Machine Learning–Enhanced Prognostic Modeling in Elderly Glioblastoma Isocitrate Dehydrogenase-Wildtype: A Multidimensional Single-Center Cohort Study

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■ BACKGROUND: **Glioblastoma isocitrate dehydrogenase IDH-wildtype (GBM IDHwt) in elderly patients presents challenges due to biological heterogeneity and underrepresentation in clinical trials. Despite rising incidence, prognostication remains inadequate, with treatment decisions based on subjective criteria.**

■ OBJECTIVE: **To determine clinical, radiological, surgical, and molecular determinants of survival in elderly GBM IDHwt patients and explore prognostic utility of machine learning (ML) models using clinical and pretreatment data.**

■ METHODS: **We analyzed 155 patients aged ≥70 years with confirmed GBM IDHwt who underwent neurosurgery at a tertiary care institution. We examined variables related to clinical presentation, imaging, surgery, and molecular markers using multivariate regression and Histogram Gradient Boosting Regression ML models. Two ML models were developed: one incorporating full dataset variables, and another focusing on preoperative features.**

■ RESULTS: **Median overall survival (OS) was 11.3 months for patients undergoing resection and 3.7 months for biopsy. Independent predictors of prolonged OS included gross total resection (GTR), O6-methylguanine-DNA methyltransferase promoter methylation, nonacute symptom onset, and concomitant radiotherapy with temozolomide (RT + TMZ). ML models confirmed RT + TMZ and GTR as strongest predictors, while Karnofsky Performance Status showed negative importance. Body mass index (BMI) emerged as impactful; and the pretreatment model emphasized BMI and cognitive decline.**

■ CONCLUSIONS: **This study confirmed prognostic relevance of GTR, O6-methylguanine-DNA methyltransferase methylation, and RT + TMZ combination. Baseline Karnofsky Performance Status and age did not demonstrate independent prognostic value, while BMI and cognitive decline were potential preoperative predictors. Our findings advocate a multidimensional, data-driven approach to preoperative risk stratification in elderly GBM patients, which may facilitate individualized treatment strategies.**

Key words
- Elderly
- Extent of resection
- Glioblastoma prognosis
- Machine learning
- Personalized precision oncology
- Preoperative risk stratification

Abbreviations and Acronyms
BMI: Body mass index
GBM: Glioblastoma
GTR: Gross total resection
HGBR: Histogram Gradient Boosting Regression
IDH: Isocitrate dehydrogenase
IDHwt: Isocitrate dehydrogenase wild-type
KPS: Karnofsky Performance Status
MGMT: O6-methylguanine-DNA methyltransferase
ML: Machine learning
MRI: Magnetic resonance imaging
OS: Overall survival
RT: Radiotherapy
RT + TMZ: Concomitant radiotherapy and temozolomide
STR: Subtotal resection
WHO: World Health Organizatio

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INTRODUCTION

Glioblastoma isocitrate dehydrogenase (IDH)-wildtype (GBM IDHwt) is the most prevalent and lethal primary malignant brain tumor in adults, with over 50% of new diagnoses occurring in individuals aged ≥65 years and a peak incidence between 75 and 84 years.[1-4] As global demographics skew towards an aging population, the incidence and associated morbidity of GBM IDHwt in elderly patients are expected to increase.[5] Despite advances in maximal safe resection, radiotherapy (RT), and chemotherapy, outcomes remain dismal in this cohort, with a median overall survival (OS) seldom exceeding nine months.[6,7]

In the literature, chronological age, functional status, and extent of resection (EOR) are the most consistently reported factors influencing the OS in patients with GBM IDHwt,[8-11] but their assessment in older adults is fraught with challenges. Historically, older adult patients have been underrepresented in clinical trials,[12] and treatment paradigms derived from younger cohorts may not be directly applicable.[6] Moreover, older adult patients frequently carry a higher burden of comorbidities, display variable frailty profiles, and exhibit heterogeneous tolerability to chemoradiation, all of which confound risk—benefit analyses.[6,13-16] However, in practice, treatment decisions often hinge on subjective clinician judgment and basic metrics such as age and Karnofsky Performance Score (KPS), rather than on objective, disease-specific geriatric assessments.[17-20]

In the absence of standardized guidelines or validated assessment tools tailored to neuro-oncology, there is an urgent need for a multidimensional prognostic framework that integrates clinical, surgical, radiological, and biological variables to guide individualized management of GBM IDHwt in the elderly. Recent retrospective and population-based analyses have tried to overcome this gap.[6,8,13,15,16,21] Notably, Ius et al. employed a machine learning (ML) approach using a random forest classification model, achieving superior predictive performance (Harrell's c-index of 0.79) compared to conventional methods.[22,23]

Encouraged by their promising results and recognizing the potential of ML to capture complex nonlinear prognostic interactions, we sought to apply a similar data-driven approach in our elderly GBM IDHwt cohort. Thus, we retrospectively analyzed 155 patients aged ≥70 years with histologically confirmed GBM IDHwt who underwent neurosurgical procedures at a tertiary care institution. Alongside conventional statistical modeling, we employed a Histogram Gradient Boosting Regression (HGBR) algorithm to develop 2nullML models: one incorporating comprehensive pretreatment and post-treatment data and the second restricted solely to preoperative clinical features. Our objective was not only to validate established prognostic indicators but also to uncover novel predictive relationships, thereby supporting the development of a tailored preoperative stratification model to support individualized treatment decisions in this vulnerable population.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed all consecutive patients aged ≥70 years with histologically confirmed GBM IDHwt grade 4 according to the 2021 World Health Organization (WHO) CNS classification, who underwent neurosurgical intervention at the Istituto di Ricovero e Cura a Carattere Scientifico Institute of Neurological Sciences of Bologna between January 2010 and May 2022. Among the cohort of 799 adult patients diagnosed during this period, 155 met the inclusion criteria and were selected for analysis. Eligible patients were required to be ≥ 70 years of age, with no prior surgery, chemotherapy, or RT. All patients underwent presurgical evaluation using the Charlson Comorbidity Index,[24] and preoperative tumor volumes were measured by manual segmentation of contrast-enhancing regions on axial T1-weighted magnetic resonance imaging (MRI). The volumes were calculated by summing the segmented areas across consecutive slices. Segmentation was performed by experienced neuroradiologists using institutional imaging platforms. The EOR was estimated using postcontrast T1-weighted MRI.

Histopathological specimens were revised in accordance with the 2021 WHO CNS tumor classification. We excluded tumors diagnosed as GBM solely based on molecular criteria without histologic features such as necrosis or microvascular proliferation to maintain a homogeneous histopathologic cohort and reduce classification ambiguity during the early years of the dataset (pre-WHO 2021 adoption). Assessment of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and IDH1/IDH2 mutation status was performed for all included cases. Only patients with complete follow-up data were included in the final cohort.

The study protocol was approved by the local Institutional Review Board of the Istituto di Ricovero e Cura a Carattere Scientifico Institute of Neurological Sciences of Bologna (No. 186/2019/OSS/AUSLBO-19031; March 2019). All data were anonymized in accordance with the national data protection regulations. Given the retrospective nature of the study, the requirement for informed consent was waived.

Clinical Evaluation

Demographic information, clinical presentation, and functional status at the time of diagnosis were obtained from the institutional medical records. Neurological symptoms at onset, including motor deficits, seizures, cognitive impairment, and aphasia, were systematically recorded. The preoperative performance status was assessed using the KPS scale. The burden of comorbidities was evaluated using the age-adjusted Charlson Comorbidity Index.

All patients underwent preoperative MRI, which was reviewed to determine tumor laterality, multifocality, involvement of eloquent areas, presence of midline shift, and evidence of corpus callosum infiltration, defined as tumor spread across the midline via the callosal commissure. Surgical interventions were categorized by the EOR based on early volumetric analysis of postoperative MRI: gross total resection (GTR, no residual contrast-enhancing tumor), subtotal resection (STR, residual volume <30%), partial resection (PR, residual volume >30%), or biopsy (>75% of tumor volume remaining).

Histopathological diagnoses were established according to the 2021 WHO classification. When available, molecular characterization included IDH1/IDH2 mutation status and MGMT promoter methylation. The latter was assessed by pyrosequencing at

the institutional pathology department, with a threshold of ≥20% used to define the methylation status. Postoperative evaluations included clinical reassessment, imaging, documentation of surgical and medical complications, and KPS re-evaluation. Decisions regarding adjuvant therapy (RT, chemotherapy, or re-do surgery) were made by a dedicated multidisciplinary tumor board.

Statistical Analysis

Descriptive statistics were reported as medians for non-normally distributed variables and means for normally distributed variables. OS time was defined as the time from surgery until patient death and was estimated using the Kaplan–Meier approach. The association between the variables and survival distribution was tested using univariate and multivariate analysis models performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

Univariate logistic regression models were initially constructed to evaluate the association between the individual predictor variables and OS. Multivariate analysis was performed using linear least squares regression to identify independent predictors of survival, with the results reported as beta coefficients to reflect the direction and magnitude of the association with OS.

ML Workflow

All analyses were performed using Python (version 3.12.11) and scikit-learn library (version 1.5.2). The reporting of the ML model followed the principles outlined in the TRIPOD-AI guidelines (https://www.tripod-statement.org/scope/), although not all checklist items could be fulfilled due to the retrospective nature and lack of external validation.

Models and Variables

To complement conventional statistical methods and explore the multidimensional determinants of survival, we developed two supervised ML models. The first model incorporated only preoperative variables, including demographic data, comorbidity profiles, presenting symptoms, preoperative neurological status, and radiological tumor characteristics of the patients. The second comprehensive model included all preoperative factors and postoperative and treatment-related variables, such as the EOR, postoperative neurological status, and receipt of concomitant radiotherapy with temozolomide (RT + TMZ).

ML Algorithm

In this study, the HGBR was selected because of its suitability for small to medium clinical datasets. It efficiently manages tabular data, captures nonlinear relationships between features, and includes native regularization mechanisms, such as early stopping and learning-rate shrinkage.[25,26] These features help reduce the risk of overfitting compared to bagging-based ensemble methods and lessen the need for extensive preprocessing.

Data Preprocessing

Data preprocessing was performed using a standardized pipeline implemented in our internal codebase. Date variables were converted into numerical Unix time format to ensure compatibility with the regression algorithms. Categorical variables, such as tumor location, American Society of Anesthesiologists classification, and focal neurological deficits, were encoded using one-hot encoding technique. Missing values were not imputed because the selected algorithm (HGBR) natively handles missing entries by learning the optimal split directions for Na values during the tree-building process. OS in months was modeled as a continuous variable. Model hyperparameters were kept at default settings/optimized through randomized search with internal cross-validation to balance performance and interpretability.

Model Validation

Because no external dataset was available, the generalizability of the model was assessed through internal validation using repeated k-fold cross-validation, which is the recommended approach for limited clinical cohorts. Specifically, we applied 5-fold cross-validation repeated 10 times, yielding 50 independent train–test resamples. In each resample, the data were randomly partitioned into 80% training and 20% testing subsets, ensuring that every patient contributed to both the training and validation across repetitions. This resampling strategy provides a robust estimate of the variance and reduces the instability associated with single train–test splits in small datasets.

Permutation Importance

Feature relevance was assessed using permutation importance, which was computed using held-out test folds. For each predictor, the values were randomly permuted, and the resulting decline or improvement in the predictive accuracy was recorded across repeated permutations. These values were averaged and ranked to generate model-agnostic estimates of feature importance, which were exported in both tabular and graphical formats using our analysis scripts.

RESULTS

The demographic, clinical, neurophysiological, and radiological features of the study population are summarized in **Tables 1–5**.

Survival Outcomes

At the time of the last follow-up, the disease status was categorized as stable disease, progressive disease, or death. Among these, 11 patients (6.71%) demonstrated stable disease, 18 patients (10.98%) exhibited disease progression, and 128 patients (78.05%) died.

Early postoperative mortality, defined as death occurring within 30 days of surgery, was observed in 5 patients (3.05%). Of these, 4 patients (13.33%) belonged to the biopsy cohort (n = 4/30), while one patient (0.61%) from the resection group had undergone partial resection. The median OS for the entire cohort was 10 months, with a significant survival benefit observed in the resection group (11.3 months) compared with the biopsy group (3.7 months) (**Figure 1**).

Predictive Factors of OS Identified by Traditional Statistics

Univariate analysis identified several factors significantly associated with prolonged OS in elderly patients with GBM, including lower preoperative American Society of Anesthesiologists grade ($P = 0.03$), larger EOR ($P < 0.01$), nonacute clinical onset ($P < 0.01$), absence of corpus callosum FLAIR involvement ($P = 0.02$), adjuvant therapy consisting of RT+TMZ ($P < 0.01$), and surgery

Table 1. Clinical Characteristics of Patients

Variable	Total	Biopsy	Resection
Number of patients	155	26 (16.77%)	129 (83.33%)
Female	55 (34.15%)	10 (36.67%)	45 (33.58%)
Median age (range)	74 y (70–82)	73 y (70–79)	74.2 y (70–82)
BMI	26.1	27	26
Mean preoperative KPS (range)	81 (50–100)	77 (50–80)	81 (50–100)
KPS ≥70	138 (89.63%)	18 (73.33%)	120 (93.28%)
KPS <70	17 (10.37%)	8 (26.67%)	9 (6.72%)
General symptoms			
Confusion	119 (72.56%)	6 (23.33%)	113 (83.58%)
Seizures	43 (26.22%)	7 (23.33%)	36 (26.87%)
Cognitive decline	37 (22.56%)	5 (16.67%)	32 (23.88%)
Headache/nausea/vomit	33 (20.12%)	4 (13.33%)	29 (21.64%)
Mood changes	11 (6.71%)	3 (10.00%)	8 (5.97%)
Focal neurological deficits	123 (75.00%)	22 (86.67%)	101 (72.39%)
Motor	36 (21.95%)	11 (36.67%)	25 (18.66%)
Sensory	13 (7.93%)	4 (13.33%)	9 (6.72%)
Speech	51 (32.32%)	9 (36.67%)	42 (31.34%)
Visual	20 (12.20%)	3 (10.00%)	17 (12.69%)
CN palsy	18 (12.20%)	4 (20.00%)	14 (10.45%)
Higher functions	25 (15.85%)	3 (13.33%)	22 (16.42%)
Gait disturbances and vertigo	25 (15.85%)	7 (26.67%)	18 (13.43%)
Charlson comorbidity index			
0–3	142 (86.59%)	27 (90.00%)	115 (85.82%)
>3	22 (13.41%)	3 (10.00%)	19 (14.18%)
Comorbidity			
Cardiological	117 (73.17%)	17 (66.67%)	100 (74.63%)
Metabolic	68 (43.29%)	14 (56.67%)	54 (40.30%)
Oncological	45 (27.44%)	6 (20.00%)	39 (29.10%)
Gastroenterological	39 (23.78%)	6 (20.00%)	33 (24.63%)
Pneumological	26 (16.46%)	4 (16.67%)	22 (16.42%)
Neurological	17 (10.98%)	1 (6.67%)	16 (11.94%)
Renal	8 (4.88%)	1 (3.33%)	7 (5.22%)
Other	39 (23.78%)	4 (10.00%)	35 (26.87%)
Antiplatelet therapy			
Aspirin	25 (15.24%)	5 (16.67%)	20 (14.93%)
Clopidogrel	7 (4.27%)	1 (3.33%)	6 (4.48%)
Ticlopidine	1 (0.61%)	0	1 (0.75%)
Fondaparinux	1 (0.61%)	0	1 (0.75%)
Anticoagulant therapy			
Coumadin	3 (1.83%)	0	3 (2.24%)

Continues

Table 1. Continued

Variable	Total	Biopsy	Resection
Direct-acting oral anticoagulant (DOAC)	4 (2.44%)	0	4 (2.99%)
ASA			
1	2 (1.22%)	1 (3.33%)	1 (0.75%)
2	53 (33.54%)	10 (40.00%)	43 (32.08%)
3	96 (60.37%)	14 (56.67%)	82 (61.19%)
4	6 (3.66%)	1	5 (4.48%)
5	0	0	0
E	1 (0.61%)	0	1 (0.75%)

ASA, American Society of Anesthesiologists; KPS, Karnofsky Performance Status; BMI, body mass index.

for recurrences ($P < 0.01$) (Table 6). However, multivariate least squares regression analysis demonstrated that OS was independently influenced by a subset of these variables, specifically EOR ($P = 0.03$), acute symptom onset ($P = 0.04$), cognitive decline ($P = 0.02$), methylated MGMT status ($P = 0.02$), and concomitant RT+TMZ ($P = 0.01$). (Figure 2, Table 7).

Table 2. Radiological Findings

Variable	Total	Biopsy	Resection
Number of patients	155	26 (16.77%)	129 (83.33%)
Hemisphere involved			
Right	79 (50.00%)	10 (43.33%)	69 (51.49%)
Left	75 (46.34%)	12 (43.33%)	63 (47.01%)
Both	6 (3.66%)	4 (13.33%)	2 (1.49%)
Lobe involved			
Frontal	61 (38.41%)	13 (46.67%)	48 (36.57%)
Parietal	49 (31.10%)	10 (30.00%)	39 (31.34%)
Temporal	77 (48.78%)	6 (20.00%)	71 (55.22%)
Occipital	21 (13.41%)	5 (20.00%)	16 (11.94%)
Insular	17 (10.98%)	1 (3.33%)	17 (12.69%)
Deep	20 (12.80%)	14 (50.00%)	6 (4.48%)
N. of lobe involved			
1	87 (56.71%)	12 (50.00%)	75 (55.97%)
2	51 (31.71%)	9 (33.33%)	42 (31.34%)
3	16 (10.98%)	4 (13.33%)	12 (10.45%)
4	1 (0.61%)	1 (3.33%)	0
Multifocal lesions	26 (15.85%)	10 (33.33%)	16 (11.94%)
Midline shift (≥5 mm)	38 (25.61%)	7 (26.67%)	31 (25.37%)
Corpus callosum involvement	15 (10.98%)	3 (13.33%)	12 (10.45%)
Ependymal diffusion	5 (3.66%)	2 (10.00%)	3 (2.24%)

Predictive Modeling Results

To complement these findings, we employed two ML models: a preoperative-only HGBR model and a comprehensive model that integrates both preoperative and postoperative variables. In the preoperative model, no feature demonstrated statistically significant importance, as all 95% confidence intervals encompassed 0. Body mass index (BMI) and cognitive decline exhibited small positive mean importance values, indicating weak but potentially relevant pretreatment signals. Traditional preoperative markers, including age, baseline KPS, comorbidity indices, and radiological characteristics, exhibited negligible or negative importance, suggesting a limited predictive value when considered in isolation (Table 8, Figure 3).

In contrast, the comprehensive model revealed a clear and biologically coherent hierarchy of the predictors. Concomitant RT + TMZ was the most significant contributor to OS prediction, followed by GTR, sequential chemoradiation, postoperative KPS,

Table 3. Surgical and Molecular Data

Variable	Total	Biopsy	Resection
Number of patients	155	26 (16.77%)	129 (83.33%)
Extent of resection			
Gross total resection (GTR)	41 (26.45%)	0	41 (31.78%)
Subtotal resection (STR)	49 (31.61%)	0	49 (37.98%)
Partial resection (PR)	39 (25.16%)	0	39 (30.23%)
Needle biopsy	22 (15.85%)	22 (86.67%)	0
Open biopsy	4 (2.44%)	4 (13.33%)	0
MGMT status			
Methylated	69 (44.52%)	9 (36.62%)	60 (46.51%)
Unmethylated	72 (55.48%)	17 (65.38%)	69 (53.49%)
Unknown	19 (11.59%)	4 (13.33%)	15 (11.19%)

MGMT, O6-methylguanine-DNA methyltransferase.

Table 4. Clinical and Surgical Outcome

Variable	Total	Biopsy	Resection
Number of patients (%)	155	26 (16.77%)	129 (83.23%)
Neurological evaluation			
Unchanged	113 (72.90%)	20 (76.92%)	93 (72.09%)
Improved	14 (9.03%)	2 (7.33%)	12 (9.30%)
Worsened	28 (17.68%)	4 (13.33%)	24 (18.66%)
Postoperative KPS			
Unchanged	101 (87.80%)	21 (86.67%)	80 (88.06%)
Improved	19 (3.05%)	1 (3.33%)	18 (2.99%)
Worsened	35 (9.15%)	4 (10.00%)	31 (8.96%)
Mean preoperative KPS (range)	80 (40—100)	75 (40—80)	80 (50—100)
Perioperative complications	48 (29.27%)	6 (20.00%)	42 (31.34%)
No. of perioperative complications			
1	38 (23.17%)	4 (13.33%)	34 (25.37%)
>1	10 (6.10%)	2 (6.67%)	8 (5.97%)
Wound infection/abscess	3 (1.83%)	0	3 (2.24%)
CSF leak with meningitis	1 (0.61%)	0	1 (0.75%)
Haemorrhage/cerebral hematoma	4 (2.44%)	0	4 (2.99%)
Hydrocephalus with ventricular peritoneal shunt	2 (1.22%)	1 (3.33%)	1 (0.75%)
Deep vein thrombosis	18 (10.98%)	2 (6.67%)	16 (11.94%)
Pulmonary embolism	6 (3.66%)	2 (6.67%)	4 (2.99%)
Myocardial infarction	3* (1.83%)	2* (6.67%)	1 (0.75%)
Seizures	10 (6.10%)	0	10 (7.46%)
Atrial fibrillation/heart failure	3 (1.83%)	0	3 (2.24%)
Pneumonia	6 (3.66%)	0	6 (4.48%)
Urinary disorders	4 (2.44%)	0	4 (2.99%)
Sepsis	4 (2.44%)	1 (3.33%)	3 (2.24%)

CSF, cerebrospinal fluid; KPS, Karnofsky Performance Status.
*One patient presented sudden cardiac death during hospitalization.

and MGMT promoter methylation. Sequential RT/TMZ was the only feature whose 95% confidence interval did not encompass zero, indicating consistent directional influence across cross-validation resamples. Once treatment-related variables were included, nearly all preoperative demographic, symptomatic, comorbidity, and radiological features were of zero importance. The baseline KPS showed a negative importance value, suggesting that postoperative functional status carries a substantially greater prognostic weight than preoperative performance (Table 9, Figure 3).

DISCUSSION

This retrospective study examined the clinical, radiological, surgical, and molecular predictors of survival in elderly patients (≥70 years) with histologically confirmed GBM IDH-wt. Our findings underscore the value of a multimodal approach: GTR, MGMT promoter methylation, combined RT+TMZ, and certain clinical features, such as nonacute symptom onset and preserved cognitive function, which were independently associated with improved OS. The observed median OS was significantly longer in patients who underwent resection than in those who underwent biopsy alone (11.3 vs. 3.7 months), highlighting the critical role of maximal safe resection in carefully selected elderly patients.

Predictors of OS: Literature Comparison

To complement the conventional statistical methods, we applied an HGBR model with permutation feature importance to assess the prognostic relevance of a wide array of variables. Encouragingly, both the statistical and ML models consistently identified RT + TMZ, and the EOR was the most influential predictor.

Table 5. Adjuvant Therapies and Follow-Up

Variable	Total	Biopsy	Resection
Number of patients (%)	155	26 (16.77%)	129 (83.33%)
Adjuvant therapies			
Yes	122 (76.22%)	15 (50.00%)	107 (82.09%)
No	33 (19.51%)	11 (43.33%)	22 (14.18%)
Type of adjuvant therapies			
Radiotherapy alone	36 (22.56%)	8 (26.67%)	28 (21.64%)
Chemotherapy alone	1 (0.61%)	0	1 (0.75%)
Radiotherapy and chemotherapy	49 (53.05%)	7 (23.33%)	42 (59.70%)
Surgery for recurrence	5 (4.27%)	0	5 (5.22%)
Status at follow-up			
Stable disease	9 (6.71%)	2 (6.67%)	7 (6.72%)
Progression	16 (10.98%)	2 (6.67%)	14 (11.94%)
Death	127 (78.05%)	22 (76.67%)	105 (78.36%)
Median overall survival (months)	10 (0—116)	3.7 (0—15)	11.3 (0—116)

Consistent with prior evidence, our analysis reinforced the central prognostic value of RT + TMZ in elderly patients, in line with the findings of the Stupp trial and subsequent studies.[12] This treatment emerged as the strongest predictor in the ML model, emphasizing the importance of identifying patients with adequate functional and molecular profiles who would benefit from full adjuvant therapy.

Similarly, our results reaffirmed the survival benefit of extensive resection in this population, in agreement with prior studies by Almenawer et al., Pessina et al., and Oszvald et al.[8,10,11,14,27-33]

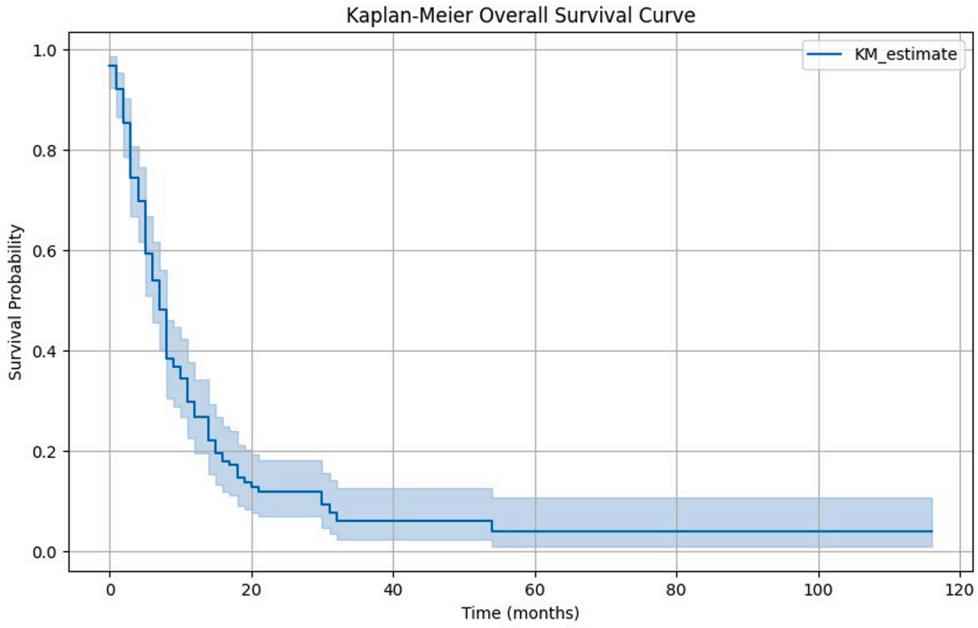

Figure 1. Kaplan-Meier curves displaying the overall survival (OS) of the GBM patients included in the study. KM, Kaplan-Meier; GBM, glioblastoma.

Table 6. Predictors of Overall Survival in Multivariate Analysis

Variables	Estimate HR	Std. Error	95% CI	Z	*P* Value
ASA	−1.501	1.768	2.003 to −5.005	0.300	0.78
Postoperative KPS	−0.154	0.114	0.072 to-0.380	0.406	0.70
EOR (GTR vs. STR)	2.194	1.159	4.590 to −1.032	2.126	0.03
Acute onset (<1 m)	3.809	2.712	8.183 to −1.850	2.059	0.04
Headache/nausea/vomit	−0.628	2.704	4.732 to −5.987	0.105	0.92
Confusion	−0.214	2.462	4.665 to −5.092	0.042	0.97
Cognitive decline	4.112	2.451	7.970 to −1.746	2.355	0.02
KPS ≥70	−1.355	4.631	7.821 to −10.530	0.129	0.91
Multicentric/multifocal	−2.890	3.080	3.214 to −8.993	0.321	0.76
Corpus callosum flair	−3.611	3.724	3.769 to −10.990	0.329	0.76
Methylated MGMT	2.421	2.186	6.753 to −1.010	2.397	0.02
Adjuvant therapies (N)	1.638	2.363	3.229 to 1.110	1.476	0.14
RT alone	−1.279	3.082	4.828 to −7.386	0.173	0.87
Concomitant RT+TMZ	8.891	2.840	14.520 to 3.264	2.724	0.01
Other agents	1.237	3.671	7.512 to −6.038	0.205	0.85
Surgery for recurrence	1.377	3.575	7.464 to −6.710	0.205	0.85

ASA, American Society of Anesthesiologists; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; RT, radiotherapy; RT + TMZ, concomitant radiotherapy and temozolomide.

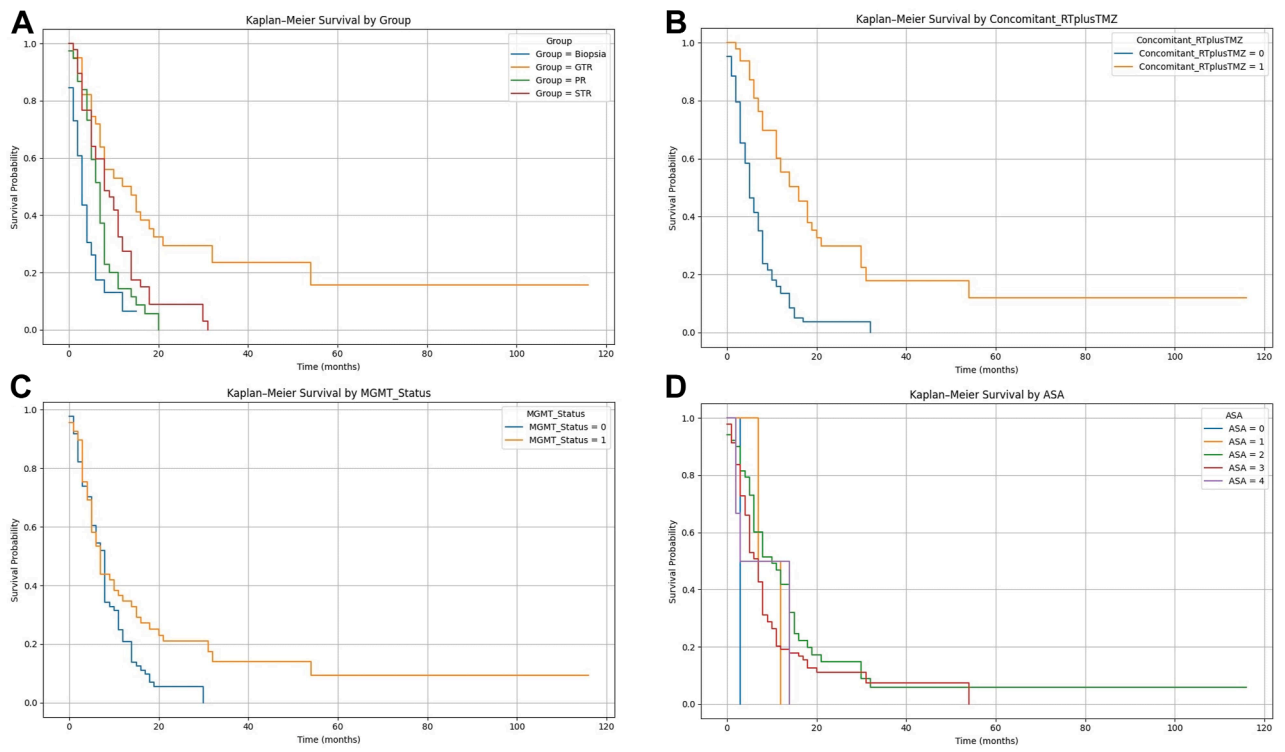

Figure 2. Kaplan-Meier curves displaying OS of GBM patients according to EOR (**A**), Concomitant RT+TMZ (**B**), MGMT promoter methylation status (**C**), and age (**D**). KM, Kaplan-Meier; OS, overall survival; GBM, glioblastoma; EOR, extent of resection; RT + TMZ, concomitant radiotherapy and temozolomide; MGMT, O6-methylguanine-DNA methyltransferase.

Table 7. Predictors of Overall Survival Identified by Permutation Importance (Comprehensive Model)

Feature	Mean Importance	Std Importance	CI Lower	CI Upper	Significance	Effect Size	*P* Value
Concomitant RT + TMZ	0.23	0.14	−0.06	0.39	0.90	1.64	0.10
EOR_GTR	0.10	0.06	−0.02	0.21	0.93	1.65	0.07
Sequential RT and TMZ	0.03	0.02	0.00	0.06	1.00	1.82	0.00
BMI	0.01	0.01	−0.01	0.03	0.63	0.64	0.37
CCI age-adjusted	0.00	0.00	0.00	0.01	0.93	1.69	0.07
Postoperative KPS	0.00	0.00	0.00	0.01	0.90	1.22	0.10
RT alone	0.00	0.00	0.00	0.00	0.80	0.92	0.20
Age	0.00	0.00	0.00	0.00	0.63	0.56	0.37
MGMT+	0.00	0.00	0.00	0.00	0.43	−0.14	0.57
Frontal lobe	0.00	0.00	0.00	0.00	0.30	−0.84	0.70
Temporal lobe	0.00	0.00	0.00	0.00	0.20	−0.78	0.80
EOR_STR	0.00	0.00	−0.01	0.01	0.20	−0.89	0.80
Baseline KPS	−0.09	0.04	−0.15	−0.02	0.00	−2.03	1.00

CI, confidence interval; RT, radiotherapy; TMZ, temozolomide; EOR, extent of resection; GTR, gross total resection; BMI, body mass index; CCI, Charlson Comorbidity Index; MGMT, O6-methylguanine-DNA methyltransferase; KPS, Karnofsky Performance Status; STR, subtotal resection.

When performed with appropriate precautions and patient selection, cytoreductive surgery not only directly improves survival but may also enhance eligibility for adjuvant therapies, amplifying its impact.[34] MGMT promoter methylation also retained prognostic relevance, supporting its continued integration into routine GBM management, particularly for treatment stratification in older patients. These findings are consistent with those of previous studies, such as that of Bruno et al.[9]

Beyond KPS: Towards Multidimensional Preoperative Decision-Making

One particularly intriguing observation concerns the KPS. Traditionally, KPS has been crucial in treatment selection; however, in our multivariate models, it did not independently predict survival and consistently ranked low in ML feature importance analysis. This finding aligns with recent ML-based analyses, such as that by Ius et al.,[22] but contrasts with traditional regression results, where KPS has often demonstrated a strong prognostic value, especially when used alongside frailty or comorbidity indices.[16,21] In our cohort, patients with poor functional status (KPS $\leq$ 50) were excluded, resulting in a predominantly high-functioning sample (nearly 90% had KPS $\geq$ 70), which likely reduced the variability and prognostic impact of KPS in our models. Additionally, because KPS often influences subsequent treatment decisions, its effect may be indirectly embedded within retrospective models.

These findings do not diminish the clinical utility of KPS; however, they question its primacy as a solitary preoperative criterion. In exploratory analyses, BMI showed a modest, directionally positive signal in the preoperative-only model; however, estimates were small and confidence intervals crossed 0, so this observation should be viewed as hypothesis-generating. The

Table 8. Preoperative Predictors of Overall Survival Identified by Permutation Importance

Feature	Mean Importance	Std Importance	CI Lower	CI Upper	Significance	Effect Size	*P* Value
BMI	0.03	0.02	−0.01	0.06	0.87	1.35	0.13
Cognitive decline	0.01	0.01	0.00	0.03	1.00	1.14	0.00
CCI age-adjusted	0.00	0.01	−0.01	0.01	0.60	0.25	0.40
Temporal lobe	0.00	0.01	−0.01	0.00	0.33	−0.70	0.67
Age	−0.01	0.02	−0.04	0.01	0.27	−0.66	0.73
Baseline KPS	−0.07	0.08	−0.19	0.07	0.23	−0.87	0.77

CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index; KPS, Karnofsky Performance Status.

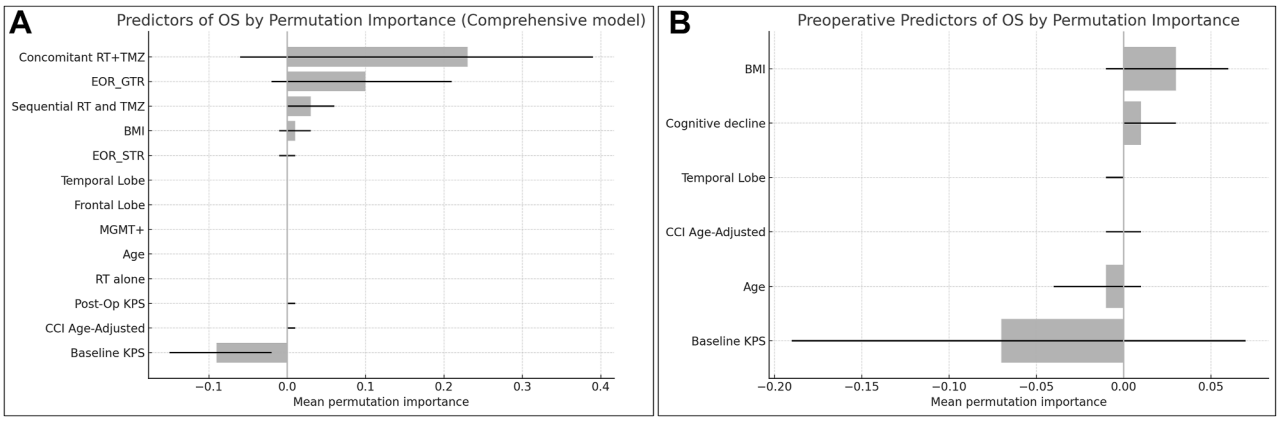

Figure 3. Permutation feature importance values, illustrating their relative contribution to overall survival prediction in HGBR models for elderly patients with GBM. Comprehensive model (**A**) and preoperative-only model (**B**). GBM, glioblastoma; HGBR, Histogram Gradient Boosting Regression.

biological rationale remains plausible: systemic metabolic dysregulation may influence prognosis through inflammation, immune competence, and reduced physiological reserves. Taken together, these observations support moving beyond KPS alone towards multidimensional preoperative assessment and evaluation of disease-specific, functionally oriented geriatric tools to better capture physiological reserve in the elderly.[6,13,15,16,35]

Although the preoperative-only model in this study did not demonstrate sufficient discriminative performance, early risk stratification remains crucial for multidisciplinary planning and counseling that aligns with patient goals and anticipated treatment tolerance. To identify which preoperative domains are consistently informative and how they should be integrated into existing decision-making frameworks, prospective multicenter studies with standardized variables and external validation are necessary. Only after such validation should the prediction instruments be translated into practical, user-friendly digital tools such as clinician-oriented mobile applications or web-based platforms. These tools could facilitate real-time evaluation, improve the distinction between frail and nonfrail patients, and promote more personalized treatment strategies in elderly GBM care.

Table 9. Predictors of Overall Survival Identified by Permutation Importance (Comprehensive Model)

Feature	Mean Importance	Std Importance	CI Lower	CI Upper	Significance	Effect Size	*P* Value
Concomitant RT + TMZ	0.23	0.14	−0.06	0.39	0.90	1.64	0.10
EOR_GTR	0.10	0.06	−0.02	0.21	0.93	1.65	0.07
Sequential RT and TMZ	0.03	0.02	0.00	0.06	1.00	1.82	0.00
BMI	0.01	0.01	−0.01	0.03	0.63	0.64	0.37
CCI AGE-ADJUSTED	0.00	0.00	0.00	0.01	0.93	1.69	0.07
Postoperative KPS	0.00	0.00	0.00	0.01	0.90	1.22	0.10
RT alone	0.00	0.00	0.00	0.00	0.80	0.92	0.20
Age	0.00	0.00	0.00	0.00	0.63	0.56	0.37
Histology MGMT	0.00	0.00	0.00	0.00	0.43	−0.14	0.57
Frontal lobe	0.00	0.00	0.00	0.00	0.30	−0.84	0.70
Temporal lobe	0.00	0.00	0.00	0.00	0.20	−0.78	0.80
EOR_STR	0.00	0.00	−0.01	0.01	0.20	−0.89	0.80
Baseline KPS	−0.09	0.04	−0.15	−0.02	0.00	−2.03	1.00

CI, confidence interval; RT, radiotherapy; TMZ, temozolomide; EOR, extent of resection; GTR, gross total resection; BMI, body mass index; CCI, Charlson Comorbidity Index; MGMT, O6-methylguanine-DNA methyltransferase; KPS, Karnofsky Performance Status; STR, subtotal resection.

Study Limitations and Future Directions

This study had several important limitations. First, the small sample size and absence of external validation restrict the predictive reliability of ML models. Second, its retrospective and single-center design introduced a potential selection bias and limited the generalizability of the findings. Notably, patients with poor functional status (KPS $\leq$50) were excluded from surgery and, by extension, from this analysis, potentially underrepresenting the full clinical spectrum of elderly GBM IDH-wt. Additionally, the retrospective nature of the data collection raises concerns regarding missing variables and the lack of standardized assessments.

The highlighted issues underscore the necessity for future research involving larger, multi-institutional cohorts with increased sample sizes to ensure harmonized data acquisition and consistent variable definitions. It is crucial to integrate structured geriatric and metabolic evaluations into these studies to refine the predictive models and enhance their clinical applicability. Ultimately, validating and expanding this approach in prospective settings could facilitate the development of a robust, generalizable, and multidimensional preoperative decision support tool specifically designed for elderly patients with GBM IDH-wt.

CONCLUSIONS

In conclusion, this study underscores the importance of integrating ML with traditional statistical methods to enhance prognostic modeling in elderly patients with GBM. Our findings emphasize the significance of GTR, MGMT promoter methylation, and the combination of RT+TMZ in improving survival outcomes. In contrast, baseline KPS and age were not independently informative, whereas BMI and cognitive decline were potential preoperative predictors. Although exploratory, we posit that the results of this study support the development of multidimensional preoperative profiles that incorporate cognition, nutritional/metabolic status, comorbidity structure, and objective function to augment KPS and more accurately reflect physiological reserve. Prospective multicenter validation with standardized variables will be essential before any preoperative model can be considered for clinical deployment as a decision-support tool.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work, the author used OpenPaperpal for grammar rans spell checking. After using this tool, the author reviewed and edited the content as needed and took full responsibility for the content of the published article.

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Noa Ben Dor: Conceptualization, Data curation, Formal analysis, Methodology, Writing — original draft, Writing — review & editing. **Filippo Friso:** Conceptualization, Methodology, Writing — review & editing. **Gal Ziv:** Data curation, Formal analysis, Methodology. **Carlo Bortolotti:** Resources. **Matteo Martinoni:** Resources. **Filippo Badaloni:** Resources. **Giuseppe Corazzelli:** Data curation. **Arianna Rustici:** Resources. **Damiano Balestrini:** Resources, Writing — review & editing. **Antonino Scibilia:** Resources. **Tamara Ius:** Methodology. **Sofia Asioli:** Resources, Writing — review & editing. **Caterina Tonon:** Resources. **Elisa D'Angelo:** Resources. **Enrico Franceschi:** Methodology, Validation, Writing — review & editing. **Raffaele Lodi:** Supervision. **Alfredo Conti:** Conceptualization, Project administration, Resources, Supervision, Validation, Writing — review & editing.

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