CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

Evaluation of Neutrophil Lymphocyte Ratio and IDH Mutation in Patients with Glioblastoma

Glioblastoma Hastalarında Nötrofil Lenfosit Oranı ve IDH Mutasyonunun Değerlendirilmesi

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Abstract

Objective: One of the prognostic factors for glioblastoma (GBM) is isocitrate dehydrogenase (IDH) status. In addition, it has been stated that the neutrophil lymphocyte ratio (NLR) in GBM effects prognosis. In this study, we aimed to reveal the relationship between preoperative NLR and IDH status in GBM patients.

Methods: Age, gender, preoperative NLR value, IDH status, Ki67 and p53%, and ATRX status of the patients were recorded in two groups: IDH mutant 7 patients and IDH wild type (IDH-Wt) 24 patients.

Results: When the two groups were examined, no statistical difference was found between the loss of ATRX expression, Ki67 and p53 markers, and pre-operative NLR values. Only IDH mutant patients were younger (p=0.037).

Conclusion: Although it is seen that the pre-operative NLR value is not useful in determining the IDH status in GBM patients, it can be said that low NLR may have a positive effect on overall survival.

Keywords: Glioblastoma, IDH, neutrophil, lymphocyte

Öz

Amaç: Glioblastom (GBM) için prognostik faktörlerden biri izositrat dehidrojenaz (IDH) durumudur. Ayrıca GBM'deki nötrofil lenfosit oranının (NLR) prognoza etkisi olduğu belirtilmiştir. Bu çalışmada GBM hastalarında ameliyat öncesi NLR ile IDH durumu arasındaki ilişkinin ortaya konması amaçlandı.

Yöntem: Hastaların yaş, cinsiyet, ameliyat öncesi NLR değeri, IDH durumu, Ki67 ve p53%, ATRX durumu IDH Mutant 7 hasta ve IDH-wild tip (IDH-Wt) 24 hasta olmak üzere iki grupta kaydedildi.

Bulgular: İki grup incelendiğinde ATRX ekspresyon kaybı, Ki67, p53 belirteçleri ve ameliyat öncesi NLR değerleri arasında istatistiksel fark bulunmadı. Sadece IDH mutant hastaların yaşı daha gençti (p=0,037).

Sonuç: GBM hastalarında ameliyat öncesi NLO değerinin IDH durumunu belirlemede yararlı olmadığı görülse de, düşük NLO'nun genel sağkalımı olumlu yönde etkileyebileceği söylenebilir.

Anahtar Kelimeler: Glioblastom, IDH, nötrofil, lenfosit

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Introduction

Gliomas constitute nearly 81% of primary intracranial tumors. The most frequent type of gliomas is Glioblastoma (GBM)[1]. The most commonly seen malign primary brain tumor in adults is GBM[2] and the first step of current standard treatment is surgical maximum resection and then radiation therapy with chemotherapy and adjuvant temozolomide chemotherapy[3]. It is set forth that despite the standard treatment, the clinical results of GBM patients differ because of the heterogeneity of the tumor and more than one systemic factor[4].

Factors such as a patient's Karnofsky performance status, age, tumor localization, tumor resection rate, and isocitrate dehydrogenase (IDH) are common prognostic factors[5]. In terms of IDH situation, IDH wild type (IDH-Wt) is seen at a rate of 90%, and IDH mutant is seen at a rate of 10%, and it is known that IDH-Wt GBM patient prognosis is worse[6].

Due to the low cost and being easily accessible, recent studies investigate the association of neutrophil lymphocyte ratio (NLR) with prognosis. It indicates a systematic inflammatory response and can be measured from peripheral blood. Rare studies were found regarding the fact that high NLR was correlated with poor prognosis in GBM patients. Apart from other factors, NLR >4 GBM patients were associated with prognosis[7,8].

The present study addressed the association between NLR and IDH in GBM patients in whom preoperative peripheral blood was collected.

Materials and Methods

Ethics Committee approval was received from SBU İzmir Tepecik Education and Research Hospital SUAM dated 15.02.2022 and decision numbers 2022/02-35. After receiving the approval of the local ethical committee, 31 GBM patients who underwent surgery by the same experienced neurooncological team were retrospectively examined at a single center between 2020 and 2021. Two groups were formed as IDH mutant 7 patients and IDH-Wt 24 patients. Patients diagnosed for the first time and not having a history of surgery were included in the study. Patients who were receiving the steroid treatment, had active infection in some other areas of their body, had used medication having anti-inflammatory property, and whose IDH condition had not been examined were excluded. Age, sex, pre-op NLR values, IDH status, Ki67 and p53%, and ATRX status of patients were recorded.

Statistical Analysis

Continuous data in descriptive statistics were given with their median, minimum, and maximum values. In statistical comparison of the data, Kolmogorov-Smirnov analysis and Mann-Whitney U test were used for the suitability in terms of a normal distribution. Fisher exact test was used for categorical data. A p value under 0.05 in 95% confidence interval was considered significant regarding statistical significance. Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 21.0 was used for statistical analyzes.

Results

When both groups were examined, no statistical difference between sex and ATRX expression loss was found (Table 1). Moreover, when Ki67, p53 indicators and results of pre-op NLR values were examined, no statistical difference between both groups was found. In addition, the ages of IDH mutant patients were found to be younger (p=0.037) (Table 2).

Discussion

It was found that some inflammatory indicators were associated with GBM prognosis[9,10]. However, as an indicator of inflammatory response, NLR prognostic importance on GBM patients before operation is still uncertain. In many

Table 1. Results showing gender and ATRX status between the two groups								
		IDH		IDH-Wt		Total		
		Number	%	Number	%	Number	%	P*
Sex	M	6	85.7	15	62.5	21	67.7	0.379
	F	1	14.3	9	37.5	10	32.3	
ATRX	0	6	85.7	22	91.7	28	90.3	0.55
	1	1	14.3	2	8.3	3	9.7	
Total		7	100	24	100	31	100	
*The result of Fisher exact test, M: Male, F: Female, IDH: Isocitrate dehydrogenase, IDH-Wt: IDH-wild type								

Table 2. Results showing age p53 and NLR status between the two groups							
	IDH			IDH-Wt			
	Median	Min	Max	Median	Min	Max	P*
Age	49.0	31.0	75.0	65.0	44.0	78.0	0.037
NLR	2.5	1.7	5.2	3.1	1.6	19.9	0.345
Ki67	25.0	5.0	70.0	25.0	0.0	70.0	0.924
p53	5.0	0.0	30.0	12.5	0.0	90.0	0.220

*The result of the Mann-Whitney U test, IDH: Isocitrate dehydrogenase, IDH-Wt: IDH-wild type, Min: Minimum, Max: Maximum, NLR: Neutrophil lymphocyte ratio

studies, various results have been set forth. The role of NLR was examined in different types of cancer such as ovarian cancer, pancreatic cancer, breast cancer, colorectal cancer, urothelial and renal cell cancers and myeloma and it was noted that the highness was inversely proportional with survival ratio as it was the case in GBM[11]. Moreover, it was indicated that it could serve as a cost-effective prognostic indicator to determine high-risk patients[11].

It was found that more than 4 NLR values for GBM patients were statistically associated with better survival[7,12,13]. In one of their studies, Wang et al.[12] reported that decreased NLR had a positive effect on survival in GBM patients. Similarly, it can be concluded that low NLR in the IDH mutant group of the patient group revealed the positive impact of NLR on the survival rates.

A result of another study revealed that patients with high NLR values compared with patients with low NLR values have a better prognosis. However, no statistical difference was found[14]. Moreover, Lopes et al.[15] did not find any association between survival and NLR.

Wang et al.[16] have indicated that NLR the best indicator to distinguish IDH-Wt GBM from other gliomas and that NLR does not correlate with IDH mutation. In another study by Wang et al.[12], it was found that NLR was not associated with IDH mutations.

In this study, the ages of patients in the IDH mutant group were found to be younger (p=0.037). No statistically significant difference was found between the examined parameters and NLR rates. Also, it was found that the NLR rate for the diagnosis of IDH-Wt GBM was not significantly high but higher compared to the IDH mutant group.

On the other hand, Sharma et al.[17] stated that NLR among indicators has the highest accuracy for GBM diagnosis and has maximum diagnostic value to distinguish IDH-Wt GBM from IDH-mutant GBM.

Study Limitations

As for the limitations of the study, it was a retrospective study and the sample size was limited. For this reason, this study is a pioneer for prospective trials with large series.

Conclusion

It was found that NLR values were not useful in identifying the IDH status of GBM patients. Moreover, it should be noted that low NLR may have a positive effect on overall survival. For this reason, a prospective comprehensive study is planned.

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Ethics

Ethics Committee Approval: Ethics Committee approval was received from SBU İzmir Tepecik Education and Research Hospital SUAM dated 15.02.2022 and decision numbers 2022/02-35.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., Concept: Ç.T., M.Ç., Design: Ç.T., Data Collection or Processing: Ç.T., Analysis or Interpretation: M.Ç., Literature Search: Ç.T., Writing: Ç.T.

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References

1. Ostrom QT, Gittleman H, Stetson L, Virk SM, Barnholtz-Sloan JS. Epidemiology of gliomas. Cancer Treat Res 2015;163:1-14.

2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.

3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.

4. Aum DJ, Kim DH, Beaumont TL, Leuthardt EC, Dunn GP, Kim AH. Molecular and cellular heterogeneity: the hallmark of glioblastoma. Neurosurg Focus 2014;37:E11.

5. Nakagawa Y, Sasaki H, Ohara K, et al. Clinical and Molecular Prognostic Factors for Long-Term Survival of Patients with Glioblastomas in Single-Institutional Consecutive Cohort. World Neurosurg 2017;106:165-73.

6. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803-20.

7.   Bambury RM, Teo MY, Power DG, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. J Neurooncol 2013;114:149-54.

8. McNamara MG, Lwin Z, Jiang H, et al. Factors impacting survival following second surgery in patients with glioblastoma in the temozolomide treatment era, incorporating neutrophil/lymphocyte ratio and time to first progression. J Neurooncol 2014;117:147-52.

9. Han S, Zhang C, Li Q, et al. Tumour-infiltrating CD4(+) and CD8(+) lymphocytes as predictors of clinical outcome in glioma. Br J Cancer 2014;110:2560-8.

10. Lohr J, Ratliff T, Huppertz A, et al. Effector T-cell infiltration positively impacts survival of glioblastoma patients and is impaired by tumor-derived TGF-β. Clin Cancer Res 2011;17:4296-308.

11. Lei YY, Li YT, Hu QL, Wang J, Sui AX. Prognostic impact of neutrophil-to-lymphocyte ratio in gliomas: a systematic review and meta-analysis. World J Surg Oncol 2019;17:152.

12. Wang PF, Song HW, Cai HQ, et al. Preoperative inflammation markers and IDH mutation status predict glioblastoma patient survival. Oncotarget 2017;8:50117-23.

13. Han S, Liu Y, Li Q, Li Z, Hou H, Wu A. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. BMC Cancer 2015;15:617.

14. Ozlem Y, Eylem O, Ozge O, Yasemin K. Prognostic significance of pre-treatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with glioblastoma. Mol Clin Oncol 2018;9:453-8.

15. Lopes M, Carvalho B, Vaz R, Linhares P. Influence of neutrophil-lymphocyte ratio in prognosis of glioblastoma multiforme. J Neurooncol 2018;136:173-80.

16. Wang PF, Meng Z, Song HW, et al. Preoperative Changes in Hematological Markers and Predictors of Glioma Grade and Survival. Front Pharmacol 2018;9:886.

17. Sharma G, Jain SK, Sinha VD. Peripheral Inflammatory Blood Markers in Diagnosis of Glioma and IDH Status. J Neurosci Rural Pract 2021;12:88-94.