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The Prognostic Impact of Neutrophil Lymphocytic Ratio (NLR) on Survival of Patients with Glioblastoma Multiforme (GBM): A Retrospective Cohort Study

Amal Rayan[1] & Aiat M. M. Morsy[1]

[1]Clinical oncology department, Assiut faculty of medicine, Egypt

Correspondence: Amal Rayan, Clinical oncology department, Assiut faculty of medicine, Egypt. Tel: 002-01022454482. E-mail: amal3774rayan@gmail.com

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Abstract

Background and aim: Neoplasia related inflammation now is proved to be a factor determining the outcomes in patients with cancer including glioblastoma, we aimed to determine the prognostic value of NLR on the progression free (PFS) and overall survival (OS) for patients with GBM.

Methods: The baseline complete blood picture prior to the initiation of any corticosteroid and cancer therapy (surgery and RT) was obtained then NLR was determined and correlated with PFS and OS for patients with GBM.

Results: patients with NLR ≤4 had a significantly better PFS (the median PFS=12±1.614 months, CI=8.836-15.164 for those with NLR ≤4 vs. a Median PFS=6±1.239 months, CI=3.572-8.428 for those with NLR>4, P<0.009) and OS (the median OS=15±3.627 months, CI=7.890-22.110 vs. a median OS=7±1.038 months, CI=4.966-9.034, P<0.002 for those with NLR≤4 vs. those with NLR>4 respectively). And this effect of NLR was dependant on other prognostic factors.

Conclusion: NLR had a prognostic effect on PFS and OS, but it wasn't an independent factor for survival.

Keywords: glioblastoma multiforme, neutrophil-lymphocytic ratio, progression free survival, overall survival

1. Introduction

Gliomas are the most common primary brain tumors (Dolecek et al., 2012), the prognosis for patients with glioblastoma (GBM) is dismal with an estimated median survival of 14.6 months, and the standard treatment of GBM with maximal excision followed by temozolomide (TZM) based radiation then adjuvant TZM results in modest improvement in survival (Stupp et al., 2005).

There was sufficient evidence that immune defects were implicated in the pathogenesis of different cancers including glioblastoma (Grossman et al., 2011).

Inflammation status is now proved to be a predictor determining the outcomes in patients with cancer.

Among the markers of inflammation examined in the past years for their prognostic impact on treatment outcomes was neutrophil/lymphocytic ratio (NLR).

The neutrophil-to-lymphocyte ratio (NLR) was examined in many cancers and was found to be elevated in patients with advanced and aggressive disease (Lang et al., 2014; Xue et al., 2014; Ozdemir et al., 2014; Chang et al., 2014; Xiao et al., 2014).

Infiltration of gliomas with lymphocytes postulates that adaptive immunity maintains the tumor in a stable state (Koebel et al., 2007), which means that improved immunity is able to control and delay tumor progression.

The role of inflammatory neutrophils in controlling infections was well defined, however; they had immunosuppressive effect in cancers (Nagaraj et al., 2010), as many cancers had high blood levels of neutrophlia due to uncertain mechanisms but GM-CSF and other cytokines could be implicated in some tumors.

Bambury RM et al. Proved that patients of GBM with NLR > 4 had a worse median overall survival at 7.5 months versus 11.2 months in patients with NLR ≤ 4 (hazard ratio 1.6, 95 % CI 1.00–2.52, p = 0.048)

(Bambury et al., 2013).

We aimed to determine the prognostic value of NLR on the progression free (PFS) and overall survival (OS) of patients with GBM.

2. Patients and Methods

We retrospectively performed an analysis of 58 patients with GBM who were treated with TZM based chemoradiation and adjuvant TZM with or without previous excision at clinical oncology department, Assiut university hospital during a period of two years (January 2012-December 2013).

The baseline complete blood picture was obtained prior to the initiation of any corticosteroid and cancer therapy (surgery and RT) then NLR was determined and correlated with PFS and OS for these patients.

NLR >4 was considered a threshold of significance based on its results from other cancers.

Univariate regression test was used to determine the significance of NLR, age, sex, PS, extent of resection, response on the survival.

Multivariate regression test was used to determine the prognostic independency of NLR.

After confirmation of prognostic value of NLR on survival, patients were classified into two groups with NLR>4 and NLR≤4. Then survival curves for the two groups were drawn and compared.

Log rank test was used to compute survival curves for each group and compare the proportions surviving at any specific time.

PFS was defined as the time from diagnosis to demonstration of tumor progression on follow-up MRI.

OS time was defined as the time between the date of diagnosis and the date of death.

Statistical significance was defined by a *p*-value of<0.05, moderately significant *p*-value of <0.01, and highly significant *p*-value <0.001

3. Results

Characteristics of 58 patients with GBM were mentioned in table 1 including their significant impact on PFS and OS where age, KPS, extent of resection, response, and NLR had a significant effect on survival.

Table 1. Clinical and treatment characteristics of patients with GBM

characteristics		**NO**	%	**Significance**	
				PFS	OS
Age mean ± SE		49.72 ±14.04		M.S.	M.S.
				P<0.002	*P*<0.002
Sex	M	38	65%		N.S.
	F	20	35%	*P*=0.703	*P*=0.484
KPS	>70%	19	32.76%	Sig.	M.S.
	≤70%	39	67.24%	*P*<0.022	*P*<0.006
Lateralization					N.S.
No		3	5.2%	*P*=0.343	*P*=0.255
Rt		19	32.8%		
Lt		36	62.1%		
Extent of resection				H.S.	H.S.
No surgery		14	24.1%		
Biopsy		14	24.1%	*P*<0.000	*P*<0.000
Debulking		16	27.59%		
Subtotal excision		14	24.1%		
Response				H.S.	H.S.
CR		12	20.7%		
PR		15	25.9%	*P*<0.000	*P*<0.000
SD		20	34.5%		
DP		11	19%		
NLR	≤4	19	32.8%	M.S.	M.S.
	>4	39	67.2%	*P*<0.009	*P*<0.002

Sig. =significant, M.S.= moderately significant, H.S.= highly significant, NLR=neutrophil-lymphocytic ratio, CR=complete response, PR=partial response, SD=stable disease, DP=disease progression, SE=standard error, KPS= Karnofsky performance status.

PFS and OS for GBM patients with NLR≤4 versus those with NLR>4 were mentioned in table 2 and graphed in figures 1, 2 respectively.

Table 2. PFS and OS in patients with NLR≤4 versus those with NLR>4

NLR	PFS	OS
≤4	Median PFS=12 ±1.614	Median OS=15 ±3.627
	95% CI=8.836-15.164	95% CI=7.890-22.110
>4	Median PFS=6 ±1.239	Median OS=7 ±1.038
	95% CI=3.572-8.428	95% CI=4.966-9.034

CI= confidence interval

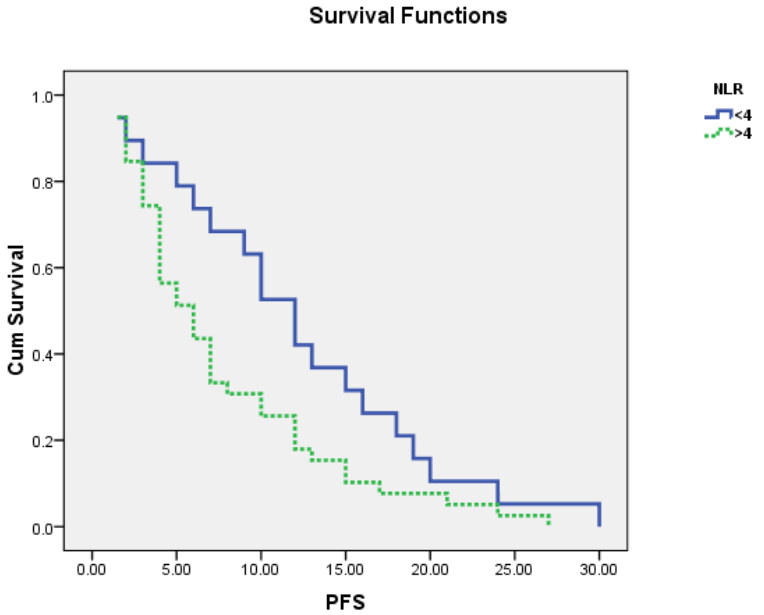

Figure 1. Median PFS for patients with NLR≤4 equals 12±1.614 (95% CI=8.836-15.164) months, versus those with NLR>4 and median PFS equals 6 ±1.239 (95% CI=3.572-8.428) months, with a significant effect, p<0.009.

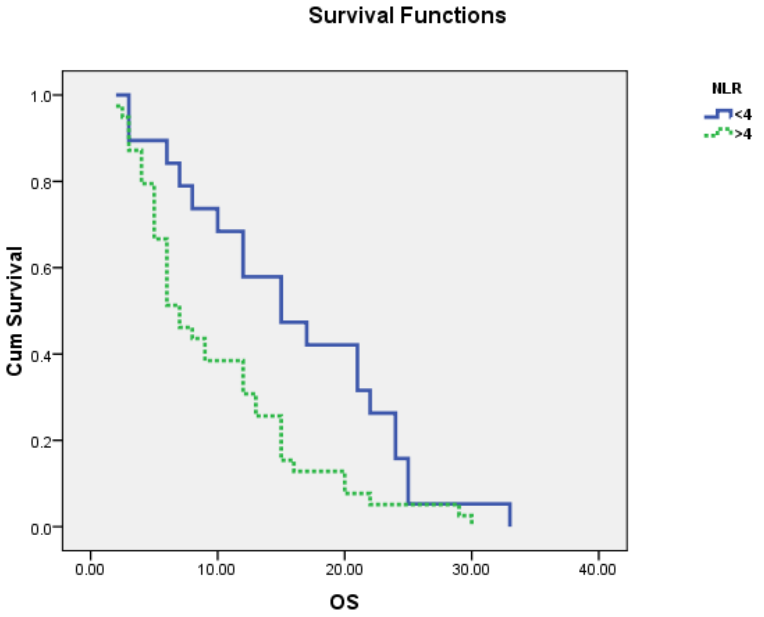

Figure 2. OS for patients with GBM in those with NLR≤4 (Median OS=15 ±3.627, 95% CI=7.890-22.110) versus those with NLR>4 (Median OS=7 ±1.038, 95% CI=4.966-9.034), with a significant effect, p<0.002.

Table 3. Multivariate analysis of prognostic factors

factor	*P* value(<0.05)			
	PFS		OS	
Response	H.S.	P<0.000	H.S.	P<0.000
KPS	M.S.	P<0.004	M.S.	P<0.001
Age	M.S.	P<0.009	Sig.	P<0.016
Extent of resection	S.	P<0.04	M.S.	P<0.006
Lateralization	N.S.	P=0.322	N.S.	P=0.688
NLR	N.S.	P=0.583	N.S.	P=0.960

KPS= Karnofsky performance status, H.S. =highly significant, M.S. =moderately significant, N.S. =non significant, Sig. = significant.

4. Discussion

In this study, patients with NLR≤4 had a significantly better PFS, and OS. Other demographic and clinical data with a significant effect on survival included age, KPS, extent of resection and response. But on multivariate analysis; NLR≤4 wasn't an independent factor for survival in glioblastoma patients.

A meta-analysis of nine studies including 5397 patients with nasopharyngeal carcinomas (Takenaka et al., 2017) proved that NLR greater than the cutoff values was associated with poor OS (HR 1.51, 95% CI 1.27-1.78), disease specific survival (HR 1.44 95% CI 1.22-1.71), PFS (HR 1.53 95% CI 1.22-1.90), and distant metastasis free survival (HR 1.83 95% CI 1.14-2.95).

High NLR was a poor predictor for OS with HR of 1.81 (95% CI: 1.48-2.21; P=0.005) and relapse free survival with HR of 2.07 and 95% CI: 1.65-2.6; P=0.0849 in a meta-analysis of 17 studies assessing the prognostic value of NLR in patients with urinary cancers (Wei et al., 2014).

Fifteen studies comprising a total of 8563 patients were included in a meta-analysis to evaluate the prognostic role of NLR among patients with breast cancer with a cutoff values ranging from 1.9-5 and found that NLR greater than the cutoff value was associated with worse OS (HR 2.56, 95% CI=1.96-3.35; *P*<0.001) and disease free survival (HR 1.74, 95% CI=1.47-2.07) (Josee-Lyne et al., 2017).

High NLR predicted a poor OS (HR 1.51; 95% CI=1.33-1.71; P<0.001) and PFS (HR 1.33 95% CI= 1.07-1.67; P=0.012) in patients with lung cancer (Qing-Tao et al., 2015).

A meta-analysis of 26 studies in primary liver cancer demonstrated that high NLR strongly predicted poor survival in these patients and high NLR was associated with vascular invasion and correlated with alpha-fetoprotein levels (Xue et al., 2014).

In a study done by Bambury et al. to evaluate the impact of NLR in 84 patients with GBM demonstrated that age over 65 years, gender, eastern cooperative oncology group performance status ≥ 2, frontal tumor, extent of surgical resection, completion of the adjuvant chemoradiation protocol, and NLR > 4 were significantly correlated with overall survival, and the independent prognostic indicator of NLR >4 was maintained for poor survival in multivariate analysis.

In univariate analysis; our results were comparable to the previous studies in terms of poor survival of patients with high NLR ratio, however; in multivariate analysis, our results weren't comparable to those of Proctor et al. (Proctor et al., 2012) who studied 12,118 patients with different cancers diagnosed within 2 years and found that NLR was independently associated with survival in the studied cancers, and this could be attributed to small number of patients in this study.

In multivariate analysis our results were comparable to Mason et al. (Mason et al.,) who suggested that pretreatment NLR could not be an independent predictor of OS in gliomas.

In this study, patients with high NLR were found to be of older age, KPS<70%, no or limited surgery, and no response or even disease progression was achieved on the standard treatment protocol, so that NLR when compared to the previous prognostic factors in multivariate analysis wasn't of significant effect on survival.

5. Conclusion

NLR had a prognostic effect on PFS and OS, but it wasn't an independent factor for survival.

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