Original Article

Impact of Baseline Neutrophil-to-Lymphocyte Ratio on Outcomes of Glioblastoma Multiforme Patients Treated with Standart Concurrent Chemoradiotherapy

Başlangıç Nötrofil-Lenfosit Oranının Standart Eşzamanlı Kemoradyoterapi ile Tedavi Edilen Glioblastoma Multiforme Hastalarının Sonuçları Üzerine Etkisi

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ABSTRACT

Background: Glioblastoma multiforme (GBM) is the most common and miserable prognosis primary brain tumor in adults. Previously neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation has been demonstrated to have both strong predictive and prognostic value in different cancer types, which has rarely been addressed in GBM patients. The aim of this retrospective cohort study was to evaluatethe prognostic value of pretreatment NLR on survival outcomes of GBM patients who were underwent surgery/biopsy followed by definitive chemo-radiotherapy (CRT) and accessibility of a certain cut-off worth for NLR.

Material and Methods: This study was a hospital-based retrospective observational case-series study. This study was designed to identify 144 GBM patients with full pretreatment and treatment records that underwent surgery/biopsy followed by CRT from January 2007 to December 2011 in our clinics. Age, symptoms, laboratory results and treatment modalities of patients were recorded.

Results: The median follow-up time for the whole population was 15.1 (range 1.8-49.9) months, with 95 patients (84.8%) being death at the time of this analysis. NLR cut-off values of 4.3 (AUC:78.4; 95%CI: 64.8-92) for overall- (OS) and 4.1 (AUC:72.7; 95%CI:61-84.1) for local recurrence-free survival (LRFS) were identified, respectively, by using receiver operating curve analysis. Low NLR was associated with significantly longer median OS (23.2 vs. 12.7 months p=0.001), and LRFS (13.9 vs 9.6 months; p<0.001) as well as longer median both of which retained its independent significant association with survival outcomes in the multivariate analysis (p<0.001 for each).

Conclusion: In conclusion, pre-treatment Low-NLR values associate with significantly longer OS and LRFS than those presenting with high-NLR. These findings suggest a novel strong and independent prognostic value for baseline NLR which is cheap, reproducible and easy to measure in routine clinical practice.

Keywords: Neutrophil, Lymphocyte, Glioblastoma Multiforme, survival

ÖZET

Giriş: Glioblastoma multiforme (GBM), yetişkinlerde en sık görülen ve en kötü prognoza sahip primer beyin tümörüdür. Daha önce sistemik inflamasyon belirteci olan nötrofil-lenfosit oranının (NLR), daha nadiren ele alınan GBM hastalarında da olmak üzere farklı kanser türlerinde hem güçlü prediktif hem de prognostik değere sahip olduğu gösterilmiştir. Bu çalışmanın amacı; tedavi öncesi NLR'nun cerrahi / biyopsi sonrası küratif kemoradyoterapi (KRT) alan GBM hastasının sağkalım sonuçları üzerindeki prognostik değerini ve NLR için belirli bir eşik değerin erişilebilirliğini değerlendirmekti.

Materyal-Metod: Bu çalışma, hastane temelli, retrospektif gözlemsel bir vaka serisi çalışmasıydı. Bu çalışma, kliniklerimizde Ocak 2007'den Aralık 2011'e kadar cerrahi/biyopsi ve ardından KRT uygulanan ön tedavi ve tedavi kayıtlarına sahip 144 GBM hastasını belirlemek için tasarlanmıştır. Hastaların yaş, semptom, laboratuvar sonuçları ve tedavi modaliteleri kaydedildi

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Bulgular: Tüm popülasyon için medyan takip süresi 15.1 (1.8-49.9) aydı ve bu analiz sırasında 95 hasta (%84.8) öldü. NLR cut-off değerleri curve analizi kullanılarak sırasıyla Genel sağkalım (OS) için 4.3 (EAA: 78.4; % 95 CI: 64.8-92) ve yerel rekürrenssiz sağkalım (LRFS) için 4,1 (AUC: 72.7; % 95 CI: 61-84.1) olarak tanımlanmıştır. Düşük NLR, istatistiksel olarak anlamlı şekilde daha uzun medyan OS (23.2'ye karşı 12.7 ay p = 0.001) ve LRFS (13.9vs 9.6 ay; p <0.001) ve çok değişkenli analiz (her biri için p <0,001) ile de her iki parametre için daha uzun medyan sağkalım sonuçları ile ilişkilendirildi.
Sonuç: Sonuç olarak, tedavi öncesi düşük NRL değerleri, yüksek NLR ile başvuranlara göre önemli ölçüde daha uzun OS ve LRFS ile ilişkilidir. Bu bulgular, başlangıç NLR'si için ucuz, tekrarlanabilir ve rutin klinik uygulamada ölçümü kolay yeni, güçlü ve bağımsız bir prognostik değer önerilebilir.

Anahtar kelimeler: Nötrofil, Lenfosit, Glioblastoma Multiforme, sağkalım

Introduction

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. According to the Stupp protocol the standard treatment incorporates maximal safe surgical resection, trailed by temozolomide chemotherapy concurrent with and adjuvant to focalized brain irradiation [1, 2]. However, the prognosis of such patients is extremely poor even after this aggressive treatment with a reported median and 2 years survival rates of only 14.6 months and 26.5%, respectively [3]. Therefore, GBM is invariably associated with inevitable recurrences and resultant deaths.

Albeit molecular pathology and genetic investigations on search of novel predictive and prognostic markers are advancing on a daily basis, yet there exists no universally accepted marker excluding the O6-methyl-guanine–DNA methyltransferase (MGMT) [4]. Traditional prognostic factors for GBM include the Karnofsky performance status, age, extent of resection, mental status, symptom duration at diagnosis, neurologic functionality, corticosteroid utilization, Mini-Mental State Examination score (MMSE), and radiotherapy dose [5,6]. Although combinations of these conventional factors effectively discriminate patients into groups with significantly differential outcomes they do not incorporate markers of systemic inflammation which may further be beneficial in prognostic sub-grouping of such patients.

Systemic inflammation has been demonstrated to promote local tumor progression and/or metastases by inducing angiogenesis and DNA damage repair system [7,8]. Accordingly, both the predictive and prognostic value of several biomarkers of systemic inflammation has been investigated in various tumor types [9-11]. High neutrophil-to-lymphocyte ratio (NLR) that is usually reflected by neutrophilia and lymphopenia, is one such biomarker that has been suggested to have a strong predictive and prognostic value in different cancer primaries [12-14]. Therefore, explore novel, convenient, practical and cheap biomarkers is necessary. Consequently, in this retrospective cohort study we planned to investigate the effect pretreatment NLR on survival outcomes of GBM patients who were treated with definitive CRT, and accessibility of a certain cut-off worth for NLR that may be utilized as a clinical indicator of survival outcomes in conjunction with promptly used traditional factors.

Methods and Materials:

We designed this retrospective study to identify 144 GBM patients with full pretreatment and treatment records that underwent surgery/biopsy followed by CRT from January 2007 to December 2011 in our clinics. To be eligible for the study, patients had to meet the following inclusion criteria: age ≥18 years, Karnofsky performance score (KPS) of 70 to 100, an adequate bone morrow reserve, hepatic and renal function. Additionally, patients had to have satisfactory preoperative and postoperative cranial magnetic resonance imaging (MRI) and surgery-CRT interval one month after surgery. Patients with any history of previous chemotherapy and/or cranial irradiation were

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excluded. The study protocol was reviewed and approved by our Institutional Ethics Committee before collection of patients' data (project noKA 14/37).

Patient Records and Treatment

One month after surgery underwent a CT simulation for three-dimensional radiotherapy treatment planning (RTP). Gross tumor volume (GTV) was delineated on planning CT or its fusion with diagnostic CT/MRI. The RTP for eligible patients was based on GTV, which was restricted to primary tumors T1 contrast-enhancing tumor at MRI (without edema) on preoperative for patients who underwent biopsy or the surgical tumor bed plus any residual enhancing tumor that is seen on the planning scan in patients who underwent resection. The CTV is not defined. The PTV1 should include the GTV with a margin of 1 cm. However some cases may be used to adapt the PTV1 by excluding sensitive structures, such as the optic chiasm, chiasm, and brain stem. The PTV1 is treated with a dose of 40 Gy in 20 fractions. The PTV2 should include the GTV with a margin of 2 cm, and the PTV2 should be treated with 20 Gy in 10 fractions, for a total cumulative dose of 60 Gy. Concurrent chemotherapy consisted of TMZ at a daily dose of 75 mg/m^2 on 7 days a week from the first until the last day of RT. After a 4-week of break, patients received 4-6 cycles of adjuvant TMZ (150-200 mg/m^2 /d) for 5 days every 28 days. Prophylaxis against Pneumocystis carini with either pentamidine or trimethoprim-sulfamethoxazole was mandatory during concurrent RT and TMZ [2]. The available pre-CRT blood data of each patient was utilized to calculate neutrophil-to-lymphocyte ratio before using steroid.

Statistical Analysis

The primary endpoint was the impact of NLR on overall survival (OS) which was defined as the interval between the first day of CRT and death/last visit. Secondary objective was the identification of a particular cut-off value. For this purpose we used receiver operating characteristic (ROC) curve analysis. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. To evaluate the relationship between different variables and survival, a Cox proportional hazard model was used. All tests were two-tailed. A p-value ≤0.05 was considered significant.

Results

A total of 144 patients were reviewed and 112 patients who met the criteria were included in the study.. Patient characteristics are shown in Table 1. At a median follow-up of 15.1 (range 1.8-49.9) months for the whole study population, 95 patients (84.8%) were died. The median 2-years and 4-years OS rates were 15.1 months, 23.5% and 8.8% respectively.

The search for a special NLR cut-off by utilizing ROC analysis in the whole study population demonstrated the cut-off at 4.3 point (AUC:78.4; 95%CI=64.8-92; Sensitivity: 71.9%; Specificity: 69.6%), which was almost same with the cut-off of 4 and 4.73 previously defined one study and letter by Bambury and Alexious respectively [14,15]. Subsequently separated patients at this cut-off point into two groups: Low-NLR (L-NLR≤4.3) and high-NLR (H-NLR>4.3), the comparative survival analysis exhibited that the patients in L-NLR group had significantly longer OS (23.2 vs. 12.7 months; p=0.001) than their counterparts in H-NLR group. (Table 2, Figure 1). Consequently also detected for a special NLR cut-off value for locally recurrence free survival (LRFS) in our cases demonstrated the cut-off value at 4.1 value (AUC: 72.7 (95%CI: 61-84.1), and divided patients cut-off degree into two groups: Low-NLR (L-NLR≤4.1) and high-NLR (H-NLR>4.1). According to comparative LRFS analysis demonstrated that the patient in L-NLR group had paramount extended LRFS (13.9 vs. 9.6 months; p<0.001) than other group in H-NLR (Table 2, Figure 2).

We investigated the potential association between several prognostic factors. A univariate analysis was performed on the following factors: <50 age, sex,≥80 KPS, RTOG RPA classification, ≥3 months symptom duration, type of surgery performed

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Table 1. Baseline patients and disease characteristics

Characteristic	N (%)
Age, y	
Median (range)	58 (32-69)
≤50	42 (37.5)
>50	70 (62.5)
Sex	
Male	76 (67.8)
Female	36 (32.2)
KPS	
70-80	39 (34.8)
90-100	73 (65.2)
RTOG RPA Class	
III	43(38.4)
IV	45 (40.2)
V	24 (21.4)
Extent of Surgery	
Complete resection	37 (41.9)
Partial resection	65 (58.0)
Biopsy	10 (0.10)
Symptom Duration	
<3 months	67 (59.8)
≥3 months	45 (40.2)
NLR for OS	
>4.3	46 (41.1)
≤4.3	66 (58.9)
NLR for LRFS	
>4.1	41 (36.6)
≤4.1	71 (63.4)

RTOG Radiation Therapy Oncology Group; KPS, Karnofsky Performance Score; RPA, recursive partitioning analysis; OS, overall survival; LRFS, locally recurrence free survival; NLR, neutrophil lymphocyte ratio

Table 2: Outcomes of overall and local recurrence free survival according to neutrophil-to- lymphocyte ratio

Survival	All patients	NLR ≤cut-off value*; #	NLR >cut-off value*; #	P-value
Overall survival*				
Median (mo, %95 CI)	15.1(12.9-17.3)	23.2(19.5-26.9)	12.7(9.7-15.7)	0.001
2 year (%)	23.5	43.2	13.9	
4 year (%)	8.8	20.6	0	
LRFS#				
Median (mo, %95 CI)	10.8 (9.3-12.3)	13.9 (11.2-16.6)	9.6 (8.3-10.9)	<0.001
2 year (%)	12.9	24.4	9.0	
4 year (%)	6.3	24.4	0	

NLR, neutrophil lymphocyte ratio; LRFS, Locally recurrence free survival * NLR ROC defined cut-off for overall survival ≤4.3, >4.3; #≤4.1, >4.1; NLR ROC defined cut-off for LRFS; mo, months; %95 CI, 95% confidence interval

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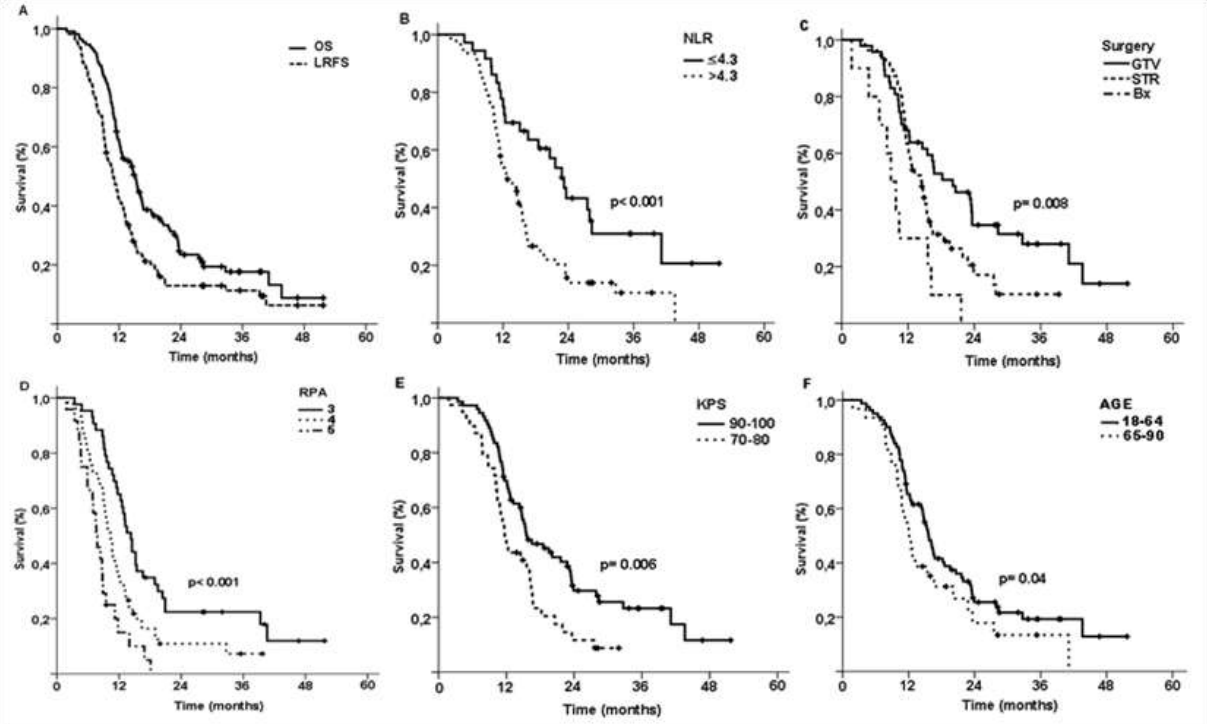


Figure 1:The whole population and comparative subgroup analysis for overall survival and locally recurrence free survival, A: Overall survival and locally recurrence free survival for whole study cohort, B. Neutrophil-to-lymphocyte ratio groups, C. Surgery type, D. Recursive partitioning analysis groups, E. Karnofsky performance score status, F. Age groups

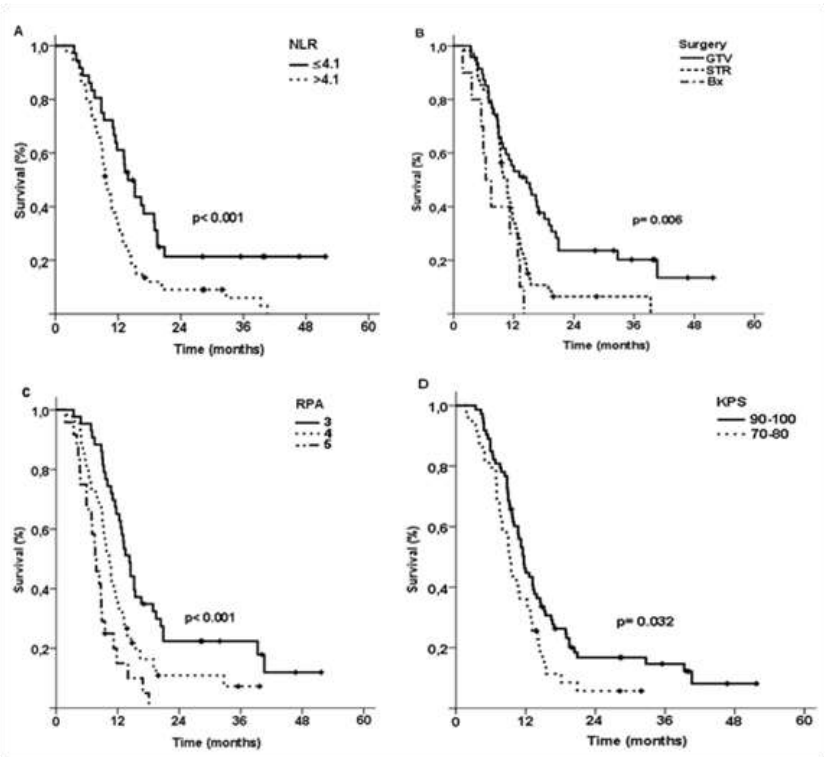


Figure 2: Outcomes of locally recurrence free survival analysis, A. Neutrophil-to-lymphocyte ratio groups, B. Surgery type, C. Recursive partitioning analysis groups, D. Karnofsky performance score status

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Table 3: Results of uni and multi-variate analyses for overall survival and local recurrence free survival

Factor	OS Months (%95 CI)	Univariate P-value	Multivariate P-value	LRFS Months (%95 CI)	Univariate P-value	Multivariate P-value
Age, y						
≤50	15.6 (14.0-17.2)	0.03	0.04	11.7 (10.1-13.3)	0.249	
>50	12.1 (10.2-14.0)			9.7 (8.2-11.2)		
Sex						
Male	14.3 (11.1-17.5)	0.29		11.0 (9.8-12.2)	0.138	
Female	16.2 (11.6-20.8)			11.5 (8.0-15.0)		
KPS						
70-80	11.7 (10.1-13.3)	0.007	0.006	9.3 (8.3-10.3)	0.036	0.032
90-100	15.5 (13.0-18.0)			11.7 (10.5-12.9)		
RPA Class						
III	20.6 (12.3-28.9)	<0.001	<0.001	14.3 (12.5-16.1)	<0.001	<0.001
IV	14.5 (10.8-18.2)			10.4 (8.8-12.0)		
V	10.4 (9.2-11.6)			7.6 (5.9-9.3)		
Extent of Surgery						
Complete resection	20.1 (11.5-28.7)			14.5 (9.3-19.7)		
Partial resection	14.5 (12.0-17.0)	<0.001	0.008	10.7 (9.4-12.0)	0.007	0.006
Biopsy	8.9 (6.4-11.4)			6.4 (3.9-8.9)		
Symptom Duration						
<3 months	16.1 (14.5-17.7)	0.041	0.08	12.1 (10.5-13.7)	0.055	
≥3 months	12.1 (10.4-13.8)			9.6 (8.7-10.5)		
NLR						
≤*, #	23.2 (19.5-26.9)	<0.001	<0.001	13.9 (11.2-16.6)	<0.001	<0.001
>*, #	12.7 (9.7-15.7)			9.6 (8.3-10.9)		

RTOG Radiation Therapy Oncology Group; RPA, recursive partitioning analysis; KPS, Karnofsky Performance Score; NLR, neutrophil lymphocyte ratio; %95 CI, 95% confidence interval; * NLR ROC defined cut-off for overall survival ≤4.3, >4.3; #≤4.1, >4.1; NLR ROC defined cut-off for LRFS

(gross total resection) were significantly longer OS (p<0.05 for each), excluding the sex (p=0.29) (Table 3).

In multivariate analyses restricted to NLR (L-NLR vs. H-NLR), <50 age, ≥80 KPS, RTOG RPA classification, type of surgery performed (gross total resection), was the variable that retained its independent significance on association with OS time (p=<0.001, 0.04, 0.006, <0.001, 0.008 respectively), except for symptom duration (p=0.08) (Figure 1, Table 3).

We also investigated the potential association between aforementioned prognostic factors and LRFS. The univariate analysis was performed on the following factors: ≥80 KPS, RTOG RPA classification, type of surgery performed (gross total resection) were significantly longer LRFS (p=0.036, <0.001, 0.007 respectively), while other factors could not demonstrate any significance (p>0.05) (Table 3).

In addition multivariate analyses restricted to NLR (L-NLR vs. H-NLR), ≥80 KPS, RTOG RPA classification, type of surgery performed (gross total resection), was the variable that retained its independent significance on association with LRFS time (p=<0.001, 0.032, <0.001, 0.006 respectively) (Figure 1, Table 3).

Discussion

The results of present retrospective investigation suggested a prognostic value for pre-treatment NLR by demonstrating a strong association between the lower NLR ratio and superior LRFS (13.9 vs. 9.6 months; p<0.001) and OS durations (23.2 vs. 12.7 months; p=0.001)in newly diagnosed GBM patients who underwent surgery/biopsy followed by Stupp protocol, which may be used potential prognostic stratification in clinical. Given its relative cost-effectiveness in routine and cheaply be measured in any ordinary oncologic laboratory use, NLR is therefore a

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suitable adjunct to other determinants of GBM prognosis.

Even if an important local control due to more than 85% of GBMs, still recurrence within the treatment field. GBMs are characterized by uncontrolled proliferation, diffuse infiltration of adjacent tissues, and revealed to identify prognostic factors in GBM patients enrolled in various clinical trials [17,18]. In the recently years, NLR is novel prognosticator marker allow the identification of inflammation and carcinogenesis which reflect disease biology, and numerous studies have suggested that an increased NLR is collaborated with poor survival of subject with various cancers. But there area limited number of studies in the literatureon this subject in GBM patients [15, 16,19].

In our study demonstrated that high neutrophil infiltration the progression of earlier can become. According to LRFS analysis demonstrated that the patient in H-NLR (NLR>4.1) group had paramount inferior LRFS than other group in L-NLR (NLR≤4.1) (9.6 vs 13.9 months; p<0.001). Although the exact mechanisms behind the role of increase NLR (elevated neutrophils count is associated by a decrease lymphocytes) in cancer worse prognosis effect is not to be explained with the design of our study, its reasonable to anticipate one of the possible mechanisms is association of H-NLR with inflammation, which is neutrophilia have been primary source of circulating VEGF, which has been shown to have a crucial role tumour- related angiogenesis and thus has a near relationship with vascular invasion and metastasis [20], and an inflammatory response inhibits the immune system by depressing the cytolytic activity of immune cell, and secrete tumor growth promoting factor [21-27]. On the other hands, lymphopenia is dependent to the immune escape of tumour cells from tumour-infiltrating lymphocytes (TIL) [28,29], and thus both increase infiltration of tumors and systemic is lymphocytes associated with better response to cytotoxic treatment and prognosis in cancer [30,31]. Therefore elevated neutrophils count is associated by a decrease lymphocytes means that may be immune deficiency of the patient. For this reason, due to with patient H-NRL is not sufficiency immune response, tumor may be progression earlier. Our study demonstrated that the patient in H-NLR group had paramount inferior LRFS than other group in L-NLR. For these reasons in our study thought high neutrophil infiltration that the progression of earlier can become.

Another important results of our study that patients with L-NLR (NLR≤4.3) had significantly longer median (23.2 vs 12.7; p=0.001), 2-year (43.2% vs. 13.9%) and 4-years (20.6% vs 0%) OS rates compared to those with H-NLR (NLR>4.3), suggesting a strong prognostic worth for pre-treatment NLR. In accordance with the first study performed by Bamburay et al. suggested that evaluable NLR>4 presented a worse independent prognostic factor in 84 GBM patients [15]. But Bamburay et al. study had been only 27% patient performed gross totally resection, 24% patients ECOG 2 and 58% patients were able to delivered concurrent chemoradiotherapy plus ≥2 cycles consol-idation TMZ. At the same time author only analyzed overall survival. Different in our cohort, 41.9% patients perform gross totally resection, all of them patients KPS ≥80 and were able to delivered concurrent chemo-radiotherapy plus ≥2 cycles consoli-dation TMZ. The other letter study show that pre-treatment NLR in 51 GBM patients with longer OS (NLR ratio <4.73; p=0.01). In multivariate analyses NLR ratio and extent tumor resection were recognized independent prognostic factor (p=0.01, p=0.025 respect-ively) [16]. Alike ours, these results suggested that L-NLR patients had higher local control than H-NLR therefore reflected longer survival in our study L-NLR patients, or body defenses system and immunity stronger L-NLR patients than H-NLR patients.

In GBM literature conventional prognostic factors were analyzed including age, duration time of diagnosis and surgery, sex, KPS, RTOG RPA classification, type extent of surgery resection. According to uni- and

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multivariate analysis except for the sex and symptom duration; the other factors namely ≤50, KPS>80, RTOG RPA class III, gross total resection detected OS (p=0.03, 0.007, <0.001, 0.041 and p= 0.004, 0.006, <0.001, 0.008 respectively) longer than respective counterparts. However, uni- and multivariate analysis for LRFS detected KPS>80, RTOG RPA class III, gross total resection significant longer than respective counterparts (p=0.036, <0.001, 0.007 respectively), other prognostic factor was not significant (p>0.05). During the analysis MGMT was not routinely used by our pathology, therefore we didn't analyze the potential effects of the molecular marker MGMT and NLR value correlation.

Our present study has considerable limitations. First, as with any retrospective single-institution study, unpredictable biases may have influenced our results. Second, we did not have data on MGMT methylation status in our study population. But Han et al. study demonstrated NLR levels did not correlate with O-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, they suggesting that these two prognostic factors may influence clinical outcome via different pathways and mechanisms [32]. Third, our sample size probably small, and we didn't analyzed possible predictive influence of NLR in GBM patients. Fourth; we did not investigate other potential prognostic factors ie: CPR, platelet to lymphocyte ratio, VEGF, MVP, MMP. Finally, our study warrants further confirmation in large prospective sample cohort studies with a definitive NLR cutoff value.

Conclusions

In conclusion, our study demonstrated that GBM patients presenting pre-treatment L-NLR associated with better immunity status, better response to cytotoxic treatment, prognosis, and so have significantly increased median, long-term survival rates and LRFS than those presenting with H-NLR. Such patients may be beneficial for the selection of individuals requiring more intense treatment, and may lead to a review of our current approaches for treating GBM patients with H-NLR. These findings suggest a novel, strong and independent prognosticator value for baseline NLR, which can easily, routine and cheaply are measured in any ordinary oncologic laboratory.

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