Original Article

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Preoperative De Ritis Ratio for the Evaluation of Recurrence and Progression in Non-muscle Invasive Bladder Cancer

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Abstract

Objective: This study aimed to investigate the potential predictive value of the preoperative De Ritis ratio in patients with primary non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: Of 212 patients who underwent transurethral resection of bladder tumour surgery for primary bladder cancer at a single academic centre between 2010 and 2016, we retrospectively analysed the clinical and pathological data. Blood samples were collected 1-7 days before surgery. The De Ritis ratio's potential prognostic value of was evaluated using receiver operating characteristic (ROC) curve analysis.

Results: One hundred twenty-five patients (or 59%) were found to have high-risk diseases, 17 patients (or 8%) had intermediate-risk diseases, and 70 patients (or 33%) had low-risk diseases. We investigated which cut-off value for De Ritis ratio could predict NMIBC risk groups in the preoperative period. The ROC analysis showed that there was no significant cut-off value in either low-risk [area under the curve (AUC)=0.457] or high-risk (AUC=0.551) patients. According to the European Organization for Research and Treatment of Cancer risk groups, when the quantitative values were compared, it was seen that low-risk patients were younger (p=0.005) and this group's alanine aminotransaminase (p<0.001) values were higher. De Ritis ratio was statistically similar in all patient groups.

Conclusion: According to our present results, the De Ritis ratio does not add any additional value to existing prognostic models. Investigating De Ritis ratio simultaneously with markers such as albumin, C-reactive protein, neutrophil-lymphocyte ratio, which are used successfully in many cancer types, may yield successful results in prospective, more comprehensive studies.

Keywords: Primary bladder cancer, De Ritis ratio, biological markers, prognosis

Introduction

The seventh most prevalent cancer in men and the eleventh most common cancer overall for both sexes is bladder cancer (1). 75% of bladder cancers are non-muscle invasive bladder cancers (NMIBC) at the time of diagnosis (2). Patients with NMIBC are followed up in accordance with the disease-specific risks of recurrence and progression after transurethral resection of bladder tumour (TUR-B). NMIBC development, recurrence, and disease-related death rates vary (3). As a result, the therapy of NMIBC patients is dictated by the condition's hazards and personal preferences. To predict oncological outcomes and pick the optimal course of treatment for each group of patients, it is critical to identify individuals with equivalent risks of recurrence and progression.

The World Health Organization (WHO) histological grade, the number of tumours, their size, the T-stage, and the presence of carcinoma *in situ* (CIS) are all factors that the European Organization for Research and Treatment of Cancer (EORTC) risk table uses to predict recurrence and progression (3). Numerous markers have been researched to predict the risks of progression and recurrence in routine clinical practice; however, none of them are routinely used due to their low sensitivity and specificity levels (4).

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The enzymes aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT), which are released from the liver cells into the bloodstream following hepatocellular injury, are frequently used to assess liver function (5). Fernando De Ritis originally studied the AST/ALT ratio in 1957; this ratio is now known as the De Ritis ratio (6). De Ritis ratio is changed in many conditions, including cirrhosis, viral hepatitis, and alcoholic hepatitis. The De Ritis ratio has a standard value of about 1.5 (7). Recent oncological studies have reported that AST and ALT act as catalysts in the synthesis of nucleotides and non-essential amino acids in tumour cells (8). AST and ALT levels become elevated with increases in anaerobic glycolysis and glucose and glutamine metabolism during adenosine triphosphate synthesis; this is called the Warburg effect (9,10). The De Ritis ratio is a helpful predictive indicator for individuals with malignant tumours of the lung, colon, pancreas, and upper urinary system, according to several recent studies (11,12,13,14).

In this context, we retrospectively analyzed data from NMIBC patients who underwent TUR-B to investigate whether the preoperative De Ritis ratio may predicts the risks of cancer recurrence and progression.

Materials and Methods

Ethical approval was obtained from our local ethics committee. The Medical Specialization Education Board of Samsun Training and Research Hospital granted clearance for this retrospective study with the number 203 dated 26.12.2017. The Dean of the Faculty of Medicine of the University of Health Sciences authorized this clearance with decision number 2018/4 dated 22.01.2018.

The medical records of patients with primary bladder cancer who had TUR-B at the Samsun Training and Research Hospital in Turkey between 2010 and 2016 were retrospectively reviewed. 212 NMIBC patients' individual medical records, test findings, and pathology reports were examined. Patients were excluded if they had transitional cell non-epithelial bladder cancer, concomitant tumours, chronic use of medications that elevated liver enzymes, hepatic disease, or incomplete TUR-B.

The tumour tissues had been graded using the 1973 WHO classification system (15) and staged using the 2009 tumor-node-metastasis classification system by the Union for International Cancer Control (16). The EORTC recommended using tumour size and number, recurrence rate, T-stage, concurrent CIS, and histological grade to assess the risks of progression and recurrence (3). Patients with tumours that are primary, solitary, TaG1 (low-grade, papillary urothelial neoplasm with low malignant potential), tiny (diameter 3 cm), and the absence of concomitant CIS are at low risk, according to the European Association of Urology guidelines. High-risk patients had numerous recurring TaG1/G2 tumours with diameters 3 cm, HG/G3 tumours, or CIS. Patients with tumoral characteristics, on the other hand, who range into the low- and high-risk diseases groups, are at an intermediate risk (17).

Up to one week before surgery, routine preoperative biochemical tests were conducted to evaluate the levels of AST and ALT. Automatic analyzers were used to measure the AST and ALT levels by colorimetric technique. In our biochemistry lab, the maximum standard values for AST and ALT were 40 U/L and 35 U/L, respectively. Divide AST by ALT to obtain the De Ritis ratio.

Statistical Analysis

The software program SPSS Statistics were used to examine the data (version 23; IBM Corp., Armonk, NY, USA). Using the Shapiro-Wilk test, the normality of the data distribution was evaluated. Data that weren't normally distributed were compared using the Kruskal-Wallis and Mann-Whitney U tests. To compare qualitative data, the chi-square test was employed. The De Ritis ratio was used to classify the patients, and binary logistic regression was applied to compare the independent risk factors within and between the groups. Frequencies (percentages) are used to portray qualitative data, while medians are used to present quantitative data that did not follow a normal distribution (ranges). The p-value cut-off for statistical significance was 0.05.

Results

The demographic, clinical, and histological characteristics of 212 NMIBC patients who underwent TUR-B are described in Table 1. Patients were divided into three risk groups: high (n=125; 59%), intermediate (n=17; 8%), and low (n=70; 33%).

Table 1. Demographic and clinical data of the patients

	Total (n=212)
Age	68 (23-89)
Gender	
Male	193 (91.0)
Female	19 (9.0)
The T category	
Ta	95 (44.8)
T1	117 (55.2)
WHO grade 1973	
Grade 1	95 (44.8)
Grade 2	24 (11.3)
Grade 3	93 (43.9)
Associated CIS	
No (-)	208 (98.1)
Yes (+)	4 (1.9)
Number of tumours	
Single	171 (80.7)
Multiple	41 (19.3)
Tumour diameter	
<3 cm	151 (71.2)
≥3 cm	61 (28.8)
EAU NMIBC risk group	
Low risk	70 (33.0)
Intermediate risk	17 (8.0)
High risk	125 (59.0)

WHO: World Health Organization, CIS: Carcinoma *in situ*, EAU: European Association of Urology, NMIBC: Non-muscle invasive bladder cancers

We investigated the cut-off level for the pre-treatment De Ritis ratio that could predict risk in NMIBC patients. In receiver operating characteristic curve analysis, no significant differences were identified in cut-off values between low-risk [area under the curve (AUC)=0.457] and high-risk (AUC=0.551) patients (Figure 1A-B).

Quantitative differences between risk groups showed that low-risk patients were younger (p=0.005) and had higher ALT levels (p=0.001) than high-risk patients (Table 2). The De Ritis ratio, even so, was comparable across all groups.

The De Ritis ratio was unaffected by tumour features in the univariate and multivariate studies (Table 3). Additionally, no correlation between the De Ritis ratio and the EORTC recurrence and progression scores was found to be statistically significant (Table 4).

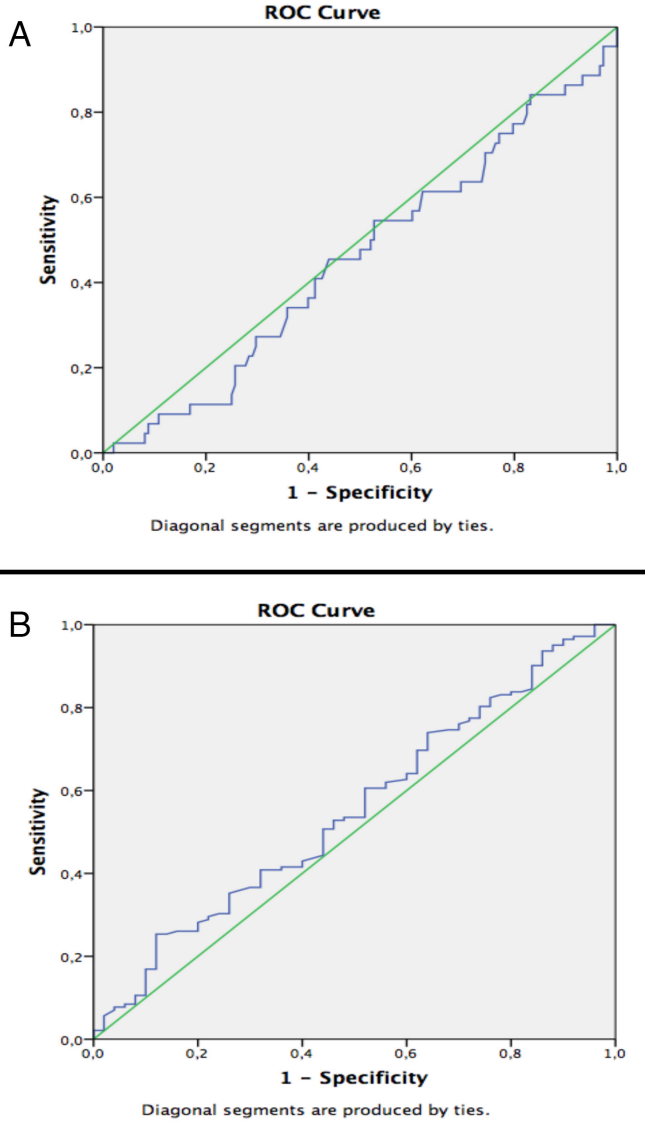

Figure 1. A- ROC curve analysis for low risk patients (AUC=0.457), B- ROC curve analysis for high risk patients (AUC=0.551)

ROC: Receiver operating characteristic, AUC: Area under the curve

Discussion

A comparison of quantitative variables between EORTC risk groups in this study revealed that low-risk patients were younger (p=0.005) and had higher ALT levels (p<0.001). Even so, preoperative the De Ritis ratio was similar across all groups.

The risks of recurrence and progression of NMIBC are determined using the EORTC risk table (3). Despite the risk stratification and use of intravesical therapy, there were high rates of recurrence (70%) and progression (30%), which poses a significant obstacle to the treatment of NMIBC (18). Pretreatment markers are required to predict the risks of recurrence and progression at the initial diagnosis and to identify misclassified or inadequately classified patients (19).

Although ALT is exclusive to the liver, AST is broadly expressed in various tissues, including the liver, brain, kidney, muscle, and even the heart (7). AST is preferentially used instead of ALT during anaerobic glycolysis; therefore, a higher De Ritis ratio is expected during periods of oxidative stress. The precise mechanism has not, however, been completely clarified (20,21,22). During frequent cell proliferation, such as in areas of tissue damage or tumours, an increase in AST is likely to increase the De Ritis ratio, which makes it an enticing potential biomarker (14). Although research on NMIBC is lacking, many recent studies have found that AST and ALT levels can help predict the development of upper urinary tract, colon, pancreatic, and lung cancers (11-14). In a study of the use of De Ritis ratio in NMIBC patients, Laukhtina et al. (23) observed a significant predictive value only in NMIBC patients with recurrence-free survival. The De Ritis ratio, according to the authors, did not influence the prognostic models.

In our study, no De Ritis ratio cut-off value could be identified that predicted a high risk. However, recent studies have reported different cut-offs for the prognosis of various types of cancer types. Patients with gastric cancer and a De Ritis ratio of greater than 0.8 have a better prognosis, according to Chen et al. (24). According to Tan et al. (13), individuals with distal cholangiocarcinoma should have a De Ritis ratio of >2.0 as a useful indicator of long-term survival. Additionally, the De Ritis ratio cut-off value that indicated survival in patients with urological malignancies ranged from 1.26 to 1.6. (25-27). Age (p=0.001), T-stage (p=0.001), and De Ritis ratio (cut-off value: 1.3) were thought to be independent predictive markers for the overall survival of patients with muscle-invasive bladder cancer after radical cystectomy by Gorgel et al. (28). In patients who underwent surgery for upper urinary tract urothelial carcinomas, Lee et al. (25) found that the De Ritis ratio (cut-off value: 1.5), age, T-stage, and lymph node involvement were related to cancer-specific survival and overall survival. Previous studies have shown that the De Ritis ratio correlated with lymph node involvement and recurrence-free survival in upper urinary tract malignancies, although we did not find correlations between the De Ritis ratio and tumour characteristics, recurrence, or progression scores (29,30). Tumour parameter analyses in our study, both univariate and multivariate, revealed that tumour parameters had no effect on the De Ritis ratio. Furthermore, no correlation was found between the EORTC recurrence and progression scores and

Table 2. Comparison of De Ritis ratio by EORTC risk groups				
	Low risk (n=70)	**Intermediate and high risk (n=142)**	**Total (n=212)**	**p-value**
Age	64 (24-87)	70 (23-89)	68 (23-89)	0.005
Recurrence probability	4 (0-9)	3 (0-9)	3 (0-9)	0.564
Progression probability	9 (0-18)	9 (0-18)	9 (0-18)	0.897
De Ritis ratio	1.26	Intermediate r. (1.17) - High r. (1.27)	1.25	0.908
AST	20 (7-68)	19 (10-56)	19.5 (7-68)	0.875
ALT	21 (8-69)	12 (3-27)	15 (3-69)	<0.001
EORTC: European Organization for Research and Treatment of Cancer, AST: Aspartate aminotransaminase, ALT: Alanine aminotransaminase, r: Range				

Table 3. Correlation between the De Ritis ratio and tumour characteristics				
	AST/ALT (Univariate)		**AST/ALT (Multivariate)**	
	Risk ratio	**p-value**	**Risk ratio**	**p-value**
Tumour diameter	0.895	0.715	0.826	0.620
The T category	0.870	0.616	0.794	0.547
Number of tumours	0.890	0.740	0.913	0.830
WHO Grade 1973	0.977	0.875	0.923	0.682
Associated CIS	1.167	0.879	1.099	0.931
AST: Aspartate aminotransaminase, ALT: Alanine aminotransaminase, WHO: World Health Organization, CIS: Carcinoma *in situ*				

Table 4. Correlation between De Ritis ratio and EORTC recurrence and progression scores	
	De Ritis ratio
Recurrence	r=0.020; p=0.770
Progression	r=0.032; p=0.639
EORTC: European Organization for Research and Treatment of Cancer, r: Spearman correlation coefficient	

the preoperative de RITIS ratio. Considering these findings, we conclude that the De Ritis ratio does not predict risk beyond the data provided by common clinical factors.

Study Limitations

The retrospective analysis of the prospectively acquired data and the lack of follow-up information regarding the specific recurrence and progression rates were the study's limitations. Moreover, undetected liver or other diseases may have affected the AST and ALT levels. The lack of additional systemic inflammatory indicators in our investigation, such as the neutrophil-lymphocyte ratio (NLR) or platelet-lymphocyte ratio, is a significant limitation. The primary goal of this study was to investigate the correlation between De Ritis ratio and NMIBC, although we discovered that the NLR value of the high-risk group was significantly higher (p=0.001) than that of the intermediate and low-risk groups.

Finally, variability in the skills of surgeons (i.e., quality of surgery) and pathologists (i.e., determination of T-staging, histological grading, and CIS evaluation) may have affected the results. Despite these limitations, our study is one of the few to look at the correlation among preoperative De Ritis ratio, disease risk categories, and tumour characteristics in NMIBC patients.

Conclusions

In NMIBC patients, the preoperative De Ritis ratio is not significantly correlated with disease risk categories, tumour characteristics, or recurrence or progression scores. As a result, the De Ritis ratio falls short of outperforms existing prognostic models. More robust results may be obtained from prospective studies with longer follow-up durations that also evaluate routine biochemical markers, such as albumin, C-reactive protein, and NLR, in various cancer types.

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Ethics

Ethics Committee Approval: The Medical Specialization Education Board of Samsun Training and Research Hospital granted clearance for this retrospective study with the number 203 dated 26.12.2017. The Dean of the Faculty of Medicine of the University of Health Sciences authorized this clearance with decision number 2018/4 dated 22.01.2018.

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Authorship Contributions

Concept: R.İ., Design: R.İ., A.B., Supervision: A.B., M.A., Data Collection-Processing: E.K., Analysis-Interpretation: M.A., Literature Review: M.K.A., L.İ., Writing: R.İ., Critical Review: M.K.A., L.İ.

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