et al[12] Showed that cancer cells use glycolysis more than normal cells, which is a fast energy resource and in which AST plays an important role. While tissue damage and metabolic changes due to rapidly proliferating cancer cells cause an increase in AST level in peripheral blood, ALT level does not change much.[13]

There are several studies in the literature examining the prognostic value of De Ritis rate in urological cancers. In a meta-analysis in which Hu et al[7] included 8 studies and 3949 patients, it was shown that high preoperative serum De Ritis rate negatively affected overall survival and cancer-specific survival in bladder and upper urinary tract cancers. Bezan et al[8] evaluated 698 non-metastatic renal cell cancer cases and showed that the De Ritis rate >1.26 was a negative prognostic factor for metastasis-free survival and overall survival. In another meta-analysis in which 8565 patients were evaluated, the rate of De Ritis was revealed to be a predictive factor for overall survival, progression-free survival, and cancer-specific survival for upper urinary tract cancer, bladder cancer, and renal cell carcinoma.[13]

The first study to assess the importance of AST and ALT levels in localized prostate cancer was managed in 2010. In this study, it was reported that a high rate of De Ritis was associated with a high Gleason score but was insufficient in predicting BCR.[14] However, the inclusion of low-grade and well-differentiated cancer patients in this study may have been effective in the emergence of this result. In another study held in 2017, the relationship between BCR and De Ritis rate after radical prostatectomy in localized prostate cancer was examined. The higher rate of De Ritis >1.325 has been shown to be associated with

a higher Gleason score after biopsy and radical prostatectomy, higher pathological tumor stage and more seminal vesicle invasion, positive surgical margin, and lymph node infiltration. Again, in this study, pathological tumor stage, Gleason score of radical prostatectomy specimen, and De Ritis rate were shown among the factors that are associated with BCR risk.[15]

In a study by Quhal et al[16] in which 214 patients who underwent salvage radical prostatectomy due to BCR after definitive radiotherapy were evaluated, the cut-off value for the De Ritis rate was considered as 1.35 and was not found to be related to the clinicopathological features of cancer. In addition, it was found that 1.8 times more BCR was observed in patients with high preoperative serum De Ritis rate, as well as 1.7 times more in those with high postoperative De Ritis rate.

In our study, similar to the results of Quhal et al[16], there was no relationship between the clinicopathological features of prostate cancer and the rate of De Ritis, while it was shown that 5.84 times higher BCR was found in patients with a De Ritis rate of >1.184. We presume that this result may be related to the inclusion of a lower number of patients in both studies compared to the others.

Neutrophil/lymphocyte ratio is also another hematological parameter whose prognostic significance has been studied in localized prostate cancer. Lee et al[17] has shown in another study that 1.36 times higher BCR was observed in patients who underwent radical prostatectomy due to localized prostate cancer with an NLR >2.5. In another study, it was shown to be an independent risk factor for poor prognosis.[18] In our study, NLR and platelet count were not found to be risk factors for BCR.

Performing retrospectively, having a low number of patients is the limitation of our study. Although patients with liver disease were not included in the study, other factors affecting liver enzymes, such as the patients' medication, could not be evaluated properly. Open retropubic radical prostatectomy was performed in all patients, yet the use of laparoscopic and robotic techniques could not be interpreted. Nonetheless, we think that our study will contribute to the literature due to the limited number of studies examining the relationship between the pathological and prognostic features of prostate cancer and the De Ritis ratio in the literature.

CONCLUSION

Although the high rate of De Ritis is not associated with the clinicopathological features of prostate cancer, it is an independent risk factor for BCR after radical prostatectomy due to localized prostate cancer, together with the Gleason score, surgical margin positivity, and the presence of seminal vesicle invasion. Preoperative serum De Ritis rate, which is an easy-to-examine method, can be used to predict BCR.

Ethics Committee Approval: This Ethics committee approval was received for this study from the ethics committee of Ankara City Hospital No.1 Clinical Research Ethics Committee (Date: March 24, 2021, Decision No: E2-21-303).

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.T.; Design – S.T.; Supervision – Y.K.; Fundings – Y.K.; Materials – Y.K.; Data Collection and/or Processing – S.T.; Analysis and/or Interpretation – O.A.; Literature Search – S.S.; Writing Manuscript – S.S.; Critical Review – O.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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

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