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Predictive Role of De Ritis Ratio in Biochemical Recurrence After Radical Prostatectomy

Radikal Prostatektomi Sonrası Biyokimyasal Rekürrens Tahmininde De Ritis Oranının Rolü

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Abstract

Aim: To analyze the role of De Ritis (aspartate aminotransferase/alanine aminotransferase) ratio in predicting biochemical recurrence (BCR) after radical prostatectomy (RP).

Methods: We retrospectively evaluated 425 patients with localised prostate cancer who underwent RP from 2009 to 2018. Patients with neo-adjuvant treatment, elevated liver enzymes, postoperative early hormone therapy, incomplete clinicopathological data and a follow-up of less than 6 months were excluded from the study. Demographic, clinical, pathological and follow-up data of the patients were recorded. Patients with and without BCR were compared. Sensitivity and specificity of De Ritis ratio in predicting BCR were calculated.

Results: According to the maximum value of the Youden index, optimal threshold of De Ritis ratio for BCR was 1.1. Sensitivity, specificity, positive predictive value and negative predictive value were 69.7%, 61.1%, 37.6% and 85.7%, respectively. Multivariate analysis showed that the De Ritis ratio (HR=1.968, p=0.014) was a significant predictor factor for BCR. BCR-free survival rate was significantly lower in patients with higher De Ritis ratio.

Conclusion: Our study suggests that elevated De Ritis ratio and detailed pathological findings could be an independent predictive factor for BCR after RP.

Keywords: De Ritis ratio, prostate cancer, biochemical recurrence, pathological findings, biochemical recurrence-free survival

Öz

Amaç: Radikal prostatektomi (RP) sonrası biyokimyasal rekürrensi (BR) tahmin etmede De Ritis (aspartat aminotransaminaz/alanin aminotransaminaz) oranının rolünü analiz etmektir.

Yöntemler: 2009-2018 yılları arasında lokalize prostat kanseri nedeni ile RP yapılan 425 hasta retrospektif olarak incelendi. Neoadjuvan tedavi alan, karaciğer enzim yüksekliği olan, ameliyat sonrası erken dönem hormon tedavisi alan, klinikopatolojik verileri eksik olan ve takip süresi 6 aydan kısa olan hastalar çalışma dışı bırakıldı. Hastaların demografik, klinik, patolojik ve takip verileri kaydedildi. BR olan ve olmayan hastalar karşılaştırıldı. BR tahmin etmede De Ritis oranının sensitivite ve spesifitesi hesaplandı.

Bulgular: Maksimum Youden indeks değerine göre, BR için optimal De Ritis oranı eşiği 1,1 olarak hesaplandı. Bu değere göre sensitivite %69,7, spesifite %61,1, pozitif prediktif değer %37,6, negative prediktif değer %85,7 olarak tespit edildi. BR'yi öngören faktörler için çok değişkenli analizde De Ritis oranı (HR=1,968, p=0,014) anlamlı değişken olarak tespit edildi. BR'siz sağkalım yüksek De Ritis oranına sahip hastalarda daha kısa olarak belirlendi.

Sonuç: Çalışmamız, artmış De Ritis oranının ve ayrıntılı patolojik bulguların RP sonrası BR için bağımsız bir öngörücü faktör olabileceğini düşündürmektedir.

Anahtar Sözcükler: De Ritis oranı, prostat kanseri, biyokimyasal rekürrens, patolojik bulgular, biyokimyasal rekürrenssiz sağkalım

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Introduction

Prostate cancer (PCa) is the most frequently diagnosed solid cancer and the second leading cause of death among men (1). Widespread use of prostate specific antigen (PSA) screening has resulted in an increased number of patients diagnosed with localised PCa. At a median follow-up of ten years, the oncologic outcomes of radical prostatectomy (RP) and external beam radiotherapy have been reported to be equal (2). Nevertheless, RP has been shown to provide tumor control, accurate staging and elimination of possible PSA sources. Patients are monitored for failure with repeated PSA testing after RP. However, biochemical recurrence (BCR) has been observed in approximately 35% patients after surgery (3). In a study including only low-risk PCa patients, the rate of BCR was found to be 25% (4). Patients who experience BCR, which can require secondary therapy, have poorer oncological outcomes. In this sense, identifying patients at high risk for BCR following RP is essential for treatment and follow-up. Several clinical and pathological findings, such as preoperative PSA levels, pathological stage, high Gleason score (GS) and positive surgical margin (PSM), are well-known predictors of BCR (5-7). Apart from these factors, in recent years some authors suggested to illustrate some other markers, systemic inflammation biomarkers, such as neutrophil-to-lymphocyte ratio and detailed pathological findings such as perineural invasion (PNI) and lymphovascular invasion (LVI) (8-10). Thus, risk assessment is of immense value for patient counseling prior to treatment decision.

Aminotransaminases, including aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), are the most commonly used liver enzymes. They are produced by both malignant and non-malignant cells. The AST-to-ALT ratio, also termed the De Ritis ratio, was initially described by De Ritis in 1957 (11). Although it has been used as an indicator for viral hepatitis and several chronic liver diseases, recently De Ritis ratio has been identified as an independent predictor of patient survival in certain types of malignancies (12-15). In this study, our main aim was to evaluate whether the De Ritis ratio and previously known clinicopathological parameters were significant predictors for BCR after RP.

Methods

Study Design

Data belonging to 425 patients who underwent RP for PCa, without neo-adjuvant treatment, at our institution from April 2009 to April 2018 were retrospectively reviewed. We excluded 123 patients from analysis, because 23 patients had previously diagnosed or preoperatively detected liver diseases (e.g., non-alcoholic fatty liver diseases, chronic hepatitis, liver cirrhosis), four patients received postoperative early hormone therapy, 62 patients had a follow-up time shorter than 6 months, 30 patients had incomplete clinicopathological data and four patients had persistent PSA after RP. While open retropubic RP was performed using the Walsh technique (16) by three different surgeons, robot-assisted laparoscopic prostatectomy was performed with da Vinci robotic surgical system (Intuitive Surgical, Sunnyvale, CA, USA) by two of the three surgeons. Patients with a lymph node metastasis risk of above 5% according to the Briganti nomogram (17) had extended lymph node dissection performed.

The patients' age and clinical history, preoperative PSA value, digital rectal examination (DRE) findings, biopsy GS, clinical T stage, postoperative GS, pathological T stage, tumor volume percent, surgical margin status, presence of PNI and LVI, extraprostatic extension (EPE), seminal vesicle invasion (SVI), presence of lymph node metastasis, the AST and ALT levels, and the De Ritis ratio were pooled from the database and analyzed. Risk stratification was performed according to D'Amico risk classification (18).

Evaluation of De Ritis Ratio

AST and ALT levels were routinely measured by spectrophotometric method (Beckman Coulter® AU5800) 3-7 days before surgery. A level of ≥50 IU/L was defined as upper reference level for AST and ALT.

Postoperative Follow-up

The patients were followed up postoperatively with PSA every 3 months for the first year, every 6 months for the second year and then annually thereafter. BCR was defined by two consecutive PSA levels ≥0.2 ng/mL. BCR-free survival was calculated from the time of RP to BCR.

Statistical Analysis

Statistical analysis was made using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). Fisher's exact test and Pearson chi-square test were performed for categorical variables. The normality assumptions were controlled by the Shapiro-Wilk test. Differences between two groups were evaluated with Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. The Kruskal-Wallis test was used for comparison of non-parametric variables between groups and the Bonferroni-Dunn test was used as a post-hoc test for significant cases. The receiver operating characteristic (ROC) curve analysis was applied to evaluate predictive performance of De Ritis ratio in determining BCR and non-BCR patients and area under the curve (AUC), sensitivity and specificity were calculated and reported with 95% confidence intervals. Youden's index was calculated to determine the optimal cut-off values. The Kaplan-Meier method and log-rank

tests were used to determine survival differences for nominal variables. A multivariate Cox proportional hazards regression model was used to identify independent prognostic factors for BCR. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported. All prognostic factors that were significant on univariate analysis were analyzed in the multivariate model. Data are expressed as n (%), mean ± standard deviation or median (min-max), as appropriate. A p value of less than 0.05 was considered statistically significant.

Results

Baseline demographic and clinical characteristics are summarized in Table 1. The mean age at the time of surgery was 63.9±6.3 years. The median PSA value was 8.18 ng/mL (3.06-107.32) during a median follow-up of 16 months (6-108). BCR was determined in 76 patients (25.2%). PSM was detected in 93 patients (30.8%). The median AST and ALT values were 21 (12-44) and 18 (6-48) IU/L, respectively. The median De Ritis ratio was 1.08 (0.6-3). De Ritis ratio cutoff value was set at 1.1, and the patients were categorized into two groups (≤1.1 and >1.1). A ROC analysis was performed to predict BCR, and the AUC value was 0.605 (0.547-0.660) (Figure 1). Using the Youden's index for cut-off point, sensitivity, specificity, positive predictive value and negative predictive value were 69.7%, 61.1%, 37.6% and 85.7%, respectively.

The relationship of BCR with preoperative clinicopathological parameters, De Ritis ratio and postoperative pathological findings after RP is shown in Table 2. PSA values, DRE, biopsy GS, D'Amico risk classification, clinical T stage, De Ritis ratio, postoperative GS, pathological T stage, tumor volume percent, PSM, PNI, LVI, EPE, SVI, lymph node involvement (LNI), multifocal PSM and upgrading were found to be statistically significant, whereas age, prostate weight, ALT and AST were not found to be related with BCR.

We also examined the impact of De Ritis ratio and clinicopathological findings on the prediction of BCR. On univariate Cox proportional hazards model, initial PSA (HR=1.034, p<0.001), intermediate risk (HR=4.391, p<0.001) and high risk (HR=10.679, p<0.001) patients according to D'Amico, positive DRE (HR=5.752, p<0.001), De Ritis ratio (HR=2.853, p<0.001), clinical T stage ≥2 (HR<.4.743, p<0.001) (HR=27.877, p<0.001), postoperative GS≥7 (HR=5.018, p<0.001) (HR=9.972, p<0.001), pathological T stage ≥3 (HR=6.637, p<0.001), PNI (HR=6.38, p=0.002), LVI (HR=5.052, p<0.001), EPE (HR=6.601, p<0.001), SVI (HR=6.466, p<0.001), LNI (HR=7.357, p<0.001), multifocal PSM (HR=5.332, p<0.001), PSM (HR=4.046, p<0.001), and upgrading (HR=2.662, p<0.001) were significant predictors for

Table 1. Patients' characteristics

Variables	n=302
Age (years) (mean ± SD)	63.9±6.3
PSA (ng/mL) (median) (min-max)	8.18 (3.06-107.32)
PSA distributions, n (%)	
<10	190 (62.9)
10-20	73 (24.2)
>20	39 (12.9)
Digital rectal examination, n (%)	
Positive	138 (45.7)
Negative	164 (54.3)
Biopsy GS, n (%)	
≤6	207 (68.5)
7	76 (25.2)
≥8	19 (6.3)
D'Amico risk classification, n (%)	
Low	150 (49.7)
Intermediate	99 (32.8)
High	53 (17.5)
Clinical stage, n (%)	
T1a	0 (0)
T1b	1 (0.3)
T1c	164 (54.3)
T2a	75 (24.8)
T2b	25 (8.3)
T2c	29 (9.6)
T3a	8 (2.6)
T3b	0 (0)
ALT (IU/L) (median) (min-max)	18 (6-48)
AST (IU/L) (median) (min-max)	21 (12-44)
De Ritis ratio	1.08 (0.6-3)
Surgical techique, n (%)	
Open retropubic	109 (36.1)
Robotic	193 (63.9)
Prostate Weight (g) (median) (min-max)	51 (20-180)
Postoperative GS, n (%)	
≤6	125 (41.4)
7	139 (46)
≥8	38 (12.6)

Table 1. Continued	
Variables	**n=302**
Pathological Stage, n (%)	
T2a	55 (18.2)
T2b	12 (4)
T2c	127 (42.1)
T3a	56 (18.5)
T3b	52 (17.2)
Tumor Volume Percent n (%) (median) (minimum-maximum)	10 (1-95)
Surgical margin status, n (%)	
Positive	93 (30.8)
Negative	209 (69.2)
Perineural invasion, n (%)	
Absent	64 (21.2)
Present	238 (78.8)
Lymphovascular invasion, n (%)	
Absent	243 (80.5)
Present	59 (19.5)
Extraprostatic extension, n (%)	
Absent	206 (68.2)
Present	96 (31.8)
Seminal vesicle invasion, n (%)	
Absent	251 (83.1)
Present	51 (16.9)
Lymph node involment, n (%)	
negative	287 (95)
positive	15 (5)
Location of PSM, n (%)	
Apical	50 (16.6)
Posterior	10 (3.3)
Posterolateral	16 (5.3)
Lateral	9 (3)
Anterior	2 (0.7)
Bladder neck	6 (2)
Negative SM	209 (69.2)
Multifocal PSM, n (%)	
No	272 (90.1)
Yes	30 (9.9)
Biochemical recurrence, n (%)	
No	226 (74.8)
Yes	76 (25.2)

Table 1. Continued	
Variables	**n=302**
Equilavence between biopsy GS and prostatectomy GS, n (%)	
Upgrading	122 (40.4)
Downgrading	13 (4.3)
Same GS	167 (55.3)

PSA: Prostate specific antigen, GS: Gleason score, ALT: Alanine aminotransaminase, AST: Aspartate aminotransaminase, PSM: Positive surgical margin, SD: Standard deviation, n: Number

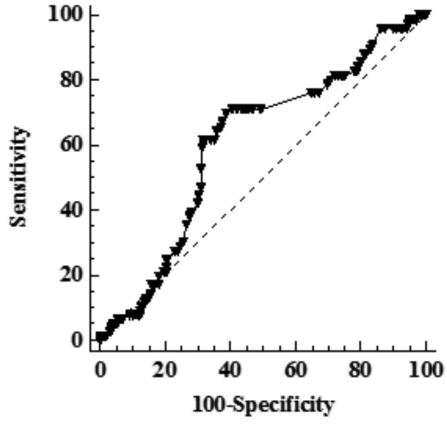

Figure 1. A ROC analysis was performed to predict BCR

ROC: Receiving operating characteristic, BCR: Biochemical recurrence, AUC: Area under curve

BCR. Multivariate analysis showed that intermediate (HR=2.228, p=0.037) and high (HR=3.316, p=0.004) D'Amico classification, De Ritis ratio (HR=1.968, p=0.014), LVI (HR=1.734, p=0.045), EPE (HR=1.970, p=0.027), SVI (HR=1.738, p=0.048), PSM (HR=1.986, p=0.008) and upgrading (HR=1.670, p=0.045) remained predictor factors for BCR (Table 3).

BCR-free survival curves according to eight predictive factors for BCR are shown in Figure 2. Kaplan-Meier estimates of BCR-free survival stratified according to high De Ritis ratio and low De Ritis ratio. (p<0.001) (Figure 2A) BCR-free survival rate was significantly lower in patients with PSM than in those having negative surgical margin (p<0.001) (Figure 2B). Furthermore, patients with higher PSA values, postoperative GS≥8, LVI, PNI, and multifocal PSM were associated with lower BCR-free survival rates.

Discussion

Our results demonstrated that De Ritis ratio was an independent predictive factor for BCR after RP. Moreover, BCR-free survival rates were significantly lower in patients

Table 2. Comparison of variables of patients with and without biochemical recurrence			
Variables	**BCR**		
	No	**Yes**	**p**
Age (years) (mean ± SD)	63.67±6.17	64.51±6.67	0.313
PSA (ng/mL) (median) (min-max)	7.15 (3.06-38.74)	13.65 (3.1-107.32)	**<0.001**
PSA distributions, n (%)			
<10	164 (72.57)[a]	26 (34.21)[b]	**<0.001**
10-20	47 (20.8)[a]	26 (34.21)[b]	
>20	15 (6.64)[a]	24 (31.58)[b]	
Digital rectal examination, n (%)			
Positive	77 (34.07)	61 (80.26)	**<0.001**
Negative	149 (65.93)	15 (19.74)	
Biopsy GS, n (%)			
≤6	178 (78.76)[a]	29 (38.16)[b]	**<0.001**
7	42 (18.58)[a]	34 (44.74)[b]	
≥8	6 (2.65)[a]	13 (17.11)[b]	
D'Amico risk classification, n (%)			
Low	138 (61.06)[a]	12 (15.79)[b]	**<0.001**
Intermediate	68 (30.09)[a]	31 (40.79)[a]	
High	20 (8.85)[a]	33 (43.42)[b]	
Clinical stage, n (%)			
T1b	1 (0.44)[a]	0 (0)[a]	**<0.001**
T1c	148 (65.49)[a]	16 (21.05)[b]	
T2a	54 (23.89)[a]	21 (27.63)[a]	
T2b	11 (4.87)[a]	14 (18.42)[b]	
T2c	12 (5.31)[a]	17 (22.37)[b]	
T3a	0 (0)[a]	8 (10.53)[b]	
ALT (IU/L) (median) (min-max)	18.5 (7-48)	18 (6-39)	0.589
AST (IU/L) (median) (min-max)	20 (12-44)	21 (14-38)	0.097
De Ritis Ratio	1 (0.6-2.44)	1.21 (0.65-3)	**0.006**
Prostate Weight (g) (median) (min-max)	50 (20-180)	54 (22-112)	0.827
Postoperative GS, n (%)			
≤6	115 (50.88)[a]	10 (13.16)[b]	**<0.001**
7	96 (42.48)[a]	43 (56.58)[b]	
≥8	15 (6.64)[a]	23 (30.26)[b]	
Pathological stage, n (%)			
T2a	53 (23.45)[a]	2 (2.63)[b]	**<0.001**
T2b	10 (4.42)[a]	2 (2.63)[a]	
T2c	111 (49.12)[a]	16 (21.05)[b]	
T3a	36 (15.93)[a]	20 (26.32)[b]	
T3b	16 (7.08)[a]	36 (47.37)b	

Table 2. Continued			
Variables	**BCR**		
	No	**Yes**	**p**
Tumor volume percent, n (%)	8 (1-80)	29 (1-95)	**<0.001**
Surgical margin status, n (%)			
Positive	47 (20.8)	46 (60.53)	**<0.001**
Negative	179 (79.2)	30 (39.47)	
Perineural invasion, n (%)			
Absent	61 (26.99)	3 (3.95)	**<0.001**
Present	165 (73.01)	73 (96.05)	
Lymphovascular invason, n (%)			
Absent	202 (89.38)	41 (53.95)	**<0.001**
Present	24 (10.62)	35 (46.05)	
Extraprostatic extension, n (%)			
Absent	183 (80.97)	23 (30.26)	**<0.001**
Present	43 (19.03)	53 (69.74)	
Seminal vesicle invasion, n (%)			
Absent	211 (93.36)	40 (52.63)	**<0.001**
Present	15 (6.64)	36 (47.37)	
Lymph node involment, n (%)			
Negative	224 (99.12)	63 (82.89)	**<0.001**
Positive	2 (0.88)	13 (17.11)	
Multifocal PSM, n (%)			
No	218 (96.46)	54 (71.05)	**<0.001**
Yes	8 (3.54)	22 (28.95)	
Equilavence between biopsy GS and prostatectomy GS, n (%)			
Upgrading	75 (33.2)[a]	47 (61.8)[b]	**<0.001**
Downgrading	10 (4.4)[a]	3 (3.9)[a]	
Same GS	141 (62.4)[a]	26 (34.2)[b]	

PSA: Prostate Specific Antigen, GS: Gleason Score, ALT: Alanine aminotransaminase, AST: Aspartate aminotransaminase, SD: Standard deviation, PSM: Positive surgical margin, min: Minimum, max: Maximum, n: Number

with higher De Ritis ratio. We also found that intermediate and high-risk D'Amico classification, LVI, EPE, SVI, PSM and upgrading in pathological specimen independently predicted BCR in multivariable regression analyses. Wang et al. (19) first reported that higher AST/ALT ratio was associated with worse pathological outcomes and higher BCR rates, in line with our results. Many studies have been performed to evaluate the pathological factor predicting recurrence in patients organ-confined PCa and different results have been obtained. A recent meta-analysis reported that SVI, PSM, EPE, LVI, LNI and PNI had a significant relationship with poor BCR-free survival (20). These parameters have an important place in patient follow-up. Serum AST and ALT levels are effective markers and widely used to monitor liver functions in clinical practice. ALT is found in the hepatocyte cytoplasm while AST is found in both the hepatocyte cytoplasm and mitochondria. AST is expressed in several organs, whereas ALT is found predominantly only in the liver. Increased metabolism in tumor cells, tissue damage and high tumor cell turnover tend to increase AST rather than ALT (21). Therefore, the De Ritis ratio, which is easily accessible and inexpensive, become a potential biomarker. Some previous studies have demonstrated that De Ritis ratio

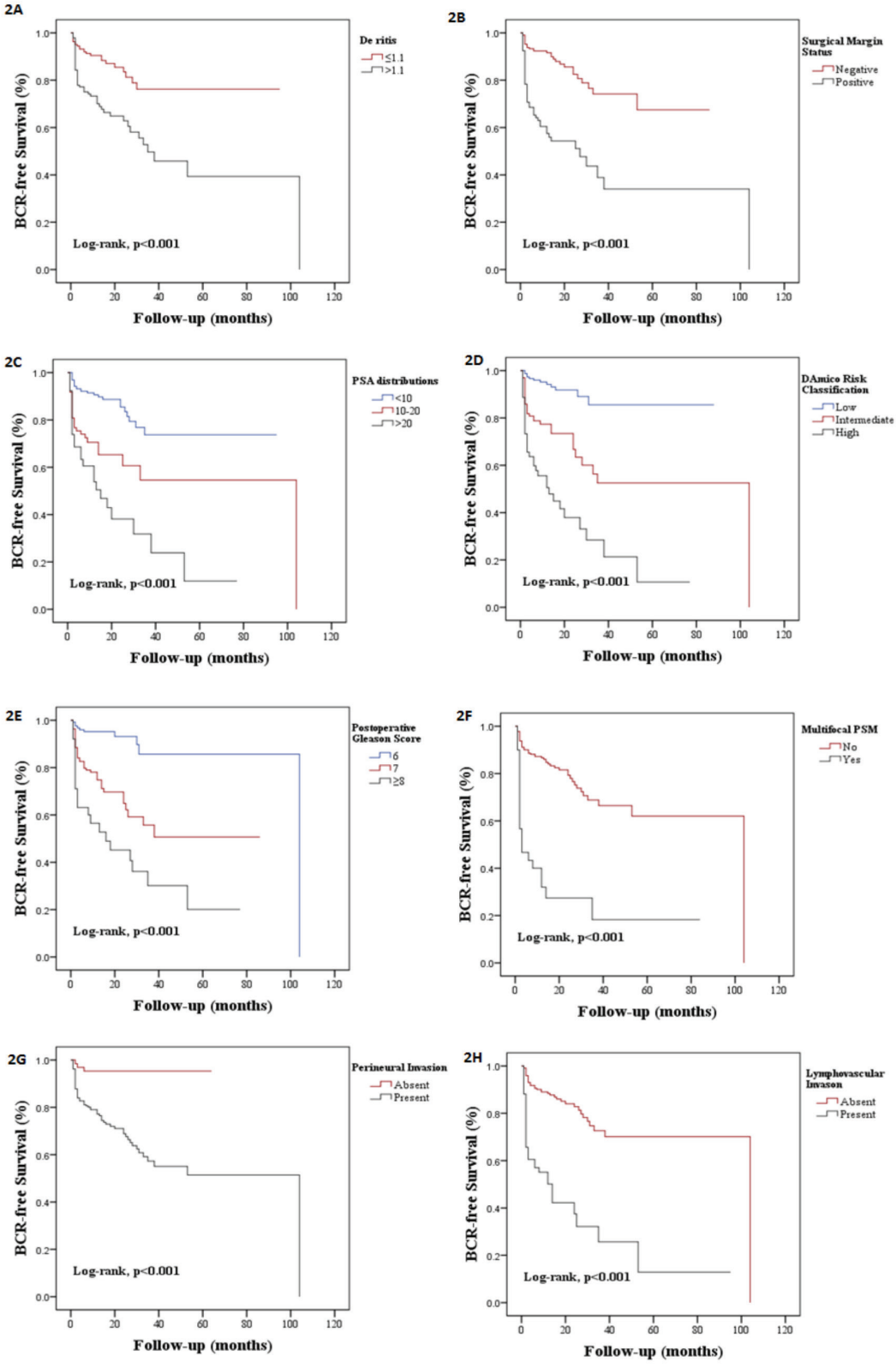

Figure 2. BCR-free survival curves according to eight predictive factors for BCR

BCR: Biochemical recurrence

Table 3. Univariate and multivariate analyses of the De Ritis ratio and clinicopathological findings in predicting BCR				
Variable	**Univariate**		**Multivariate**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**
Age	1.018 (0.981-1.057)	0.346	-	-
PSA	1.034 (1.025-1.044)	**<0.001**	-	-
D'Amico				
Low (ref)	-	**-**	-	-
Intermediate	4.391 (2.246-8.586)	**<0.001**	2.228 (1.050-4.728)	**0.037**
High	10.679 (5.507-20.706)	**<0.001**	3.316 (1.470-7.483)	**0.004**
DRE (ref: negative)	5.752 (3.216-10.288)	**<0.001**	-	-
De Ritis Ratio (ref: ≤1.1)	2.853 (1.746-4.664)	**<0.001**	1.968 (1.150-3.368)	**0.014**
Clinical stage				
T1 (ref)	-	**-**	-	-
T2	4.743 (2.669-8.429)	**<0.001**	-	-
T3	27.877 (11.63-66.818)	**<0.001**	-	-
Postoperative GS				
≤6 (ref)	-	**-**	-	-
7	5.018 (2.444-10.303)	**<0.001**	1.025 (0.375-2.802)	0.961
≥8	9.972 (4.609-21.574)	**<0.001**	0.879 (0.276-2.798)	0.827
Pathological stage				
T2 (ref)	-	**-**	-	-
T3	6.637 (3.94-11.182)	**<0.001**	0.754 (0.185-3.067)	0.693
PNI (ref: absent)	6.38 (2.009-20.266)	**0.002**	1.461 (0.403-5.300)	0.564
LVI (ref: absent)	5.052 (3.201-7.975)	**<0.001**	1.734 (1.013-2.966)	**0.045**
EPE (ref: absent)	6.601 (4.01-10.869)	**<0.001**	1.970 (1.082-3.587)	**0.027**
SVI (ref: absent)	6.466 (4.09-10.223)	**<0.001**	1.738 (1.007-3.021)	**0.048**
LNI (ref: absent)	7.357 (4.006-13.511)	**<0.001**	1.705 (0.842-3.453)	0.138
Multifocal PSM (ref: no)	5.332 (3.23-8.804)	**<0.001**	0.991 (0.497-1.976)	0.979
Concordance of GS				
Upgrading	2.662 (1.638-4.327)	**<0.001**	1.670 (1.013-2.754)	**0.045**
Downgrading	1.984 (0.597-6.587)	0.263	1.074 (0.311-3.707)	0.910
Same (ref)				
Surgical margin status	4.046 (2.547-6.428)	**<0.001**	1.986 (1.201-3.285)	**0.008**

PSA: Prostate specific antigen, DRE: Digital rectal examination, GS: Gleason score, PNI: Perineural invasion, LVI: Lymphovascular invasion, EPE: Extraprostatic extension, SVI: Seminal vesicle invasion, LNI: Lymph node invasion, PSM: Positive surgical margin, HR: Hazard ratio, CI: Confidence interval

was a significant prognostic factor in several malignancies (22-25). The mechanism of how the De Ritis ratio predicts poor oncological results remain unclear. Previous studies have pointed out the Warburg effect. Warburg (26) demonstrated that cancer cells tend to show a greater rate of aerobic glycolysis than normal tissue. Fantin et al. (27) observed that lactate dehydrogenase and high $NADH/NAD^+$ ratio were proposed to have an important role in maintaining glucose catabolism. AST has a vital role in glycolysis through the malate-aspartate shuttle pathway that allows $NADH/NAD^+$ conversion (28). Thus, elevated De Ritis ratio could be indirectly reflecting the glycolysis metabolism. Additionally, Shao et al. (29) investigated the metabolomics and transcriptomics profile in PCa. They observed significant accumulation of metabolic intermediates in tricarboxylic acid (TCA) cycle in tumor tissues, indicating TCA cycle hyperactivation. Accumulation of these metabolites could damage the mitochondria. The efficient energy production in transforming peripheral zone prostate epithelial cells implies increased oxidative

phosphorylation, and possibly increased mitochondrial reactive oxygen species production (30). We think that elevated De Ritis could be explained by increased aerobic glycolysis, mitochondrial dysfunction and oxidative stress in cancer cells.

We also investigated the association between additional pathological findings and risk of BCR following RP. In a systematic review, PSM has been consistently associated with an increased risk of PSA relapse (31). In our cohort, PSM was an independent predictor factor for BCR. Wu et al. (32) also reported that multifocal PSM had a significant impact on increased BCR risk on univariate analysis and predicting BCR-free survival, in line with our study. A large review has shown that the difference between biopsy GS and prostatectomy GS ranged from 28% to 58% (33). In our study, this rate was 40.4% and upgrading was associated with higher risk of BCR. Upgraded patients should be carefully followed due to increased risk of BCR.

Study Limitations

Our study had some limitations. First of all, it was a retrospective study with relatively few patients. Secondly, the follow-up period might not have been long enough. Lastly, the De Ritis ratio might have been changed with the presence of undetected liver disease or other diseases. Even with further evidence from future investigations, the optimal De Ritis ratio cutoff value for predicting BCR may be proved. It must be validated in large, prospective studies.

Conclusion

Our study suggests that elevated De Ritis ratio could be an independent predictive factor for BCR after RP. Additionally, LVI, EPE, SVI, PSM and upgrading can predict the risk of BCR. The De Ritis ratio can be easily calculated in routine blood tests and is a cost-effective parameter that can be used in clinical practice to predict BCR following RP. In the postoperative period, the association between the De Ritis ratio and BCR may be the subject of another study.

Authorship Contributions

Concept: K.K. Design: K.K., A.Y., İ.E., E.İ. Data Collection or Processing: Y.A., İ.E., A.Y. Analysis or Interpretation: Y.A., K.Y., M.A., T.Ö. Literature Search: K.K., K.Y., T.Ö., M.A., M.S. Writing: K.K., E.İ., M.S.

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