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Pre-operative hematological markers as predictive factors for overall survival and progression free survival in glioblastomas

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ABSTRACT

Introduction: Several hematological factors, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI) and albumin-to-globulin ratio (AGR), have been highlighted as systemic worse prognostic parameters for the outcome in gliomas. The aim of this study is to identify some pre-operative routinely blood tests as predictive parameters for the Overall Survival (OS) and Progression Free Survival (PFS) in glioblastoma (GBM).

Materials and methods: From January 2013 to April 2019, 124 patients operated for glioblastoma were analyzed. Data were collected regarding age, sex, Karnofsky performance status (KPS), IDH status, the extent of resection (EOR) and adjuvant therapy. The hematological parameters were collected at admission: neutrophils, lymphocytes and platelets, hemoglobin, lactate dehydrogenase, albumin, NLR, PLR, AGR and PNI. The OS and the PFS were considered as the end-point for the evaluation of the predictive factors.

Results: A pre-operative neutrophil count $> 7 \times 10^9$/L was a worse prognostic factor for OS and PFS at univariate analysis ($p = 0.004$ and $p = 0.025$), as well as hypo-albuminemia. Thrombocytosis, lymphopenia and NLR > 4 were associated to a worse OS, at uni- and multivariate analysis, resulting as poor predictive parameters, independently to EOR, the IDH mutation and the adjuvant therapy.

Conclusions: Still nowadays there are no sensitive or specific hematological markers which are routinely applied for detecting and monitoring the treatment-response and the prognosis of glioblastoma. In our study, a pre-operative low cost and widely used blood markers, such as NLR, lymphocytes and platelets could be predictable prognostic factors for the Overall Survival of patients affected by glioblastomas.

1. Introduction

Glioblastomas (GBM), grade IV according to WHO classification, are the most aggressive and common type of malignant primary tumors of the central nervous system [1–3]. Even if the role of tumor-infiltrating immune cells, such as neutrophils and lymphocytes, has already been highlighted [4,5]; still nowadays, unlike other kinds of cancer, there are not sensitive or specific serum markers which are routinely applied for detecting, staging and monitoring the treatment response and the prognosis [1–3,6–9]. As a result, minimally invasive biomarkers are extremely needed, such as some blood parameters, which are widely used, characterized by a low cost and easy measuring and reproducible standardized assays [3]. Consequently to these promises, many emerging studies have showed the crucial role of some routine biochemistry and coagulation blood tests, firstly in non-neurological tumors, and afterwards in gliomas [1–3,7,8,10–12].

Several factors have been proposed in order to derive an inflammation-based score. Firstly, a high value of the neutrophil-tolymphocyte ratio (NLR), which is the proportion between the number of neutrophilic cells and lymphocytes, has been showed as a systemic worse prognostic factor for the outcome in gliomas [10]. Similarly, also the platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI) and albumin-to-globulin ratio (AGR) have been investigated, but it is still controversial their role, compared with NLR [1–3,7,8,10–12]. The aim of this study is to identify some pre-operative routinely blood tests as predictive parameters for the Overall Survival (OS) and Progression Free Survival (PFS) in GBM.

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2. Materials and methods

We retrospectively enrolled all the patients who underwent a surgical procedure for a histopathological certified diagnosis of glioblastoma in our Institute from January 2013 to April 2019.

Inclusion criteria were primary non recurrent glioblastoma with pre-operative data regarding age, sex, Karnofsky performance status (KPS) as well as IDH status (determined by immunohistochemistry), the extent of resection (divided in gross total, subtotal resection and biopsy) and adjuvant therapy (according to STUPP protocol) in the post-operative. The hematological parameters were collected at admission, namely neutrophil (10^9/L), lymphocyte (10^9/L) and platelets (10^9/L), as well as hemoglobin (Hb, g/dL), lactate dehydrogenase (LDH, U/L), albumin (g/dL). Additional hematological ratio evaluated were: neutrophil-to-lymphocyte ratio (neutrophil count/lymphocyte count, which was divided in < 4 or ≥ 4), PLR (platelet count/lymphocyte count, cut-off: $<$ 175 or $\geq$175), albumin-to-globulin ratio (AGR, ratio between albumin/globulin, which was divided in < 1.75 or ≥ 1.75) and the prognostic nutrition index (PNI = albumin (g/L) + [total lymphocyte count X 5]; cut-off: 44,4). All the cut-offs were based on the previous literature papers [1,3,4,8]. The extent of resection was evaluated at the post-operative magnetic resonance imaging (MRI), stratifying it in gross total resection (GTR, defined as a complete macroscopically absence of tumor in the immediate post-operative contrast-enhancement MRI), subtotal resection (STR) and biopsy; the hematological markers sub-groups analyzed were uniform regarding the EOR and the further adjuvant therapy, in order to not create a determinant bias between different residual tumor volumes and between different adjuvant. treatment (Table 1). The exclusion criteria were patients with metabolic diseases, peri-operative corticosteroids medications, hematological or auto-immune conditions and patients with an incomplete radiological and clinical follow-up.

The Overall Survival was calculated from the date of surgery to the death"; whereas the progression-free survival was measured from the date of surgery to the radiological recurrence at the follow-up. The OS and the PFS were considered as the end-point for the evaluation of the predictive factors.

Statistical analysis was performed using SPSS software (version 25.0), by univariate and multivariate analysis according to, respectively, Kaplan-Meier and the Cox Proportional-Hazard regression-stepwise method, in order to identify the predictors of survival. Data of patients who have not progressed or died were right-censored in the analysis". A p-value < 0.05 was considered statistically significant.

3. Results

From January 2013 to April 2019, 247 patients underwent a surgical procedure for a histologically confirmed glioblastoma in our department. Nonetheless, considering the exclusion criteria the sample analyzed was composed by 124, whom main demographic and clinical characteristics are reported in the Table 1.

3.1. Overall survival and progression free survival

The Overall Survival in our sample was 11 on average months, and 5 months for the PFS. The minimum follow-up was one year and the maximum 4 years. Although the gender was not statistically significant for the OS and PFS, people under 60 years old demonstrated to have a better OS and a PFS at univariate analysis ($p = 0.031$ and $p = 0.026$).

3.2. Extent of resection

A gross total resection or a subtotal resection was achieved in 846 % of the sample analyzed, resulting a crucial predictive factor for the overall survival and progression free survival concomitantly at the uni- and multivariate analysis (as reported in Table 2).

Table 1
Baseline characteristics of the patients analyzed.

Baseline Characteristics	
Age (years)	Value (percentage)
< 60	42 (33,8 %)
≥ 60	82 (66,2 %)
Gender	
Female	59 (47,6 %)
Male	65 (52,4 %)
Focality	
Multifocal	31 (25 %)
Monofocal	91 (75 %)
Pre-operative Karnofsky performance status	
< 70	37 (29,9 %)
≥ 70	87 (70,1 %)
Extent of resection	
Biopsy	19 (15,3 %)
Subtotal	39 (31,4 %)
Gross total	64 (53,2 %)
IDH-1	
Mutation	59 (47,6 %)
Wild type	65 (52,4 %)
Post-operative Karnofsky performance status	
< 70	26 (21,0 %)
≥ 70	98 (79,0 %)
Overall Survival (months)	
Mean	11
Median	10
Progression Free Survival (months)	
Mean	5
Median	6
Adjuvant therapy	101 (81,4 %)
Hematological markers	
Hemoglobin (g/dL)	
Mean	14
< 12	14 (11,3 %)
≥ 12	110 (88,7 %)
LDH (U/L)	
Mean	187
< 240	83 (67 %)
≥ 240	41 (33 %)
Glycemia (g/dL)	Value (percentage)
Mean	111
< 137	97 (78,3 %)
≥ 137	27 (21,7 %)
Neutrophils (10^9/L)	
Mean	7.09
< 7	48 (38,8 %)
≥ 7	76 (61,2 %)
Platelets (10^9/L)	
Mean	230
< 350	114 (92 %)
≥ 350	10 (8 %)
Lymphocytes (10^9/L)	
Mean	1.33
< 1	41 (33 %)
≥ 1	83 (67 %)
NLR	
Mean	6.09
< 4	37 (29,9 %)
≥ 4	87 (70,1 %)
PLR	
Mean	182.4
< 175	60 (48,3 %)
≥ 175	64 (51,7 %)
Albumin (g/dL)	
Mean	3.4
< 3	41 (33 %)
≥ 3	83 (67 %)
PNI	
Mean	42.4
< 44.4	85 (68,6 %)
≥ 44.4	39 (31,4 %)
AGR	
Mean	1.17
< 1.75	107 (86,2 %)
≥ 1.75	17 (13,8 %)

3.3. Clinical aspects and Karnofsky performance status

A pre-operative KPS higher than 70 was associated with a better OS and PFS, in comparison to the patients with KPS less than 70 ($p = 0.01$ and $p = 0.003$, respectively). This data was also confirmed at the 2-month follow-up, in which both the OS and PFS were influenced by the post-operative KPS, at uni- and multivariate analysis (Table 2).

The majority of the patients (75 %) had a monofocal lesion.

3.4. IDH-mutation

The presence of an IDH-mutation in our complete sample was 26,7 % (66 out of 247 patients), however most of them were lost, due to the exclusion criteria (the metabolic diseases, peri-operative corticosteroids medications, hematological or auto-immune conditions and patients with an incomplete radiological and clinical follow-up). When we considered only the patients with all the inclusion criteria the percentage became surprisingly high and this data was of great interest, we assumed that some of the patients were undiagnosed secondary glioblastomas. A retrospectively confirmation by sequencing the exon 4 was not appliable in all the patients.

The IDH-mutation was a positive predictive parameter for the OS at uni- and multivariate analysis ($p = 0,022$ and $p = 0,044$) and PFS ($p = 0,037$ at univariate analysis).

MGMT

3.5. Adjuvant therapy

The adjuvant therapy, namely chemotherapy and/or radiotherapy, applied according to STUPP protocol, was a positive predictive parameter for the OS and PFS, at uni- and multivariate analysis (Table 2).

3.6. Hematological markers

Regarding the hematological markers, even if a pre-operative neutrophil count higher than 7×10^9/L was a worse prognostic factor for OS and PFS at univariate analysis ($p = 0.004$ and $p = 0.025$), this data was not confirmed at the multivariate one. In addition, a value of PLR higher than 175×10^9/L, as well as hypo-albuminemia (value < 3 g/dL) was related to a worse OS at univariate analysis ($p = 0.001$ and 0.037, correspondingly). Glycemia was not statistically relates to the OS and PFS.

The hematological poor prognostic factor for the OS, with validation also at the multivariate analysis, were platelets higher than 350×10^9/L, as well as a count of lymphocytes $< 1 \times 10^9$/L and a neutrophil-to-lymphocyte ratio (NLR) > 4 (Table 2). Therefore, we can consider the thrombocytosis, lymphopenia and NLR > 4 as independent pre-operative independent prognostic factor for the OS, because they are not influenced by the EOR, IDH mutation and the adjuvant therapy, that were statistically significant at multivariate analysis (Fig. 1). Interestingly, in our sample none of these hematological parameters were statistically significant at the multivariate analysis in relationship to the PFS (Table 2). In fact, only the extent of the resection, the post-operative KPS and the adjuvant therapy were statistically significant for the Progression Free survival at Multivariate analysis ($p = 0.033$, $p = 0.001$ and $p = 0.04$, respectively, see Table 2).

4. Discussion

Many Authors have previously highlighted a crucial linkage between the chronic inflammation and tumors [2,13,14]. In fact, it is well known that the tumorigenesis process involves a complex interaction of inflammatory cells in a particular local microenvironment in the tumor bed; previous data showed that tumoral neutrophil infiltration played a crucial role in stimulating tumor growth, angiogenesis and metastasis, resulting in a correlation and interaction between the systemic and local inflammation [2,15]. As a consequence, identifying some hematological prognostic parameters, with mainstream low-cost pre-operative blood tests, might lead to a better management and outcome. In gliomas, a positive correlation between tumor grade and the extent of neutrophil infiltration has already been demonstrated [2,16].

In our study the evidence of neutrophilia resulted a worse prognostic factor for OS and PFS, which is in accordance with Han et al., who found a correlation of increased neutrophil infiltration with shorter survival in glioblastoma patients [2]. In addition, also lymphopenia negatively influenced the OS in our sample. As a matter of fact, reduced levels of CD8+ lymphocytes, which are directly responsible for the detection and elimination of malignant tumor cells, have formerly been related to an unfavorable prognosis in patients with glioblastoma [1,2,2,7].

The association between thrombocytosis and malignancy has been

Table 2
Predictive parameters for overall survival and progression free survival (p value < 0,05), univariate and multivariate analysis according to, respectively, Kaplan-Meier and the Cox Proportional-Hazard regression-stepwise method. Hazard ratio and confidence interval reported as well.

	Overall Survival			Progression Free Survival		
	Univariate Analysis	HR (95 % CI)	Multivariate Analysis	Univariate Analysis	HR (95 % CI)	Multivariate Analysis
Baseline characteristics						
Age	**0.031**	0.97 (0.66–1.2)	0.404	**0.026**	**1.0 (0.99–1.01)**	0.282
Gender	0.749	**1.04 (0.82–1.31)**	°	0.372	0,25 (0,02−3,34)	°
Focality	**0.006**	0.78 (0.57–1.06)	0.184	0.078	0.96 (0.72–1.28)	°
Pre-operative KPS	**0.01**	**3 (1.1−4.4)**	0.088	**0.003**	0,79 (0,06−10,38)	0.939
Extent of resection	**0.037**	**2.57 (1.17–435)**	**0.04**	**0.021**	1.04 (0.75–1.45)	**0.033**
IDH-1	**0.022**	**1.75 (1.1−2.37)**	**0.044**	**0.037**	2.10 (1.26–3.50)	0.057
Post-operative KPS	**0.029**	**1.46 (0.34–2.63)**	**0.031**	**0.01**	**1.01 (1.00–1.03)**	**0.001**
Adjuvant therapy	**0.02**	**1.65 (1.03–2.26)**	**0.043**	**0.01**	1,47 **(0,26−5,62)**	**0.04**
Hematological markers						
Hemoglobin	0.942	0.88 (0.57–1.06)	°	0.813	0.8 (0.47–1.36)	°
LDH	0.924	**0.37 (0.26–0.52)**	°	0.226	1,15 **(0,26−4,62)**	°
Glycemia	0.855	0,44 (0,03−5,88)	°	0.467	0,55 (0,03−10,37)	°
Neutrophils	**0.004**	**1.92 (1.15–3.19)**	0.699	**0.025**	0,63 (0,11−2,98)	0.643
Platelets	**0.007**	**1.83 (1.15–2.75)**	**0.006**	**0.001**	**5.15 (2.86–9.25)**	0.120
Lymphocytes	**0.001**	**1.66 (1.17–2.35)**	**0.006**	**0.001**	**3.59 (2.60–8.13)**	0.120
NLR	**0.027**	3,15 **(0,73−11,62)**	**0.044**	0.55	0.94 (0.82–1.31)	°
PLR	**0.001**	**1.7 (0.97−2.32)**	0.220	**0.001**	**1.67 (1.33–2.14)**	0.217
Albumin	**0.037**	**1.87 (0.97−2.65)**	0.194	0.163	0.39 (0.20–0.93)	°
PNI	0.448	0.57 (0.47–1.73)	°	0.522	0.69 (0.50–0.93)	°
AGR	0.591	**1.09 (1.47–2.73)**	°	0.954	**2.74 (1.96–3.84)**	°

Significant values are reported in bold.

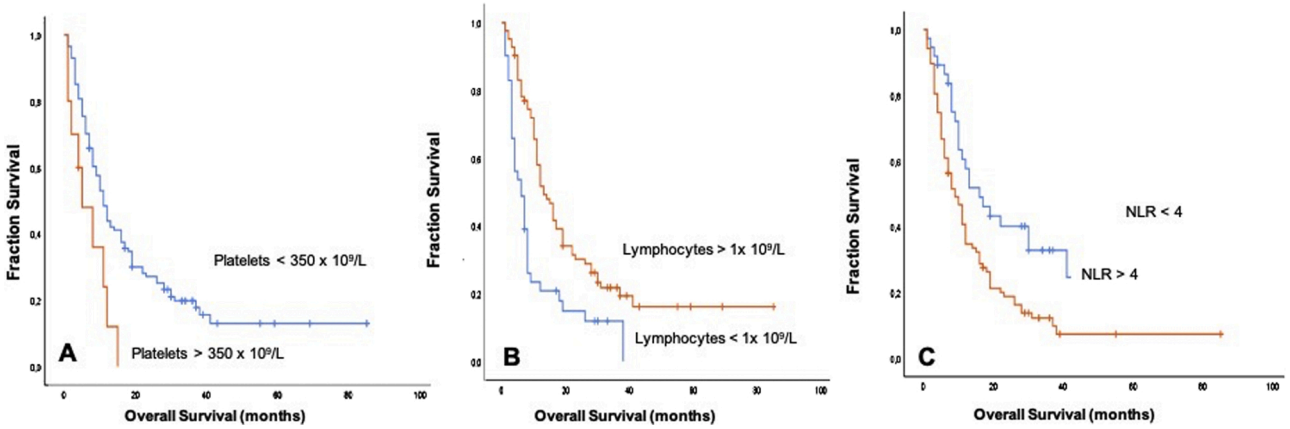

Fig. 1. A: Kaplan-Meier estimates of Overall Survival for pre-operative platelets. p = 0,007; **B:** Kaplan-Meier estimates of Overall Survival for pre-operative lymphocytes. p = 0,001; **C:** Kaplan-Meier estimates of Overall Survival for pre-operative NLR. p = 0,027.

well known for many years and its associations with worse outcomes have been reported mainly for solid tumors [7,17]. In our study thrombocytosis (platelets $> 350 \times 10^9$/L) was related to a worse OS at uni- and multivariate analysis (p = 0.007 and 0.006) as well as a shorter time to PFS (P = 0.001). This relationship has already been described by Brockmann et al., showing a linkage between thrombocytosis and a decreased overall survival in a group of 158 GBM patients [7].These results suggested that a condition of preoperative thrombocytosis may represent a prognostic factor associated with shorter survival time in patients with glioblastoma, due to an imbalance between the procoagulant and anticoagulant system resulting in hypercoagulability status in GBM patients [18].

Preoperative NLR and PLR have been identified in the past as potential biomarkers for early detection, disease staging, and monitoring of colorectal cancer [3,19,20]. Recently, several studies analyzed the influence of preoperative NLR as a predictive factor for glioblastoma [1,2,10,11]. In our sample a NLR > 4 demonstrated to be a worse prognostic factor for the OS at uni- and multi-variate analysis. In fact, Han et al. demonstrated that NLR ≥ 4 was correlated with poorer survival and a worse prognosis in GBM [1,2]. Furthermore, some Authors compared NLR between patient affected by GBM and other central nervous system tumors, demonstrating an evidence of higher level of NLR in GBM patients [1,3].

In our study, there was a statistical correlation between PLR and progression-free survival or overall survival, which is in accordance with the results of Wang et al. [1]. Nonetheless, in several studies, PLR has been demonstrated to be a prognostic factor for various cancers [3,21]. Han et al. reported that an increased level of PLR was related with poorer survival even though the prognostic significance of PLR was far less than that of NLR [2,4]. However, this data loose statistical significance at multivariate analysis.

Inflammatory markers have been reported to be useful diagnostic factors for various cancers [1–3,7–11]. However, the role of inflammatory markers in patients with glioma is still controversial [1–3,7–11]. Serum albumin, AGR and PNI are widely used as parameters for nutritional status and systemic inflammatory response; even if they have been used as prognostic factors in various cancers; however, little is known about their relationship with glioblastoma [1,22]. Generally, oncological patients frequently show malnutrition, with subsequently increased mortality and worse quality of life [11,23]. Schwartzbaum et al. firstly assumed that low serum albumin levels indicated either the presence of a systemic acute-phase response related to glioblastoma or an increased permeability of the blood–brain barrier to albumin [22]. Han et al. illustrated that patients with lower preoperative serum albumin levels had worse survival [2]. Our results revealed a correlation between hypo-albuminemia and a lower OS; however, AGR and PNI did not achieve a statistical significance in our study.

4.1. Limitations of the study

The present study has several limitations. First, as our study had a retrospective design, some unavoidable biases may exist. Second, we did not continuously monitor various prognostic factors. Furthermore, we only investigated the changes of blood indices and did not study the differences of tumor immune microenvironments. In addition, MGMT status was available only for a part of the sample. When we considered only the patients with all the inclusion criteria the percentage of IDH mutation became surprisingly high, creating an essential bias, we assumed that some of the patients were undiagnosed secondary glioblastomas.

Eventually, some confounding factors in systemic inflammatory responses, namely cardiovascular disease, hypertension, insulin resistance, uraemia, autoimmune disorders and glucocorticoid therapy are responsible of some modifications of these hematological parameters, as a result they should be taken into consideration as possible bias in case of GBM patients with some hematological variations [2,3,8].

Therefore, prospective multicenter studies, continuous perioperative monitoring, and further molecular biology experiments are needed.

5. Conclusions

In conclusion, still nowadays there are not sensitive or specific serum markers which are routinely applied for detecting, staging and monitoring the treatment response and the prognosis of glioblastoma. Our presented study supported, and it is based on the theory that the tumor bed inflammatory response is strongly linked to the systemic one. As highlighted in our study, a pre-operative low cost and widely used blood markers, such as neutrophil-to-lymphocyte ratio, lymphocytes and platelets could be predictable independent prognostic factors for the Overall Survival of patients affected by glioblastomas.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration

and its later amendments or comparable ethical standards.

All participates and authors consented to the article and its publication.

Availability of data and material

The data of this study are openly available with DOIs

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