ORIGINAL ARTICLE

AHI EVRAN MEDICAL JOURNAL
E-ISSN: 2619 - 9203

Can the de Ritis Ratio (AST/ALT) Be Used to Predict Colon Cancer Stages?

De Ritis Oranı (AST/ALT) Kolon Kanseri Evrelerini Tahmin Etmek İçin Kullanılabilir Mi?

Saygın ALTINER[1] Enes CEBECİ[1] Bedri Burak SUCU[1] Mert ÇÖL[1] Ender ERGÜDER[1]

Yılmaz ÜNAL[1] Salih TUNCAL[1] Mevlüt Recep PEKCİCİ[1]

ÖZ

Amaç: De Ritis oranı (Aspartat transaminaz/alanin transaminaz), bazı malign tümör türleri için kritik bir prognostik faktördür. Bununla birlikte, ameliyat öncesi kolon kanseri evrelemesinde De Ritis oranının prognostik değeri belirsizdir. Bu araştırmanın amacı kolon kanserinde De Ritis oranını ve kolon kanseri için prognostik önemini belirlemektir.
Araçlar ve Yöntem: Ocak 2010'dan Ocak 2018'e kadar tek merkezde malign kolon kanserli 271 bireyin klinikopatolojik verileri geriye dönük olarak analiz edildi. Ameliyat öncesi dönemde hastaların De Ritis oranı ile klinikopatolojik bulguları arasındaki ilişki değerlendirildi. Grupları karşılaştırmak için Mann-Whitney U testi ve Kruskal Wallis testi yapıldı.
Bulgular: Sonuçlar, tedavi öncesi De Ritis oranı değerlendirmesi açısından evreleme, lokalizasyon, tümör çapı, lenf nodu metastazı, yaş ve genel sağkalım açısından gruplar arasında istatistiksel olarak anlamlı bir fark olmadığını gösterdi. Bununla birlikte, erkek hastalar arasındaki T evrelemesindeki farklılıkların istatistiksel olarak anlamlı olduğu gösterildi.
Sonuç: Tedavi öncesi değerlendirilen De Ritis oranı kolon kanseri tanı ve evrelemesinde bağımsız bir değişken prognostik faktör değildi. Bununla birlikte gelecekteki çalışmalar, daha fazla katılımcıyla De Ritis oranının önemini gösterebilir.

Anahtar Kelimeler: adenokarsinom; sağkalım; prognoz

ABSTRACT

Purpose: The De Ritis ratio (Aspartate transaminase/alanine transaminase) is a critical prognostic factor for some kinds of malignant tumors. Nevertheless, the De Ritis ratio's prognostic value in preoperative colon cancer staging is unclear. The purpose of this research was to determine the De Ritis ratio and its prognostic significance for colon cancer.
Materials and Methods: The clinicopathological data of 271 individuals with malign colon cancer were analyzed retrospectively at a single center from January 2010 to January 2018. The relationship between the De Ritis coefficient and clinicopathological findings in patients was evaluated before treatment. To compare the groups, the Mann-Whitney U test and the Kruskal Wallis test were performed.
Results: The results indicated that there were no statistically significant differences between the groups in terms of pre-treatment De Ritis ratio assessment as a staging, localization, tumor diameter, lymph node metastasis, age, and overall survival. However, differences in T staging between groups of male participants were shown to be statistically significant.
Conclusions: The De Ritis ratio evaluation before treatment was not found as an independent variable prognostic factor for the diagnosis and staging of colon cancer. However, future studies may demonstrate the significance of the De Ritis ratio with more participants.

Keywords: adenocarcinoma; survival; prognosis

Received: 24.02.2022; Accepted: 18.10.2022

[1]Ankara Training and Research Hospital, Department of General Surgery, Ankara, Türkiye

Corresponding Author: Saygın Altıner, Ankara Training and Research Hospital, Department of General Surgery, Ankara, Türkiye.
e-mail: sygn0607@gmail.com

How to cite: Altıner S, Cebeci E, Sucu BB, Çöl M, Ergüder E, Ünal Y, Tuncal S, Pekcici MR. Can the de ritis ratio (ast/alt) be used to predict colon cancer stages? Ahi Evran Med J. 2023;7(2):140-144. DOI: 10.46332/aemj.1077653

INTRODUCTION

In recent years, the ratio of serum transaminases aspartate transaminase (AST) to alanine aminotransferase (ALT) has garnered interest as being a possible predictive biomarker in a variety of cancers.[1] Bezan et al. established the first link between a high AST/ALT ratio and poor survival rates in individuals with non-metastatic renal cell carcinoma. They proposed that the increased aerobic glycolysis and pyruvate synthesis (Warburg effect) found in cancer cells could biologically account for these findings.[2] Cancer cells have been demonstrated to have increased aerobic glycolysis and pyruvate synthesis for nucleotide biosynthesis and non-essential amino acid creation. AST is involved in aerobic glycolysis via the malate aspartate shuttle, which occurs in the cytoplasm via Nicotinamide Adenine Dinucleotide Hydrogen (NADH). Therefore, serum AST is an enzyme that is widely produced in many tissue types and has an important role in aerobic glycolysis.

Serum ALT is known to be more liver-specific. In comparison to ALT, a greater increase in AST is observed in clinical events characterized by a proliferative process.[3,4] Several studies have been published in the literature which linked a high preoperative serum AST/ALT ratio to a bad prognosis.[5-8] Laboratory testing, endoscopic procedures, and imaging examinations are performed during the preoperative process to evaluate the stage of the disease and to establish treatment plans. The De Ritis ratio is simple to use and widely used due to its low cost and inclusion in normal preoperative preparation.

There is no universally accepted approach for staging colon cancer, selecting a therapy strategy, or predicting prognosis. Although factors defining the pathological stage are the strongest predictors of postoperative out-come, other clinical, genetic, and histological characteris-tics may have an effect on prognosis regardless of stage.

The purpose of this project was to identify biochemical indicators that can be used more broadly and inexpensively to predict the stage of colon cancer, which is a leading cause of death and morbidity worldwide.

MATERIALS and METHODS

The study was approved by the Ankara City Hospital Ethics Committee on February 24, 2021, with reference number 604/2021. Between 01.01.2010 and 31.12.2018, 456 patients who underwent colon cancer surgery at our hospital were retrospectively analyzed. For various reasons, 185 of these patients were omitted from the study. The exclusion criteria were listed as follows: 1) 12 patients with a history of chronic liver disease, chronic obstructive pulmonary disease (COPD), or chronic alcoholism and use of hepatotoxic drugs; 2) 84 patients who received neoadjuvant chemotherapy and radiotherapy; 3) 17 patients whose colon tumor was metastatic at the time of surgery; 4) 6 patients with other known malignant disease; and 5) 66 patients with missing data. The study enrolled 271 patients who met the study's inclusion criteria. A retrospective assessment of surgery reports, patient epicrises, preoperative imaging results, and paraffin block pathology data was performed.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 23.0 for Windows (SPSS Inc. Chicago, USA) software was used for statistical data analysis. In the descriptive statistics section, categorical variables were presented as numbers and percentages, and continuous variables were presented as mean±standard deviation. To compare the groups, the Mann- Whitney U test and the Kruskal Wallis test were performed. The Spearman Correlation analysis test was used for correlation analysis. The statistical significance level was accepted as $p<0.05$.

RESULTS

The study comprised 136 female patients (50.18 percent) and 135 male patients (49.82 percent), with a mean age of 65 (57-72). The mean duration of survival was determined to be 51.3 months. When the patients' pathology reports were analyzed, there was no statistically significant relationship between preoperative De Ritis ratio and stage, lymph node involvement, or tumor invasion status. When individuals were analyzed according to gender, it was shown that women had a statistically substantially greater De Ritis Ratio than men ($p=0.028$). (Tables 1, 2).

Table 1. Comparison of De Ritis rates of the participants according to age, stage, lymph node involvement and tumor invasion status.

Variables	Number Of Cases	Percentage	AST/ALT Ratio (De Ritis)	p-value
Gender				0.028
Male	135	49,82	1.33	
Female	136	50,18	1.41	
Tumor Stages				0.140
1	70	25.83	1.31	
2a	71	26.20	1.37	
2b	7	2.58	1.75	
3a	19	7.01	1.29	
3b	95	35.06	1.38	
3c	9	3.32	1.42	
Lenf Node Status (N)				0.517
0	148	54.61	1.33	
1	99	36.53	1.36	
2	18	6.64	1.36	
3	6	2.21	1.71	
Tumor Invasion (T)				0.110
1	8	2.95	1.09	
2	82	30.26	1.31	
3	154	56.23	1.37	
4	27	9.96	1.63	

ALT: Alanin Aminotransferaz AST: Aspartat aminotransferaz

Table 2. Relation between localization of tumor.

Localization	Number Of Cases	Percent-age	AST/ALT Ratio (De Ritis)	p-value
Localization				0.511
Caecum	17	6.27	1.33	
Ascending Colon	48	17.71	1.41	
Hepatic Flexure	2	0.74	1.95	
Transvers Colon	14	5.17	1.47	
Splenic Flexure	5	1.85	1.53	
Descending Colon	24	8.86	1.47	
Sigmoid Colon	123	45.39	1.33	
Rectum	38	14.02	1.33	

ALT: Alanin Aminotransferaz AST: Aspartat aminotransferaz

Since there was a statistically significant difference between male and female patients, when the pathological results were re-examined in terms of gender, there was a statistically significant difference between the stage and tumor invasion status, as well as the De Ritis Ratio, in male participants (p=0.025) (Table 3).

Table 3. Evaluation of De Ritis Ratio in terms of stage and tumor invasion status among male patients.

Variables	De Ritis Ratio	p-value
Stage		0.087
1	1.15	
2a	1.27	
2b	1.75	
3a	1.29	
3b	1.36	
3c	1.83	
Tumor Invasion Status (T)		0.025
1	0.86	
2	1.18	
3	1.35	
4	1.79	

Additionally, the association between patient survival rate and the De Ritis Ratio was analyzed, and it was shown that the groups had an inverse correlation, which was not statistically significant (Table 4). When the survival times of patients were compared to their tumor stages, it was shown that stage 3b (74.6 months) and stage 3c (54.9 months) patients had considerably shorter survival times than stage 1 (102.04 months) patients.

Table 4. Correlation between survival times and De Ritis ratio.

Variables	Survival (month)	
	r	p
De Ritis ratio	-0.061	0.319

r: Correlation Coefficient

DISCUSSION

The serum levels of AST and ALT are routinely measured to evaluate liver function. In recent years, numerous studies have demonstrated that it is commonly used in clinics, is inexpensive, and can be used to measure the risk and prognosis of preoperative patients. The AST/ALT ratio was used to diagnose viral hepatitis, but now it is used to figure out how likely it is that HCC, RCC, breast cancer, testicular tumors, and urothelial carcinomas will spread.[9-13] A high AST/ALT ratio in HCC patients is associated with severe liver necrosis, and recurrence is more prevalent in these patients, according to a study. In the same study, it was discovered that patients with high AST/ALT ratios had a lower overall survival than those with low ratios.[9] Since people with liver metastases were not allowed to take part in this trial, it was not possible to evaluate the De Ritis Ratio correlation between metastatic and non-metastatic patients. Changes in the AST/ALT ratio in colon

cancer patients with liver metastases can be ad-dressed with additional research. Although the correlation was not statistically significant in our investigation, the AST/ALT ratio increased with increasing tumor invasion, lymph node number, and tumor stage.

The majority of AST is released by mitochondria. It is abundantly distributed throughout the brain, kidney, skeletal muscle, and liver. However, ALT is present only in the cytoplasm of hepatocytes and is hence liver-specific.[5] Stocken et al. discovered a correlation between serum AST levels and disease-free survival in 653 patients with advanced pancreatic cancer.[14] On the other hand, Tan et al. demonstrated a correlation between the AST/ALT ratio and poor survival in distal cholangiocarcinoma.[15] Canat et al. reported in another investigation on the AST/ALT ratio that it is related to renal vein and renal capsule invasion in individuals with RCC.[16] Another recent study discovered that the serum AST/ALT ratio might be used to predict the likelihood of developing prostate cancer. It has been suggested that it acts as a biochemical marker.[17]

The research demonstrates that AST is an independent predictor of overall survival in colon cancer.[18] In addition, AST/ALT ratio is a reliable predictor of overall survival in patients with colorectal tumors of grade 2-3.[19] There was no statistically significant link between the ratio of AST to ALT and overall survival in our study; nevertheless, there was a tendency for a negative correlation between OS and the AST/ALT ratio. Also, a high AST/ALT ratio was linked to the status of tumor invasion in men (T Stage). The rise in the De Ritis ratio may be caused by the fact that ALT levels are lower in colorectal cancers that haven't spread to other parts of the body than AST levels are, and this may be the main reason for the rise in the ratio. Still, more research is needed to set cut-off values and help choose treatments.

Similar to this study, numerous others have discovered a correlation between AST/ALT ratio and tumor grade and OS, but no study has uncovered a rational and universally accepted pathophysiology. Oxidative pathways, metabolic activities of tumor cells, inflammation, and oxidative stress are prominent theories, but the lack of revealing the patho-physiology prevents the determination of the cut-off value necessary for preoperative evaluation. In addition to ad-vanced clinical research, studies at the molecular level will illuminate the topic.

Our study has limitations due to the small number of patients, retrospective methodology, and short duration of follow-up. Prior to surgery, the serum AST/ALT ratio should typically be verified in large, prospective investiga-tions.

In conclusion, De Ritis ratio evaluation before treatment was not found as an independent variable prognostic factor for the diagnosis and staging of colon cancer. We think that the importance of this issue will be understood more by conducting prospective studies with a higher number of patients.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Acknowledgments

Our study was presented orally at the 18th Turkish Colon and Rectal Surgery Congress, and only the summary was published in the European Surgery journal.

Ethics Committee Permission

Approval for this study was obtained from the Ankara City Hospital Ethics Committee (24.02.2021 dated and 604/2021 numbered).

Authors' Contributions

Concept/Design: MRP. Data Collection and/or Pro-cessing: BS, EC. Data analysis and interpretation: SA. Literature Search: MÇ, EE. Drafting manuscript: SA. Critical revision of manuscript: ST, YÜ. Süpervisor: MRP.

REFERENCES

1. Chen SL, Li JP, Li LF, Zeng T, He X. Elevated Preoperative Serum Alanine Aminotransferase / Aspartate Aminotransferase (ALT/AST) Ratio Is Associated with Better Prognosis in Patients Un-dergoing Curative Treatment for Gastric Adeno-carcinoma. Int J Mol Sci. 2016;17(6):911.
2. Bezan A, Mrsic E, Krieger D, et al. The Pre-operative AST/ALT (De Ritis) Ratio Represents a Poor Prognostic Factor in a Cohort of Patients with Nonmetastatic Renal Cell Carcinoma. J Urol. 2015;194(1):30-35.

3. Varol U, Kaya E, Oflazoglu U, et al. Prognostic role of De Ritis and basal neutrophil to lympho-cyte ratio in patients with advanced stage pancre-atic cancer [IzmirOncologyGroup (IZOG) Study]. J BUON. 2020;25(2):1063-1069.
4. Knittelfelder O, Delago D, Jakse G, et al. The AST/ALT (De Ritis) Ratio Predicts Survival in Patients with Oral and Oropharyngeal Can-cer. Diagnostics (Basel). 2020;10(11):973.
5. Wu J, Chen L, Wang Y, Tan W, Huang Z. Prog-nostic value of aspartate transaminase to alanine transaminase (De Ritis) ratio in solid tumors: a pooled analysis of 9,400 patients. Onco Targets Ther. 2019;12:5201-5213.
6. Liu L, Wang W, Zhang Y, et al. Declined Pre-operative Aspartate Aminotransferase to Neutro-phil Ratio Index Predicts Poor Prognosis in Pa-tients with Intrahepatic Cholangiocarcinoma after Hepatectomy. Cancer Res Treat. 2018;50(2):538-550.
7. Mori K, Janisch F, Mostafaei H, et al. Prognostic role of preoperative De Ritis ratio in upper tract urothelial carcinoma treated with nephroureterec-tomy. Urol Oncol. 2020;38(6):601.e17-601.e24.
8. Ha YS, Kim SW, Chun SY, et al. Association between De Ritis ratio (aspartateaminotransferase / alanineaminotransferase) and oncological out-comes in bladder cancer patients after radical cystectomy. BMC Urol. 2019;19(1):10.
9. Zhang LX, Lv Y, Xu AM, Wang HZ. The prog-nostic significance of serum gamma-glutamyl transferase levels and AST/ALT in primary he-patic carcinoma. BMC Cancer. 2019;19(1):1-9.
10. Thornburg JM, Nelson KK, Clem BF, et al. Tar-geting aspartate aminotransferase in breast can-cer. Breast Cancer Res. 2008;10(5):1-12.
11. Lee H, Lee SE, Byun SS, Kim HH, Kwak C, Hong SK. De Ritis ratio (aspartatetransaminase / alaninetransaminaseratio) as a significant prog-nostic factor after surgical treatment in patients with clear-cell localized renal cell carcinoma: a propensity score-matched study. BJU Int. 2017;119(2):261-267.
12. Li Y, Fang D, Bao Z, et al. High aspartatetrans-aminase / alaninetransaminase ratio predicts poor prognosis in patients with localized upper tract urothelial cancer: a propensity score-matched study in a large Chinese center. Onco Targets Ther. 2019;12:2635-2648.
13. Durhan A, Şenlikci A, Ergüder E. et al. Is Aspar-tate Aminotransferase to Alanine Aminotransfer-ase (De Ritis Ratio) Helpful in Predicting Breast Cancer? Arch Clin Exp Med. 2021;6(1):13-16.
14. Stocken DD, Hassan AB, Altman DG, et al. Modelling prognostic factors in advanced pan-creatic cancer. Br J Cancer. 2008;99(6):883-893.
15. Tan X, Xiao K, Liu W, Chang S, Zhang T, Tang H. Prognostic factors of distal cholangiocarci-noma after curative surgery: a series of 84 cas-es. Hepatogastroenterology. 2013;60(128):1892-1895.
16. Canat L, Ataly HA, Agalarov S, Alkan I, Altun-rende F. The effect of AST/ALT (De Ritis) ratio on survival and its relation to tumor histopatho-logical variables in patients with localized renal cell carcinoma. Int Braz J Urol. 2018;44(2):288-295.
17. Zhou J, He Z, Ma S, Liu R. AST/ALT ratio as a significant predictor of the incidence risk of prostate cancer. Cancer Med. 2020;9(15):5672-5677.
18. Ahn HJ, Oh HS, Ahn Y, et al. Prognostic Impli-cations of Primary Tumor Resection in Stage IV B Colorectal Cancer in Elderly Patients. Ann Coloproctol. 2014;30(4):175-181.
19. Scheipner L, Smolle MA, Barth D, et al. The AST/ALT Ratio Is an Independent Prognostic Marker for Disease-free Survival in Stage II and III Colorectal Carcinoma. Anti cancer Res. 2021;41(1): 429-436.