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CLINICAL STUDY

The prognostic effect of neutrophil-to-lymphocyte ratio and De Ritis ratio in glioblastoma multiforme patients

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ABSTRACT

AIMS: Individuals with a higher De Ritis ratio (aspartate transaminase/alanine transaminase) and neutrophil-to-lymphocyte ratio (NLR) have an inferior survival in varied malignancies. To our knowledge, the prognostic potential of the De Ritis ratio and NLR to predict the survival in nonmetastatic glioblastoma multiforme (GBM) patients remains unclear. In this study, we aimed to explore the prognostic power of the De Ritis ratio and NLR in patients with nonmetastatic glioblastoma multiforme.

METHODS: Data of 262 patients with glioblastoma multiforme have been retrospectively analyzed. Their age, gender, tumor characteristics, AST/ALT ratio, NLR and hemogram values, including age at diagnosis and date of diagnosis were recorded.

RESULTS: The median survival time of the study group was 21 months *(95% CI: 19–23 months)*. The first-year and second-year survival rates were 73.0% and 40.5%, respectively. The univariate analysis revealed that the correlation of survival with age, gender, left/right location of tumor, mean platelet volume and De Ritis ratio did not reach the level of significance. The univariate analysis of the prognostic potential of NLR indicated that a 1-unit increase in NLR value translates to a 1.05 times higher risk of death (95% CI: 1.01–1.09).

CONCLUSION: The results of this study lead to the observation that NLR value can serve as an effective prognostic marker in predicting the outcomes of patients with glioblastoma multiforme. It can be positioned as an easily accessible and cost-effective biomarker for establishing appropriate therapeutic strategies *(Tab. 2, Fig. 1, Ref. 20)*. Text in PDF www.elis.sk

KEY WORDS: neutrophil-to-lymphocyte ratio, De Ritis ratio, glioblastoma multiforme, malignancy.

Introduction

Glioblastoma multiforme (GBM) is a rare intracranial malignant tumor of the central nervous system in adults. Standard treatment for these patients includes tumor resection followed by concomitant chemoradiotherapy and adjuvant therapy with temozolomide (TMZ) (1).

The survival of GBM patients is low, ranging from 15 to 20 months, even with aggressive treatment. The most important factors affecting survival are age, performance status, MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation status, and presence or absence of isocitrate dehydrogenase type 1 (IDH1) or isocitrate dehydrogenase type 2 (IDH2) mutation. Inflammatory factors are thought to be associated with cancer initiation, progression, invasion, and metastasis. In various types of cancer, biomarkers of inflammatory reactions have been accepted as prognostic factors (1).

NLR has emerged as a potential biomarker of cancer prognosis and is of particular clinical interest due to its accessibility and the ease of calculating the ratio from routinely conducted blood cell count examinations. The effectiveness of NLR as a prognostic marker in cancer patients remained consistent and robust, even after adjusting for additional prognostic factors. The close association between inflammation and cancer progression signals the potential of elevated values of tumor-associated neutrophils (TAN), or tumor-infiltrating neutrophils, to serve as prognostic biomarkers (2).

Serum levels of ALT and AST circulating in the body are specific markers of liver function. These transaminases participate in gluconeogenesis and amino acid metabolism by catalyzing the transfer of amino groups (3).

The glycolysis requirement of cancer tissue eminently exceeds that of healthy cells even in junction with sufficient

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supply of ATP and oxygen. Notably, AST plays a major role in the glycolysis pathway throughout the metabolic processes taking place within mitochondria. Regarding this fact, the value of De Ritis ratio might reflect the tumor metabolism in many glucose-utilizing types of cancer. In addition to the liver, amino transaminases are expressed in cellular subdivisions in various other organ tissues, including the heart, skeletal muscle, brain, kidney, and red blood cells (4).

The AST/ALT ratio, also known as the De Ritis ratio, is widely utilized in the management of various liver diseases and some other non-hepatic diseases. The De Ritis ratio has also been reported as a prognostic biomarker, predicting the outcomes for patients with renal cell, esophageal squamous cell, and urothelial carcinomas, including gastric adenocarcinoma (5, 6). This leverages the investigation of the De Ritis ratio as a cost-effective, simple, and easily accessible asset. The utility of De Ritis ratio as a marker for the prognosis in various malignancies has been investigated by many studies, however with contradicting results (5, 7).

To our knowledge, the prognostic potential of the De-Ritis ratio and NLR in the survival of nonmetastatic GBM patients remains dubious. According to several studies, individuals with elevated values of De Ritis ratio and NLR had an inferior survival in different malignancies. Therefore, we aimed to investigate the prognostic effectiveness of the De Ritis ratio and NLR as markers for stratifying the risk and treatment enhancement in patients with nonmetastatic glioblastoma multiforme.

Tab. 1. Distribution of demographic, clinical findings and laboratory findings of patients.

Characteristics (n=262)	
Male (n,%)	147 (56.1)
Age, years (median)	57 (17–80)
Blood Group (n,%)	
0+	58 (22.1)
0–	12 (4.6)
A+	96 (36.6)
A–	12 (4.6)
B+	56 (21.4)
B–	6 (2.3)
AB+	19 (7.3)
AB–	3 (1.1)
Tumor localization (n,%)	
Right	134 (51.1)
Left	128 (48.9)
Chemotherapy – radiotherapy (n,%)	214 (81.7)
Cyberknife treatment (n,%)	29 (11.1)
First-line chemotherapy (n,%)	127 (48.5)
WBC ($\times 10^9$ cells/L) (med, min–max)	8.5 (3.4–22.5)
Neutrophil ($\times 10^9$ cells/L) (med, min–max)	5.5 (2.1–19.8)
Lymphocyte ($\times 10^9$ cells/L) (med, min–max)	1.7 (0.5–6.3)
Hgb (g/dl) (med, min–max)	13.1 (9.3–17.0)
PLT ($\times 10^9$ cells/L) (med, min–max)	246.0 (85.0–544.0)
MPV (fL) (med, min–max)	9.1 (6.3–13.8)
AST (U/l) (med, min–max)	18.0 (6.0–126.0)
ALT (U/l) (med, min–max)	18.0 (7.0–143.0)
De Ritis ratio (AST/ALT) (med, min–max)	0.9 (0.1–5.0)
Neutrophil/lymphocyte ratio (med, min–max)	3.1 (0.6–20.0)
PLT ($\times 10^9$ cells/L) (med, min–max)	246.0 (85.0–544.0)

Methods

In total, 262 patients who were followed up at the Internal Medicine Department and/or Oncology clinic with the diagnosis of glioblastoma multiforme in Izmir Atatürk Training and Research Hospital between years 2006 and 2021 have been retrospectively analyzed. The study received approval from the ethics committee, dated March 24, 2022, with protocol number 0131.

The evaluation of patients was contingent upon the completeness of available data, including their age, gender, diagnosis, tumor characteristics, initial AST, ALT, and hemogram values, age at diagnosis, date of diagnosis, survival or date of death.

Inclusion criteria

Patients aged over 18 years, diagnosed with glioblastoma multiforme over 18 years old.

Exclusion criteria

Patients with incomplete data records on admission and follow-up, as well as those with the presence of fatty liver, alcoholism, other concomitant cancer disease, or diagnosis of hepatitis were excluded from the study.

Statistical analysis

SPSS for Windows version 25 was employed for statistical analysis. In the research, descriptive statistics of categorical data are presented as numbers and percentages, while descriptive statistics of continuous variables are expressed as median, minimum and maximum values. The relationships assessed within the 95% confidence interval and $p<0.05$ were accepted as statistically significant. Cox regression analysis was utilized for survival analysis.

Results

A total of 262 patients have been enrolled in this study, with male/female gender distribution of 56.1% (n=147) and 43.9% (n=115), respectively. The median age in the study group was 57 years. The Karnofsky Performance Score (KPS) of all patients was above 70. MGMT status and IDH1 or IDH2 mutation were not routinely examined in our patients.

The left/right localization of tumors was relatively even. Chemoradiotherapy had been initiated in the majority of patients (81.7%; n=214). Patients received temozolomide treatment as post-radiation chemotherapy. Cyberknife excision was performed in 11.1% (n=29). The first-line chemotherapy was initiated in 48.5% (n=127) of the individuals and absent in 51.5% (=135). The median WBC count was 8.5 $\times 10^9$ cells/L (3.4–22.5 $\times 10^9$ cells/L), with neutrophil, lymphocyte and platelet counts of 5.5 $\times 10^9$ cells/L (2.1-19.8 $\times 10^9$ cells/L), 1.7 $\times 10^9$ cells/L (0.5–6.3

$\times 10^9$ cells/L) and 246$\times 10^9$ cells/L (85–544 $\times 10^9$ cells/L), respectively. Hemoglobin, MPV, AST and ALT values were 13.1 g/dL (9.3–17.0 g/dL), 9.1 fL (6.3–13.8 fL), 18.0 U/L (6.0–126.0 U/L) and 18.0 U/L (7.0–143.0 U/L), respectively. The resultant De Ritis ratio has been calculated as 0.9 (0.1–5.0). All these parameters are presented in Table 1.

The median survival time of the study group was 21 months (95% CI: 19–23 months). While the first-year survival rate was 73.0%, the second-year survival rate decreased to 40.5% (Fig. 1).

The survival rate was evaluated through univariate analyses. The primary objective was to identify the effect of laboratory data on the disease outcomes independently of age and gender. The results of the univariate analysis imply that age, gender, left/right localization of tumor, MPV and De Ritis Ratio had no impact on the survival. The univariate analysis of NLR revealed that its 1-unit increase is linked to a 1.05 (95% CI: 1.01–1.09) times higher risk of death (Tab. 2).

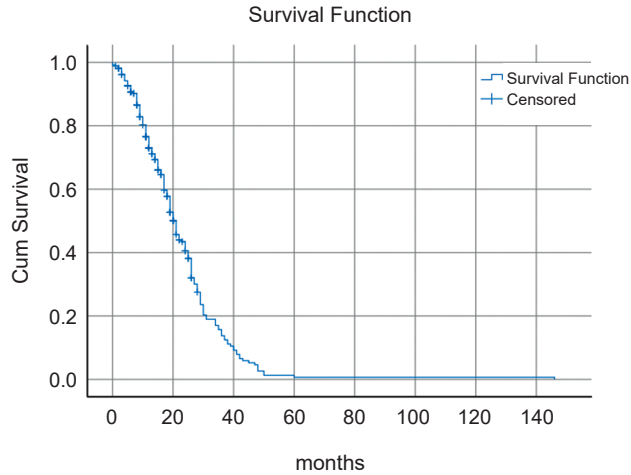

Fig. 1. The median survival time of the study group was 21 months (95% CI: 19–23). While the first-year survival rate is 73.0%, the second-year survival decreased to 40.5%.

Discussion

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. The majority of the cases are classified as primary glioblastomas (90%) that develop *de novo* at a mean age of 55 years, without clinical and/or histopathological findings. Secondary glioblastomas are linked to a better prognosis and are seen at a younger age, e.g., at 40 (1). At this stage, physicians need an easily accessible, cost-effective and practical prognostic factor.

Circulating neutrophils have been shown to contain and secrete vascular endothelial growth factors, tumor necrosis factor, and other cytokines contributing to cancer progression. Additionally, increased neutrophil levels subsequently suppress the cytolytic activity of lymphocytes, leading to lymphocytopenia or decreased lymphocyte function (8,9).

However, it is worth accentuating that the prognostic value of NLR extends beyond glioblastoma multiforme. It has been underscored in various other malignancies such as colorectal, prostate, bladder, and gastric cancers, as well as metastatic renal cell carcinoma, metastatic melanoma, and advanced non-small-cell lung cancer. Mounting evidence emerges from previous studies reporting that the increased presence of lymphocytes around the tumor or in peripheral blood were associated with better prognosis, whereas more pronounced occurrence of neutrophils signals poor prognosis. Briefly, elevated NLR values correlate with a poor prognosis and lower survival rate (2, 8, 9).

NLR is assumed to reflect the balance between the activation of the inflammatory pathway and the anti-tumor immune function. Two retrospective studies (10, 11) reported that NLR values of <4 and <5, respectively, have been shown to be associated with longer overall survival in glioblastoma multiforme patients. McNamara et al. (2014) assessed the prognostic value of NLR before second surgery in glioblastoma multiforme patients and demonstrated that low NLR values were linked to longer overall survival after the second surgery (12, 14).

Bambury et al (2013) reported that on univariate analysis, NLR>4 was associated with deteriorated median overall survival. Furthermore, on multivariate analysis, NLR>4 remained an independent prognostic indicator for poor outcomes (13). These results were corroborated by Huszno et al (2019), highlighting the NLR value of ≥5 as an independent predictor of poorer overall survival (8). Wang et al (2017) concluded that NLR≤4 was associated with higher overall survival in glioblastoma multiforme patients (10). McNamara et al (2014) investigated the factors impacting survival in patients undergoing a second surgery for glioblastoma multiforme, concluding that in these patients, the NLR values of ≤4 and >4 correlated with median overall survivals of 9.7 and 5.9 months, respectively (12). In our study, the median survival time of the study group was 21 months. On univariate analysis of neutrophil/lymphocyte ratio, a 1-unit increase indicates a 1.05 (95% CI: 1.01–1.09) times higher risk of death.

Kiba et al (2014) found increased AST and LDH levels to be associated with lower overall survival in multiple myeloma patients (15). The benefits of the De Ritis ratio as a predictor of recurrence-free survival in patients with upper urinary tract urothelial carcinoma following nephroureterectomy has first been

Tab. 2. Results of Univariate Cox Regression Analysis of factors affecting survival.

	Univariate	
	HR (95% CI)	**p**
Male Gender	1.08 (0.81–1.44)	0.595
Age	1.01 (0.99–1.02)	0.209
Tumor location (left vs right)	1.10 (0.83–1.46)	0.496
MPV	1.03 (0.93–1.13)	0.507
De Ritis ratio	1.11 (0.88–1.41)	0.355
Neutrophil/lymphocyte ratio	**1.05 (1.01–1.09)**	**0.033**

published by Nishikawa et al (2016) in a retrospective analysis of 109 patients (16). Gorgel et al (2017) have published similar results in non-metastatic bladder cancer (17).

Alongside well-recognized prognostic factors, the De Ritis ratio can provide critical information highly valued in clinical practice. To date, only a limited number of studies have explored the prognostic power of the De-Ritis ratio in patients with various solid organ malignancies such as cancers of the urinary and biliary tracts, renal cells, and bladder, including head and neck cancers (16, 17). Lee et al (2017) have explored the prognostic potential of the De-Ritis ratio in 623 patients who underwent nephroureterectomy for urothelial cancer. They concluded that a high preoperative De Ritis ratio predicted poor disease-free, cancer-specific, and overall survivals ($p<0.001$) (18).

The aforementioned studies suggest that an increase in the De-Ritis ratio is linked with elevated aerobic glycolysis, a phenomenon known as the Warburg effect. Increased intensity of glycolysis is known to be linked to various alterations in mitochondrial activities associated with nicotinamide adenine dinucleotide-related enzymes and glucose transporters (19). Furthermore, recent studies have shown that rapidly proliferating cancer cells exhibit augmented glutamine metabolism alongside aerobic glycolysis to sustain nucleotide biosynthesis (20). These processes are also catalyzed by AST and ALT. In cancer cells, enhanced glutamine catabolism supports metabolites of the tricarboxylic acid cycle. ALT catalyzes the conversion of pyruvate and glutamate to alanine and alpha-ketoglutarate, participating in both glycolysis and glutaminolysis. Thus, compared to serum AST levels, the increased metabolism in aggressive cancer cells leads to ALT depletion, eventually raising the value of De Ritis ratio. This hypothesis likely explains the variation in the AST/ALT ratio (19).

To the best of our knowledge, the prognostic power of the De Ritis ratio, specifically in glioblastoma multiforme patients, has not been previously addressed. Therefore, our study aimed to assess its utility as prognostic marker in GBM. However, unlike other studies that have identified the preoperatively evaluated De Ritis ratio as a prognostic factor for disease-free and overall survivals in various types of cancer, our study did not yield the same conclusion.

The main limitation of this study stems from its retrospective nature. Nevertheless, the strength of our research lies in the larger size of the patient cohort compared to previous literature.

Conclusion

The results of this study lead to the observation that unlike the De Ritis ratio, the NLR value can effectively serve as a prognostic marker in predicting outcomes of patients with glioblastoma multiforme. It can be positioned as an easily accessible and cost-effective biomarker for establishing appropriate therapeutic strategies.

Further prospective studies are warranted to provide in-depth information on the prognostic significance of the De-Ritis ratio in predicting disease-free and overall survivals in GBM.

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