Original Investigation

DOI: 10.4274/jarem.galenos.2024.84755
J Acad Res Med

Investigation of the Predictive Value of De Ritis Ratio and Inflammatory Markers in Prostate Cancer Patients Suitable for Active Surveillance

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Cite this article as: Gezmiş CT, Özkan A, Kalkanlı A, Çilesiz NC, Özdemir E, Hazar Aİ. Investigation of the Predictive Value of De Ritis Ratio and Inflammatory Markers in Prostate Cancer Patients Suitable for Active Surveillance. J Acad Res Med.

ABSTRACT

Objective: To demonstrate the role of inflammatory markers and the De Ritis ratio (aspartate aminotransferase/alanine aminotransferase) in selecting patients with localized prostate cancer for active surveillance.

Methods: A total of 83 patients who met the criteria for active surveillance and underwent radical prostatectomy in our clinic between January 2010 and June 2017 were included in the study. Preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-hemoglobin (Plt/Hb) ratio, red cell distribution width (RDW), and De Ritis ratio were retrospectively evaluated with postoperative outcomes.

Results: NLR, PLR, RDW, and Plt/Hb ratios were not significantly associated with upgrade and upstage. Twenty-three patients (27.7%) underwent upgrade, 10 patients (12%) underwent upstage, and 29 patients (34.9%) were found unsuitable for active surveillance of radical prostatectomy results. A high De Ritis ratio was significantly associated with increased upgrade and unsuitability for active surveillance.

Conclusion: Preoperatively, a high De Ritis ratio is associated with poor pathological outcomes, and a high De Ritis ratio can be used as a cost-effective and accessible marker for selecting patients for active surveillance.

Keywords: Active surveillance, De Ritis ratio, inflammatory markers, prostate cancer, upgrade, upstage

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men (1). For patients with low-risk PCa [clinical category T1c-T2a, prostate specific antigen (PSA) level <10 ng/mL and Gleason 6], radical prostatectomy operation and radiotherapy are the preferred approaches for curative treatment (2). However, PCa treatment types have long-term side effects, such as urinary incontinence (20-21%) and erectile dysfunction (70-74%), which negatively affect patients' quality of life (3). This has led researchers to investigate conservative treatments. Active surveillances based on the principle that due to possible side effects in low-risk patients, curative treatment is applied when patients move to a higher risk group. Recent studies have shown that long-term overall survival (81-100%) and cancer-specific survival (98-100%) are achieved in active surveillance practices (4,5). Active surveillance has become routine practice PCa management and is recommended according to the criteria defined in international guidelines (6,7). Although various institutions have different criteria, most clinicians select patients for active surveillance by considering Gleason score 6, clinical stage T1c or T2a, PSA <10 ng/mL, PSA density (PSAD) <0.15 ng/mL/cc, and low tumor volume in biopsy (5,6). However, many issues such as optimal patient selection, long-term outcomes, disease-specific mortality, follow-up strategies, and the time to start active treatment. To overcome these uncertainties, additional clinical, radiological, tissue-level, and biochemical parameters are needed in addition to the existing criteria when selecting patients (8-10).

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Received Date: 21.03.2024 **Accepted Datei:** 08.07.2024

The inflammatory response is well known to have an important role in the formation and progression of tumors, and inflammatory markers play predictive roles in some malignancies (11). The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (De Ritis) was first defined by De Ritis in 1959 for the evaluation of viral hepatitis and was subsequently demonstrated to be a useful marker for predicting prognosis in many types of cancer (12-15). Although AST and ALT are generally thought to be associated with liver function, AST is expressed in more common tissue types, whereas ALT is more liver-specific (16). A high degree of proliferation, high tumor cell turnover, and tissue damage may cause AST to increase more than ALT in cancer patients; therefore, the high De Ritis rate may be due to systemic changes related to possible tumor proliferation (17-19). In glucose metabolism, AST is activated more than ALT and plays an important role in aerobic glycolysis (16,20). This mechanism has also been demonstrated in bladder tumors (21). In previous studies, increased De Ritis rates were found to be associated with biochemical recurrence after radical prostatectomy in PCa, increased Gleason scores, and disease progression in castration-resistant cases (8,22).

In this study, we aimed to evaluate the use of inflammatory markers and the De Ritis ratio as criteria in patient selection for active surveillance.

METHODS

Patient Selection

Approval for the study was obtained from the University of Health Sciences Türkiye, Taksim Training and Research Hospital Clinical Research Ethics Committee under decision number 127 (date: 24.01.2018). A total of 245 patients who underwent radical prostatectomy for PCa between January 2010 and June 2017 were retrospectively evaluated. Among these patients, 103 low-risk patients were included in the study based on the following criteria: clinical stage ≤T2a, PSA ≤10 ng/mL, Gleason score ≤6, and ≤3 foci of PCa identified, accounting for ≤50% of the biopsy material. An additional 20 patients were excluded from the study due to exclusion criteria, such as chronic inflammatory and autoimmune diseases, rheumatologic pathology, hepatitis, and chronic liver disease. Consequently, the study was completed in 83 patients.

Evaluation

Demographic information (age, body mass index, comorbidities) of the patients was noted by compiling their electronic medical records, patient archive files, and outpatient clinic follow-up cards. Preoperative digital rectal examination, clinical stage, serum PSA levels, prostate volume, biopsy pathology results (tumor type, Gleason score, number of positive cores for PCa, tumor percentage), and type of surgery (open retropubic or laparoscopic) were evaluated. Postoperative pathological results (Gleason score, extraprostatic extension, seminal vesicle invasion) were recorded. Patients were staged according to the TNM (American Joint Committee on Cancer) staging system. Radical prostatectomy results were compared with biopsy pathology results to determine upgrades (Gleason ≥7) and upstaging.

Preoperative blood sample results (liver function tests and complete blood count tests) were noted. Hemoglobin (Hb), red cell distribution width (RDW), platelet count (Plt), lymphocyte count, neutrophil count, AST, ALT values were noted from the blood samples. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-hemoglobin (Plt/Hb) ratio, and De Ritis ratio were calculated based on these values. The correlation between biochemical parameters and upgrades, upstaging, and suitability for active surveillance in preoperative and postoperative pathology results was statistically investigated.

Statistical Analysis

Descriptive statistics, such as mean, standard deviation, median, minimum, maximum, frequency, and ratio, were used for data descriptions. The distribution of variables was measured using the Kolmogorov-Smirnov test. The independent sample t-test, Mann-Whitney U test were used in the analysis of quantitative independent variables. The significance level and cut-off value were determined using the receiver operating characteristic curve. SPSS 22.0 software was used for the analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 61.8±7 years. Open radical prostatectomy was performed in 70 (83.2%) patients, and laparoscopic radical prostatectomy was performed in 13 (15.7%) patients. Seven patients had various comorbidities. The mean preoperative prostate volume measured by transrectal ultrasonography was 48.7±17.9 mL. The mean pre-biopsy PSA was 6.6±2.1 ng/mL. The mean tumor length on biopsy was 4.6±2.9 mm, and the mean tumor percentage was 24.3±13. Seventy four (89.2%) patients were classified as T1 and 9 patients were classified as T2A (10.8%) (Table 1).

The mean Hb was 14.1±1.1 g/dL, neutrophil count was 4.4±1.4 10^3/μL, lymphocyte count was 2.1±0.7 10^3/μL, Plt was 232.7±62.6 10^3/μL, AST was 20.6±5.5 U/L, ALT was 19.5±8.3 U/L, RDW was 14.1±2.9%, NLR ratio was 2.2±0.8, PLR ratio was 118.5±42.6, Plt/Hb ratio was 16.6±4.8, De Ritis ratio was 1.2±0.3 (Table 2).

Sixty (72.3%) patients had a Gleason score of 6 (3+3), 22 (26.6%) patients had Gleason 7, and 1 (1.2%) patient had Gleason 8 (4+4). Seminal vesicle invasion was present in 2 (2.4%) patients. Ten (12%) patients underwent extraprostatic extension (T3), whereas 23 (27.7%) underwent upgrades. When patients with upgrades and/or upstaging were grouped as unsuitable for active surveillance, 54 (65.1%) patients were suitable for active surveillance, while 29 (34.9%) were unsuitable (Table 3).

The RDW, NLR, PLR, and Plt/Hb values were not significantly associated with upgrades, upstaging, or suitability for active surveillance ($p>0.05$) (Table 4).

The De Ritis ratio was significantly higher in the upgrade group than in the non-upgrade group (p=0.001). There was no significant difference in the De Ritis ratio between the upstage group and the non-upstage group (p=0.812). The De Ritis ratio was statistically significant between patients suitable and those unsuitable for active surveillance (p=0.004) (Table 4).

The cut-off value of 1.08 for the De Ritis ratio showed significant efficacy [area under the curve 0.693 (0.575-0.810)] in distinguishing between these groups (p=0.004). The sensitivity was 79.3%, positive predictive value was 51.1%, specificity was 59.3%, and negative predictive value was 84.2% (Figure 1).

DISCUSSION

Active surveillance has been used worldwide over the past decade to reduce PCa overtreatment and to provide a reliable follow-up protocol for slow-progressing disease (23). Despite its widespread use, definite criteria for active surveillance have not been established. Thomsen et al. (24) included patients with clinical stage ≤T2a, PSA ≤10, Gleason 6, positive core number ≤3, and tumor percentage in the core ≤50% as inclusion criteria. Similarly, in our study, we included patients with clinical stage ≤T2a, PSA ≤10, Gleason ≤3+3, positive core number ≤3, and tumor percentage in the core ≤50%.

Table 1. Preoperative findings of the patients

		Min-max	Median	Mean ± SD/n-%
Age		**45-77**	**62**	**61.8±7.0**
BMI		17.9-31.2	25	24.6±3.4
Comorbidity	No			76 (91.6%)
	Yes			7 (8.4%)
	DM			2 (2.4%)
	HT			4 (4.8%)
	CAD			2 (2.4%)
Surgery type	Open			70 (84.3%)
	Laparoscopic			13 (15.7%)
PV (mL)		20-105	44	48.7±17.9
PSA (ng/mL)		2-9.9	6.5	6.6±2.1
Tumor length (mm)		0.1-15	4	4.6±2.9
Tumor percentage (%)		2-50	23	24.3±13.0
Preoperative clinical stage	T1			74 (89.2%)
	T2A			9 (10.8%)

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, PV: prostate volume, SD: standard deviation, PSA: prostate specific antigen, BMI: body mass index

Suitability for active surveillance	AUC	Cut-off	95% CI	p-value
AST/ALT	0.693	1.08	0.575-0.810	**0.004**
			Sensitivity	79.3%
			Positive prediction	51.1%
			Specificity	59.3%
			Negative prediction	84.2%

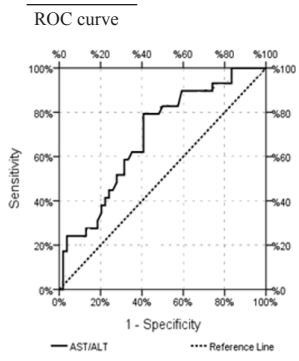

Figure 1. De Ritis cut-off value and confidence interval

AUC: area under the curve, CI: confidence interval, ROC: receiver operating characteristic, AST/ALT: aspartate aminotransferase/alanine aminotransferase

Table 2. Preoperative laboratory values of the patients

	Min-max	Median	Mean ± SD
Hb	11.8-17.0	14.0	14.1±1.1
Neutrophil	1.8-10.7	4.2	4.4±1.4
Lymphocyte	1.0-4.8	2.0	2.1±0.7
Platelet	118.0-398.0	220.0	232.7±62.6
AST	11.0-39.0	19.2	20.6±5.5
ALT	8.0-46.0	17.0	19.5±8.3
RDW	10.8-36.0	13.9	14.1±2.9
NLR	0.8-4.6	2.1	2.2±0.8
PLR	50.8-252.2	111.3	118.5±42.6
Plt/Hb	7.9-32.1	15.8	16.6±4.8
AST/ALT	0.5-2.1	1.1	1.2±0.3

AST: aspartate aminotransferase, ALT: alanine aminotransferase, RDW: red cell distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, Plt/Hb: platelet-to-hemoglobin, SD: standard deviation, min-max: minimum-maximum

Table 3. Evaluation of patients after radical prostatectomy

		n-%
Gleason score	GS 6	60 (72.3%)
	GS 7	22 (26.6%)
	GS 8	1 (1.2%)
Seminal vesicle invasion	No	81 (97.6%)
	Yes	2 (2.4%)
Pathological stage	T2	73 (88%)
	T3	10 (12%)
Upgrade		23 (27.8%)
Upstage		10 (12%)
Suitability for active surveillance	Yes	54 (65.1%)
	No	29 (34.9%)

Although patients suitable for active surveillance are selected from low-risk PCa patients, some patients meeting the active surveillance criteria who undergo radical prostatectomy have been found to have more aggressive tumor characteristics. In our study, we found Gleason score 7 in 26.5% of patients, Gleason score 8 in 1.2%, seminal vesicle invasion in 2.4%, and extraprostatic extension (T3) in 12% of patients. One of the largest studies on patients suitable for active surveillance who underwent radical prostatectomy was conducted by Thaxton et al. (25). In this study, radical prostatectomy was performed in 4265 patients who were categorized according to three different active surveillance criteria, and their radical prostatectomy pathology results were evaluated. Gleason 8-10 was found in 3-4% of patients, extracapsular extension in 15-18%, and seminal vesicle invasion in 3-5%. These findings were consistent with our study, except for patients with Gleason 8. Thaxton al. (25) also included Gleason 7 patients in their study, which may explain this difference. Similarly, da Silva et al. (26) included 945 patients meeting the PRIAS criteria (clinical stage T1/T2, Gleason ≤6, PSA <10 ng/mL, ≤2 positive cores, and PSAD <0.2 ng/mL) in their study and found Gleason ≥7 in 38% of patients and extraprostatic extension (T3) in 10.3%, which was similar to our study.

Wang et al. (8) investigated the role of the De Ritis ratio in predicting pathological outcomes and prognosis in patients with localized PCa who underwent radical prostatectomy. According to this study, the median De Ritis ratio of the 438 patients was 1.33 (1.11-1.60), and the cut-off value was determined to be 1.325. When patients were grouped as high or low based on their De Ritis ratio, a high De Ritis ratio was found to be statistically significantly associated with high clinical and pathological stage, high Gleason score on biopsy and final pathology, high seminal vesicle invasion, and positive surgical margin. In our study, the mean De Ritis ratio was 1.2±0.3. A high De Ritis ratio was significantly associated with upgrades (p=0.001), which is consistent with the literature. In our study, the De Ritis ratio was statistically significant between patients suitable and those unsuitable for active surveillance (p=0.004). However, no significant difference was found in the De Ritis ratio for predicting extraprostatic extension in radical prostatectomy pathology (p=0.812). Taştemur et al. (22) investigated the role of the De Ritis ratio in predicting biochemical recurrence in 198 intermediate-high-risk patients who underwent radical prostatectomy. In this study, the cut-off value for De Ritis was 1.184, and the De Ritis ratio was found to be an independent risk factor for biochemical recurrence (22).

Inflammation plays a key role in the initiation and progression of many malignancies (27). NLR, which is used as a cancer-related inflammation marker, has been shown to be useful in predicting response to treatment and prognosis in some malignancies (28). High NLR indicates an increase in inflammation-dependent neutrophil count and decrease in lymphocyte count, which are associated with carcinogenic environments (29,30). One of the largest studies evaluating the NLR ratio in patients suitable for active surveillance who underwent radical prostatectomy was conducted by Kwon et al. (31). In this study, 217 patients with PSA <10 ng/mL, Gleason 6, clinical stage T2a, positive core number ≤3, and tumor in the core ≤50%, and 217 were included.

Table 4. Evaluation of markers in terms of upgrade, upstage, and suitability for active surveillance

	Upgrade					Upstage					Suitability for active surveillance				
	Yes		No		p-value	Yes		No		p-value	Yes		No		p-value
	Mean	Median	Mean	Median		Mean	Median	Mean	Median		Mean	Median	Mean	Median	
RDW	14±2.1	13.1	14.1±3.2	14	0.623	14.7±2.1	14.6	14±3	13.5	0.122	14.1±3.3	13.9	14.1±2	13.6	0.836
NLR	2.1±0.58	2.06	2.29±0.87	2.23	0.452	2.16±0.65	2.01	2.25±0.83	2.14	0.845	2.31±0.89	2.23	2.1±0.6	2.06	0.385
PLR	106.1±34.9	98.3	123.3±44.5	113.2	0.200	128.3±38.7	120.7	117.2±43.2	108.8	0.218	122.1±44.3	113.2	111.9±39.1	104	0.528
Plt/Hb	15.8±4.8	14.8	16.9±4.7	16.1	0.46	17.8±5.1	16.1	16.4±4.7	15.8	0.334	16.7±4.6	16.1	16.4±5.1	14.8	0.774
De Ritis	1.36±0.32	1.25	1.08±0.31	1.05	**0.001***	1.18±0.29	1.14	1.15±0.07	1.11	0.812	1.08±0.32	1.05	1.3±0.32	1.21	**0.004***

RDW: red cell distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, Plt/Hb: platelet-to-hemoglobin

The rates of upgrade and upstaging in the postoperative pathology results were 26.7% and 8.3%, respectively, which were similar to our study. However, there was no significant difference in terms of upgrade, upstaging, or positive surgical margin between the groups categorized according to NLR (NLR ≥2.5 and NLR <2.6) (p>0.05). Our study also did not find a significant difference in upgrade, upstaging, or positive surgical margin concerning NLR. Maeda et al. (32) compared the preoperative and postoperative results of 73 patients who underwent radical prostatectomy and found no relationship between NLR and poor pathological outcomes. In a study by Sun et al. (9), which included 226 patients diagnosed with PCa and 100 healthy volunteers, the NLR, PLR, and RDW were found to be significantly higher in patients with PCa than in the control group, and increased NLR and PLR were associated with poor prognosis, high Gleason scores, and PSA. However, NLR, PLR, Plt/Hb, and RDW did not significantly differ in terms of upgrade and upstaging. This difference can be attributed to the inclusion of patients with high PSA and Gleason scores in the Sun et al. (9) study.

Study Limitations

The limitations of the study included its retrospective nature, a limited sample size, and its conduct at a single center.

CONCLUSION

Although active surveillance in localized PCa is a safe method, the patient selection criteria have not been clarified. Our findings suggest that the De Ritis ratio can be used to select suitable patients for active surveillance. However, further prospective studies with longer durations and larger sample sizes are needed to support these findings.

Ethics Committee Approval: Approval for the study was obtained from the University of Health Sciences Türkiye, Taksim Training and Research Hospital Clinical Research Ethics Committee under decision number 127 (date: 24.01.2018).

Informed Consent: Retrospective study.

Author Contributions: Surgical and Medical Practices - E.Ö., A.İ.H.; Concept - C.T.G., A.Ö.; Design - A.Ö., E.Ö.; Data Collection and/or Processing - A.K., N.C.Ç.; Analysis and/or Interpretation - C.T.G., A.K.; Literature Search - C.T.G., N.C.Ç.; Writing - C.T.G., A.İ.H.

Conflict of Interest: The authors have no conflict of interest to declare.

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

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