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Evaluation of Five Prognostic Scores in Patients Receiving Chemoradiation for Primary Glioblastoma Multiforme

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Abstract. *Background/Aim: Prognostic factors can facilitate treatment personalization in patients with glioblastoma multiforme (GBM). This study investigated different Glasgow prognostic scores (GPS) and the LabBM score in patients with GBM receiving chemoradiation following resection or biopsy. Patients and Methods: Four GPS versions, LabBM score, and 10 other factors were retrospectively investigated for progression-free survival (PFS) and overall survival (OS) in 86 patients. GPS versions included original GPS (oGPS), modified GPS (mGPS), high-sensitivity mGPS (HS-mGPS), and high-sensitivity oGPS (HS-oGPS). Results: On multivariate analysis, higher oGPS was significantly associated with worse OS (p=0.006). On univariate analyses, trends were found for associations between higher mGPS and worse OS (p=0.098) and between higher LabBM scores and worse PFS (p=0.059). Conclusion: The oGPS was an independent predictor of OS in patients receiving chemoradiation for GBM and can help personalizing the treatment for these patients. The LabBM score may be useful for predicting PFS.*

The concept of treatment personalization is increasingly used to improve the outcomes of patients with malignant diseases, including patients with metastatic disease and those with poor prognoses (1-4). This accounts also for patients with newly diagnosed glioblastoma multiforme (GBM) (5). In addition to other factors including the patient's treatment preferences, social situation, biological age, and general health condition, treatment personalization should always consider the patient's survival prognosis. For example, for patients with longer expected survival times, late treatment-related toxicity and long-term disease control become more important. For patients with GBM, several patient- and tumor-associated predictors of overall survival (OS) have been identified (5). In addition, pre-clinical markers and prognostic scores may be of predictive value for patients with GBM.

In 2018, Topkan *et al*. suggested that the original Glasgow prognostic score (oGPS), which is based on C-reactive protein (CRP, cut-off=10 mg/l) and albumin (cut-off=35 g/l), may be useful for estimating OS in patients with GBM treated with radiotherapy and temozolomide (TMZ) (6). The predictive value of the oGPS was previously described for various cancer types including lung cancer, head-and-neck cancers, breast cancer, and different gastro-intestinal malignancies (7-17). In 2007, McMillan *et al*. presented a modified version of the GPS (mGPS), also based on CRP (cut-off=10 mg/l) and albumin (cut-off=35 g/l) (18). Besides for several cancer types and sarcoma, the mGPS was investigated in patients with recurrent high-grade gliomas (18-31). In the latter group, the mGPS was found to be independently associated with OS (31). Despite these promising results, the prognostic value of the oGPS and the mGPS was not further investigated in patients with GBM. Another version of the GPS, the high-sensitivity modified GPS (HS-mGPS), uses a cut-off level of 3 mg/l for CRP (32-38). The HS-mGPS has been tested for several cancer types and sarcoma but not yet for GBM. Considering the studies available so far, it becomes obvious that additional studies are required investigating the prognostic value of oGPS, mGPS, and HS-mGPS for patients with GBM.

The present study was performed to evaluate three versions of the GPS with respect to progression-free survival (PFS) and OS in patients with GBM receiving chemoradiation

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following resection or biopsy. In addition, we investigated a new high-sensitivity version of the oGPS (HS-oGPS) using a cut-off level of 3 mg/l for CRP. Moreover, we evaluated the prognostic role of the LabBM score for patients with GBM, which was initially developed to predict OS in patients with brain metastases and later also used for patients with non-metastatic lung cancer (39-43). Associations between one or more of the five investigated scoring instruments and PFS or OS may help physicians select a personalized treatment for a patient assigned to chemoradiation for GBM.

Patients and Methods

Eighty-six patients with GBM treated with chemoradiation after resection of biopsy were included in this retrospective study, which was approved by the Ethics Committee of the University of Lübeck (file number=2022-509). Concurrent chemoradiation was performed between 2014 and 2022 and consisted of conventionally fractionated radiotherapy (54-60 Gy in 30 to 33 fractions of 1.8 or 2.0 Gy) and TMZ (75 mg/m^2 daily). Seventy patients (81%) received additional chemotherapy with TMZ following concurrent chemoradiation. In five of these 70 patients, TMZ was replaced by procarbazine/lomustine after a median of 3 (range=1-5) courses, and in one patient, TMZ was supplemented by lomustine (CCNU). Nine of the 86 patients received additional treatment with tumor-treating fields.

In the entire cohort, we investigated the prognostic value of four versions of the GPS and 10 additional factors with respect to PFS and OS. The four versions of the GPS are based on the levels of CRP and albumin assessed prior to or at the beginning of chemoradiation. In the original GPS (oGPS), 0 points are given in case of CRP ≤10 mg/l and albumin ≥35 g/l, 1 point in case of CRP >10 mg/l or albumin <35 g/l, and 2 points in case of CRP >10 mg/l and albumin <35 g/l (7). In the modified GPS (mGPS), assignment of 0 and 2 points is the same as for the oGPS; 1 point is given in case of CRP >10 mg/l and albumin ≥35 g/l (18). For the analyses of PFS and OS, we combined 1 and 2 points to one subgroup for the mGPS, because the 1-point group included only three patients. For the high-sensitivity mGPS (HS-mGPS), a cut-off value of 3 mg/l (instead of 10 mg/l) is used for CRP, otherwise criteria are the same as for the mGPS (32). In addition to these three previously published GPS versions, we have created a fourth version, namely the high-sensitivity original GPS (HS-oGPS) using the same criteria as for the oGPS but a cut-off level of 3 mg/l (instead of 10 mg/l) for the CRP. For all versions of the GPS, scores range between 0 and 2 points, and higher scores represent worse treatment outcomes.

In addition to the different versions of the GPS, the LabBM score could be calculated in 52 patients. This score is based on five parameters, *i.e.*, CRP, albumin, hemoglobin, platelet count, and lactate dehydrogenase (LDH) (39). One point each is assigned in case of elevated (above normal values) CRP and LDH levels, and 0.5 points each in case of decreased (below normal values) levels of hemoglobin, platelet count, and albumin. Thus, scores can range between 0 and 3.5 points, and higher scores represent worse outcomes.

Ten other potential prognostic factors (Table I) were also investigated with respect to PFS and OS, including number of lesions (single *vs.* multiple), main location (temporal/parietal *vs.* other), maximum cumulative diameter (<40 *vs.* ≥40 mm), Karnofsky performance score (KPS ≤80 *vs.* 90-100), sex (female *vs.* male), MGMT (O6-methylguanine-DNA methyl-transferase) promoter methylation (no *vs.* yes), type of resection (gross total=GTR *vs.* subtotal=STR *vs.* biopsy), and adjuvant (=maintenance) chemotherapy (no *vs.* yes).

Table I. *Distribution of potential prognostic factors.*

Factor	Subgroup	Number of patients (%)
Original GPS (7)	0 Points	55 (64)
	1 Point	26 (30)
	2 Points	5 (6)
Modified GPS (18)	0 Points	78 (9)
	1-2 Points	8 (9)
High-sensitivity modified GPS (32)	0 Points	58 (67)
	1 Point	15 (17)
	2 Points	13 (15)
High-sensitivity original GPS	0 Points	43 (50)
	1 Point	30 (35)
	2 Points	13 (15)
LabBM score (39)	0-1.0 Points	42 (49)
	1.5-2.5 Points	10 (12)
	Not available	34 (40)
Number of GBM lesions	1	67 (78)
	≥2	19 (22)
Main site of GBM	Temporal/parietal	43 (50)
	Other sites	43 (50)
Maximum cumulative diameter	<40 mm	40 (47)
	≥40 mm	46 (53)
Karnofsky performance score	≤80	45 (52)
	90-100	41 (48)
Sex	Female	34 (40)
	Male	52 (60)
Age at radiotherapy	≤59 Years	46 (53)
	≥60 Years	40 (47)
MGMT promoter methylation	No	35 (41)
	Yes	45 (52)
	Not available	6 (7)
Extent of resection	GTR	29 (34)
	STR	42 (49)
	Biopsy only	15 (17)
Adjuvant chemotherapy	No	16 (19)
	Yes	70 (81)

GBM: Glioblastoma multiforme; GPS: Glasgow prognostic score; GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection.

Both PFS and OS were calculated from the first day of radiation therapy. For univariate analyses, we used the Kaplan-Meier method and the log-rank test. After Bonferroni adjustment (14 tests), *p*-values <0.0036 represented an alpha level of <5% and were, therefore, considered significant. A *p*-value <0.05 indicated a strong trend for an association with PFS or OS, and a *p*-value <0.10 indicated a trend for such an association. Factors that were significant or showed a strong trend on univariate analyses were additionally evaluated for independence using a Cox proportional hazards model. In the multivariate analyses, *p*-values <0.05 indicated significance and *p*-values <0.10 a trend.

Table II. *Progression-free survival rates (univariate analyses).*

Factor	Subgroup	6 Months (%)	12 Months (%)	*p*-Value
Original GPS (7)	0 Points	58	31	0.67
	1 Point	50	26	
	2 Points	40	40	
Modified GPS (18)	0 Points	55	29	0.71
	1-2 Points	50	33	
High-sensitivity modified GPS (32)	0 Points	53	30	0.94
	1 Point	67	27	
	2 Points	46	35	
High-sensitivity original GPS	0 Points	55	33	0.65
	1 Point	57	24	
	2 Points	46	35	
LabBM score (39)	0-1.0 Points	59	32	0.059
	1.5-2.5 Points	30	0	
Number of GBM lesions	1	63	38	**<0.001**
	≥2	24	0	
Main site of GBM	Temporal/parietal	63	39	0.29
	Other sites	46	21	
Maximum cumulative diameter	<40 mm	67	41	0.057
	≥40 mm	43	20	
Karnofsky performance score	≤80	39	13	**0.003**
	90-100	71	47	
Sex	Female	53	25	0.18
	Male	56	33	
Age at radiotherapy	≤59 Years	58	41	0.1
	≥60 Years	50	16	
MGMT promoter methylation	No	51	17	0.034
	Yes	58	39	
Extent of resection	GTR	76	40	0.004
	STR	50	31	
	Biopsy only	22	0	
Adjuvant chemotherapy	No	30	30	0.057
	Yes	60	32	

GBM: Glioblastoma multiforme; GPS: Glasgow prognostic Score; GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection; after Bonferroni adjustment, *p*-values <0.0036 are considered significant and given in bold; *p*-values <0.05 are considered indicating a strong trend.

Results

On univariate analyses of PFS (Table II), improved outcomes were significantly associated with a single lesion ($p<0.001$) and KPS 90-100 ($p=0.003$). *MGMT* promoter methylation ($p=0.034$) and GTR of GBM ($p=0.004$) showed a strong trend for an association with better PFS. The LabBM score ($p=0.059$), maximum cumulative diameter <40 mm ($p=0.057$) and administration of maintenance chemotherapy ($p=0.057$) each showed a trend for such an association. In the multivariate analysis of PFS (Table III), a single lesion was significant ($p=0.023$), and trends were found for KPS 90-100 ($p=0.060$) and *MGMT* promoter methylation ($p=0.081$).

On univariate analyses of OS (Table IV), a single lesion ($p<0.001$), KPS 90-100 ($p=0.003$), *MGMT* promoter methylation ($p=0.003$), GTR of GBM ($p<0.001$), and maintenance chemotherapy ($p<0.001$) were significantly associated with better outcomes. Strong trends were found for lower oGPS ($p=0.017$, Figure 1) and maximum cumulative diameter <40 mm ($p=0.015$). In addition, lower mGPS showed a trend ($p=0.098$) for better OS. In the multivariate analysis of OS (Table V), oGPS ($p=0.006$), a single lesion ($p=0.015$), KPS 90-100 ($p=0.047$), *MGMT* promoter methylation ($p=0.011$), and maintenance chemotherapy ($p<0.001$) were significant. Moreover, trends were found for maximum cumulative diameter <40 mm ($p=0.071$) and GTR ($p=0.070$).

Discussion

Many patients with GBM receive adjuvant chemoradiation following resection or, if only a biopsy of the tumor can be safely performed, definitive chemoradiation. Radiotherapy is often performed using conventional fractionation with 1.8 or

Table III. *Progression-free survival rates (univariate analyses).*

Factor	Hazard ratio	95% Confidence interval	*p*-Value
Number of GBM (1 *vs.* ≥2)	2.33	1.13-4.84	**0.023**
Karnofsky performance score (≤80 *vs.* 90-100)	0.60	0.35-1.02	0.060
MGMT promoter methylation (no *vs.* yes)	0.63	0.38-1.06	0.081
Extent of resection (GTR *vs.* STR *vs.* biopsy only)	1.14	0.75-1.75	0.54

GBM: Glioblastoma multiforme; GTR: Gross total resection; MGMT: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection; significant *p*-values given in bold.

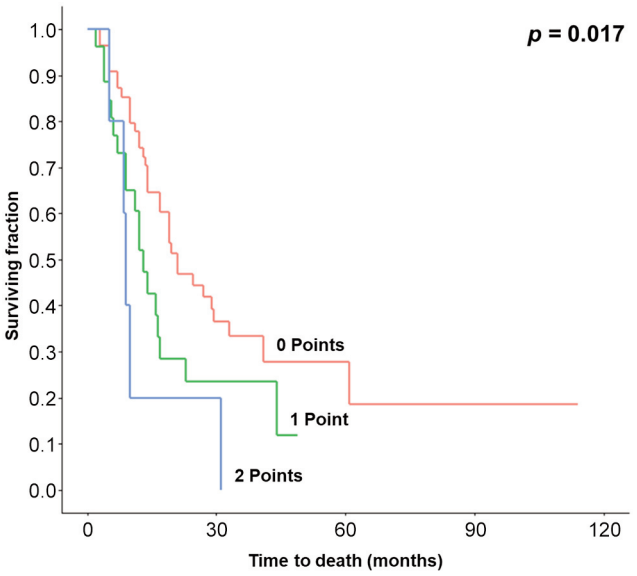

Figure 1. *Comparison of subgroups achieving 0, 1, and 2 points according to the original Glasgow prognostic score (oGPS) with respect to overall survival (7).*

2.0 Gy per fraction up to 59.4 or 60.0 Gy (44, 45). Since Roa *et al*. demonstrated that hypo-fractionated radiotherapy with 40 Gy in 15 fractions of 2.66 Gy was not inferior to conventionally fractionated treatment in elderly patients with GBM, hypo-fractionation is increasingly used for elderly or frail GBM patients (46). The main advantage of hypo-fractionation is the shorter overall treatment time of three weeks compared to six to 6.5 weeks in case of conventional fractionation. However, lower doses per fraction as used for conventional fractionation are generally associated with less late toxicity, which was shown for irradiation of brain metastases already 35 years ago (47). Moreover, in a retrospective study of 277 patients with GBM of any age, total doses of 59.4 or 60.0 Gy were suggested to result in better PFS and OS when compared to 40 Gy in 15 fractions (45). Thus, particularly patients with GBM and more favorable OS prognoses can benefit from conventional fractionation. In contrast, elderly or frail patients with short OS times appear to be suitable candidates for hypo-fractionation (46). Patients with very poor prognoses may even be considered for the concept of ultra-hypo-fractionated radiotherapy with 25 Gy in five fractions over one week. In a randomized trial of the International Atomic Energy Agency performed in elderly and/or frail patients with GBM, 25 Gy in five fractions was not inferior to 40 Gy in 15 fractions with respect to PFS, OS, and quality-of-life (48).

These data show that it is important to be able to judge a patient's remaining lifespan as precisely as possible to select the most appropriate dose-fractionation regimen. Estimation of a patient's OS prognosis is facilitated by application of prognostic factors or scores. In our previous study, OS of patients irradiated for GBM was significantly associated with a single lesion of GBM, a cumulative maximum diameter of 40 mm or less, a KPS of 90-100, methylation of *MGMT* promoter, GTR of GBM, and adjuvant chemotherapy on univariate analyses. In the multivariate analysis, single lesion, KPS of 90-100, *MGMT* promoter methylation, and adjuvant chemotherapy were still significant (5). Similarly, in the current study, a single GBM lesion, KPS 90-100, *MGMT* promoter methylation, GTR, and adjuvant chemotherapy were significantly associated with improved OS on univariate analyses, and a maximum cumulative diameter <40 mm showed a strong trend. Moreover, these factors were significant or showed at least a trend in the multivariate analysis of OS. These similarities demonstrate consistency of the results of our present study.

In addition to the previously identified clinical predictors, the present study investigated the prognostic value of five prognostic scores based on laboratory parameters. The oldest of these scores is the oGPS, which is based on CRP and albumin (7). Since 2003, the oGPS has been tested for several cancer types (7-17). In addition, a retrospective study of 142 patients investigated its prognostic role in patients receiving radio-chemotherapy for GBM in 2018 (6). Median OS times were 22.5 months in patients with 0 points, 15.7 months in patients with 1 point, and 9.9 months in patients with 2 points, respectively, and 2-year OS rates were 41,7%, 16.2%, and 0%, respectively ($p<0.001$). Moreover, median PFS times were 16.4, 8.9, and 7.5 months, respectively, and 2-year PFS rates were 27.5%, 5.0%, and 0%, respectively ($p<0.001$). The multivariate analysis also showed a significant correlation between a higher oGPS and worse OS. Accordingly, a higher oGPS was significantly associated with poorer OS in the multivariate analysis of our present

Table IV. *Overall survival rates (univariate analyses).*

Factor	Subgroup	6 Months (%)	12 Months (%)	*p*-Value
Original GPS (7)	0 Points	91	73	0.017
	1 Point	77	54	
	2 Points	80	20	
Modified GPS (18)	0 Points	86	66	0.098
	1-2 Points	88	43	
High-sensitivity modified GPS (32)	0 Points	86	67	0.17
	1 Point	100	80	
	2 Points	69	35	
High-sensitivity original GPS	0 Points	88	72	0.27
	1 Point	90	66	
	2 Points	69	35	
LabBM score (39)	0-1.0 Points	88	68	0.1
	1.5-2.5 Points	70	40	
Number of GBM lesions	1	94	74	**<0.001**
	≥2	56	28	
Main site of GBM	Temporal/parietal	95	74	0.67
	Other sites	76	55	
Maximum cumulative diameter	<40 mm	95	72	0.015
	≥40 mm	78	58	
Karnofsky performance score	≤80	77	54	**0.003**
	90-100	95	75	
Sex	Female	73	64	0.86
	Male	94	65	
Age at radiotherapy	≤59 Years	87	62	0.99
	≥60 Years	85	67	
MGMT promoter methylation	No	91	54	**0.003**
	Yes	84	78	
Extent of resection	GTR	93	79	**<0.001**
	STR	88	66	
	Biopsy only	65	29	
Adjuvant chemotherapy	No	47	16	**<0.001**
	Yes	94	74	

GBM: Glioblastoma multiforme; GPS: Glasgow prognostic score; GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection; after Bonferroni adjustment, *p*-values <0.0036 are considered significant and given in bold; *p*-values <0.05 are considered indicating a strong trend.

study. Thus, patients with oGPS of 0 points or 1 point appear good candidates for conventionally fractionated radiotherapy, whereas patients with 2 points may benefit from hypofractionated radiotherapy.

Four years after creation of the oGPS, the mGPS was presented (18). In addition to various cancer types and sarcoma, the mGPS was investigated in patients with recurrent high-grade gliomas (18-31). The retrospective study of Alan *et al*. included 85 patients with an initial diagnosis of GBM (59 patients) or anaplastic grade III glioma (26 patients), who received systemic treatment with bevacizumab alone or bevacizumab plus irinotecan for recurrent disease (31). Median OS times for mGPS of 0, 1, and 2 points were 13.8 months, 7.3 months, and 3.6 months, respectively (p=0.003). Moreover, mGPS was identified as an independent predictor of OS. In our current study, a higher mGPS showed a trend (p=0.098) for an association with worse OS on univariate analysis. Since the study of Alan *et al*. included patients with grade III gliomas in addition to patients with GBM and investigated systemic treatment in a recurrent situation, the results of their study may not be comparable to our study (31). In 2013, another version of the GPS, the HS-mGPS, was presented (32). The prognostic significance of this score had been investigated in several cancer types and sarcoma but not yet in patients with GBM (32-38). In our study, the HS-mGPS was not significantly associated with OS. The same held true for the additionally investigated HS-oGPS.

In addition to the four GPS versions (oGPS, mGPS, HS-mGPS, HS-oGPS), we have investigated the potential prognostic role of the LabBM score, initially created to predict OS in patients with brain metastases (39). Evaluation of the LabBM score was not yet performed in patients with GBM. In contrast to the four GPS versions that were based

Table V. *Multivariate analysis of overall survival.*

Factor	Hazard ratio	95% Confidence interval	*p*-Value
Original GPS (7) (0 *vs.* 1 *vs.* 2 points)	1.96	1.21-3.18	**0.006**
Number of GBM lesions (1 *vs.* ≥2)	2.71	1.21-6.07	**0.015**
Maximum cumulative diameter (<40 *vs.* ≥40 mm)	1.72	0.95-3.11	0.071
Karnofsky performance score (≤80 *vs.* 90-100)	0.53	0.28-0.99	**0.047**
MGMT promoter methylation (no *vs.* yes)	0.46	0.25-0.84	**0.011**
Extent of resection (GTR *vs.* STR *vs.* biopsy only)	1.60	0.96-2.65	0.070
Adjuvant chemotherapy (no *vs.* yes)	0.15	0.06-0.36	**<0.001**

GBM: Glioblastoma multiforme; GPS: Glasgow prognostic score; GTR: Gross total resection; *MGMT*: O^6-methylguanine-DNA methyltransferase; STR: subtotal resection; significant *p*-values are given in bold.

on CRP and albumin, the LabBM score additionally considered LDH, platelet count, and hemoglobin. Since all five required laboratory parameters were available only in 52 of the 86 patients, testing the LabBM may be considered a subgroup analysis with limited validity. Given this limitation, a higher LabBM showed a trend (p=0.059) for an association with worse PFS and almost a trend (p=0.10) for an association with worse OS. One may speculate whether the results regarding PFS and OS would achieve significance in a larger patient cohort. Thus, additional studies including more patients are required. In addition to the comparably small sample size of our study, its retrospective nature including the risk of hidden selection biases should be taken into account during the interpretation of our results.

In conclusion, given its limitations, this study showed that the oGPS was an independent predictor of OS in patients receiving chemoradiation for GBM. In addition, the mGPS showed a trend for an association with OS and the LabBM score for an association with PFS. These prognostic factors may help personalizing the treatment for patients with GBM receiving chemoradiation. However, these results need to be confirmed in a larger cohort of patients, ideally in a prospective trial.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

All Authors were involved in the study design. The data were collected by O.Z. and D.R.; analyses were performed by D.R. and N.Y.Y. The article, which was drafted by D.R., was finally approved by all Authors.

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