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Is age an additional factor in the treatment of elderly patients with glioblastoma? A new stratification model: an Italian Multicenter Study

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OBJECTIVE Approximately half of glioblastoma (GBM) cases develop in geriatric patients, and this trend is destined to increase with the aging of the population. The optimal strategy for management of GBM in elderly patients remains controversial. The aim of this study was to assess the role of surgery in the elderly (≥ 65 years old) based on clinical, molecular, and imaging data routinely available in neurosurgical departments and to assess a prognostic survival score that could be helpful in stratifying the prognosis for elderly GBM patients.

METHODS Clinical, radiological, surgical, and molecular data were retrospectively analyzed in 322 patients with GBM from 9 neurosurgical centers. Univariate and multivariate analyses were performed to identify predictors of survival. A random forest approach (classification and regression tree [CART] analysis) was utilized to create the prognostic survival score.

RESULTS Survival analysis showed that overall survival (OS) was influenced by age as a continuous variable ($p = 0.018$), *MGMT* ($p = 0.012$), extent of resection (EOR; $p = 0.002$), and preoperative tumor growth pattern (evaluated with the preoperative T1/T2 MRI index; $p = 0.002$). CART analysis was used to create the prognostic survival score, forming six different survival groups on the basis of tumor volumetric, surgical, and molecular features. Terminal nodes with similar hazard ratios were grouped together to form a final diagram composed of five classes with different OSs ($p < 0.0001$). EOR was the most robust influencing factor in the algorithm hierarchy, while age appeared at the third node of the CART algorithm. The ability of the prognostic survival score to predict death was determined by a Harrell's c-index of 0.75 (95% CI 0.76–0.81).

CONCLUSIONS The CART algorithm provided a promising, thorough, and new clinical prognostic survival score for elderly surgical patients with GBM. The prognostic survival score can be useful to stratify survival risk in elderly GBM

ABBREVIATIONS CART = classification and regression tree; CCI = Charlson Comorbidity Index; EGBM = elderly GBM; EOR = extent of resection; GBM = glioblastoma; HR = hazard ratio; KPS = Karnofsky Performance Scale; OS = overall survival; PFS = progression-free survival; RHR = relative HR.

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patients with different surgical, radiological, and molecular profiles, thus assisting physicians in daily clinical management. The preliminary model, however, requires validation with future prospective investigations. Practical recommendations for clinicians/surgeons would strengthen the quality of the study; e.g., surgery can be considered as a first therapeutic option in the workflow of elderly patients with GBM, especially when the preoperative estimated EOR is greater than 80%.

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KEYWORDS glioblastoma surgery; elderly; prognostic score; extent of resection; CART model; classification and regression tree; decision tree diagram

The prognosis of glioblastoma (GBM) is universally poor, especially in elderly patients, in whom the median survival ranges from 4 to 9 months.[1–9] Approximately half of GBM cases occur in geriatric patients, and this trend is destined to increase with the aging of the population.

The optimal strategy for management of GBM in elderly patients (EGBM) remains controversial, especially in regard to the effects of extent of resection (EOR) on survival outcomes.[10–19] There is overwhelming evidence to suggest that survival and neurological function[4] outcomes can be optimized through maximal safe resection in younger patients with GBM. However, many neurosurgeons tend to avoid aggressive surgical interventions in EGBM patients because of the probable increased risk of perioperative complications.[1,17–19] Life expectancy, overall health status, and quality of life in the elderly, however, are all increasing globally, which makes a strong case for redefining the concept of "elderly" and reframing it in the context of GBM surgical management.

Considering that the incidence of GBM is higher within this expanding age group of the older population, it is of utmost importance to identify prognostic factors and effective therapeutic strategies for improving survival and quality of life.[17,18] An increasing number of prognostic survival tools are being developed to combine clinical, radiological, and molecular variables in an all-inclusive risk stratification model.[20–22] Given the importance of each individual factor, it is often difficult to establish how these interact with each other and how they impact prognosis in the complexity of clinical settings. Cox survival analysis generally detects risk factors without highlighting how their interactions or various combinations influence the prognosis. The algorithms and computational statistics have already demonstrated an excellent performance in outcome predictions for a wide range of conditions, thus paving the way for a personalized medicine model.[23]

In light of this evidence, a multiparametric model for prognosis was elaborated, inclusive of radiological, molecular, and surgical variables, to assess prognosis in postoperative EGBM cases prior to postoperative treatment.

Methods

The methods of this study were based on a previous study in which a scoring system for patients of all ages with GBM was elaborated.[21]

Study Population and Inclusion Criteria

A shared cooperative retrospective database of 322 adult patients surgically treated for newly diagnosed GBM between January 2015 and December 2018 was created. There is no generally agreed upon criterion for the definition of "older people."[17] To provide results that can be widely applied across countries, we used an age cutoff of 65 years old for defining older patients in the current research.

Patients were enrolled according to the following criteria: 1) age ≥ 65 years; 2) no previous surgery; 3) no preoperative chemo- or radiotherapy; 4) presurgical evaluation using the Charlson Comorbidity Index (CCI);[24] 5) objective evaluation of preoperative tumor volume on MR images in DICOM format based on postcontrast T1- and T2-weighted MRI sequences; 6) objective estimation of EOR on postcontrast T1-weighted MRI sequences; 7) revision of histopathological specimens using the new 2016 WHO classification of tumors of the CNS; and 8) *MGMT* promoter methylation and *IDH1*/*IDH2* mutation status assessment. Exclusion criteria included needle biopsy, incomplete imaging data, follow-up interval, and multifocal tumors.

Volumetric Analysis

The neuroradiological tumor growth pattern, expressed by the preoperative T1/T2 MRI index, and EOR were computed as previously described. Briefly, the achieved EOR in each case was objectively evaluated using pre- and postoperative MR images (DICOM format), based on the contrast area of postcontrast T1-weighted MRI sequences, using the following formula: (preoperative tumor volume − postoperative tumor volume)/preoperative tumor volume. With the aim of evaluating the role of tumor growth pattern on overall survival (OS), the preoperative MRI index was assessed as follows: T1/T2 = preoperative volumetric tumor volume on postcontrast T1-weighted images/preoperative volumetric tumor volume on T2-weighted images.[21,25]

Statistical Analysis

Categorical variables were reported as percentages and continuous variables were reported as means ± standard deviations or medians and ranges as appropriate, according to the data distribution. Normality of the continuous variables was tested using the Shapiro-Wilk test.

OS and progression-free survival (PFS) were estimated using the Kaplan-Meier approach. The association between variables and survival distribution was tested using univariate and multivariate Cox proportional hazard models (after verification of proportional hazard assumptions). Patients with unknown survival were censored as of their last scan date. The variables we considered for univariate analysis were age, sex, Karnofsky Performance Scale

(KPS) score, preoperative tumor volume computed on postcontrast T1- and T2-weighted MR images, tumor location, tumor side, EOR, postoperative adjuvant protocol used, *IDH1/2* mutation, *MGMT* methylation status, and Ki-67. EOR was modeled as both a continuous and an ordinal variable (≤ 79%, 80%–89%, 90%–99%, and 100%) in univariate analysis to ensure consistency with previous studies that focused on the impact of glioma resection in terms of volumes.

In the univariate Cox regression, the preoperative T1/T2 MRI index was initially analyzed as a continuous variable. To better understand the variable's association pattern, the Cox regression model was then applied to the quintiles for this variable. Subsequently, the variable was dichotomized using a cutoff we identified at the quintile that showed a significant hazard ratio (HR). The variables that were significantly associated in the univariate model ($p < 0.05$) were included in the multivariate regression model, according to the stepwise-backward selection method. All statistical analyses were performed by Stata/IC (version 13.0, StataCorp LP).

Classification and Regression Tree Method

To determine subgroup patients with different clinical prognoses, we used the decision tree model with the classification and regression tree (CART) method.[21,26] This method is a machine learning model composed of hierarchical decision rules involving optimal cutoff values that recursively split independent factors into different groups. The groups of individuals are called nodes and form a branch node tree. Terminal nodes are groups of individuals that cannot be further subdivided on the basis of the established parameters (minimum size of subgroup, minimum number of events, and maximum p value required) to proceed in further subdivisions. In our study, nodes were required to have a minimum size of 20 patients, a minimum of 10 events, and a maximum p value of 0.05. The significant variables in the univariate analysis were considered to generate the model. Once the regression tree was generated, the nodes of the terminal branches were pruned (aggregated) on the basis of their relative HRs (RHRs) to obtain final groups with homogeneous mortality risk. The final groups were converted into a prognostic survival score ordered according to their RHRs.

Differences in terms of OS probability among the score categories were investigated using univariate Cox regression analysis. The performance of the prognostic survival score in predicting time to death was estimated using Harrell's c-index.[27] All statistical analyses were performed by Stata/IC (version 13.0, StataCorp LP).

Results

Survival Risk Factors

Table 1 lists the various features of the EGBM patients included in the study. The 1- and 2-year OS and PFS rates for the cohort were 42.07% and 14.89% (OS rates) and 24.8% and 9.64% (PFS rates), respectively. Univariate analysis indicated significantly improved OS in EGBM cases with the following features: young age ($p = 0.035$), high EOR ($p < 0.0001$), methylation of the *MGMT* promoter ($p = 0.002$), presence of low residual tumor ($p < 0.0001$), no corpus callosum involvement (0.040), and low preoperative T1/T2 MRI index ($p < 0.0001$). In the final model, variables with significant univariate analysis p values were included. Age ($p = 0.018$), tumor involvement of the corpus callosum ($p = 0.023$), preoperative T1/T2 MRI index ($p = 0.002$), EOR ($p = 0.002$), and *MGMT* methylation status ($p = 0.012$) were found to be independent survival risk factors (Table 2).

CART Model

The CART analysis was applied to elaborate a promising, thorough, and new clinical prognostic survival score for EGBM patients based on surgical, neuroradiological, and molecular determinants. Specifically, the model generation is based on 3 phases of analysis as reported in our previous study:[21] 1) the Kaplan-Meier approach was used to identify the most important survival factors; 2) a decision tree algorithm was applied to stratify OS in different prognosis groups; and 3) the prognostic survival score was computed. In detail, the CART model derives from independent predictor factors detected by the univariate analysis (age, preoperative tumor T1/T2 MRI index, tumor involvement of corpus callosum on preoperative MRI, EOR, *MGMT* methylation status, residual tumor evidenced on postcontrast T1-weighted MR images, and *IDH1/2* mutation status).

First, the CART analysis was performed on 250 cases that met all the selection criteria, leading to the definition of 6 terminal nodes. Terminal nodes with similar RHRs were grouped together to form a final diagram composed of 5 classes with different OSs ($p < 0.0001$), which were used to create the prognostic survival score. Specifically, patients belonging to scores 1, 2, 3, 4, and 5 had RHR values of ≤ 0.40, 0.57–0.73, 1.37, 1.87, and > 2.60, respectively (Fig. 1A). The score performance in predicting death was defined by a Harrell's c-index of 0.75 (95% CI 0.76–0.81). Subsequently, to investigate the impact of *IDH1/2* mutation on OS, the CART model was applied to *IDH1/2* wild-type EGBM patients (239 cases). A score from 1 to 4 was obtained from the 4 terminal nodes (Harrell's c-index of 0.74, 95% CI 0.69–0.78; Fig. 1B). The 1-year estimated OS was computed for each score category (Tables 3 and 4). Overall, to facilitate the visualization of the survival analysis stratified by the score groups resulting from the CART models, Kaplan-Meier curves were generated (Fig. 2).

Discussion

In this retrospective investigation based on 322 elderly cases with newly diagnosed GBM, OS was analyzed based on the stratification of clinical, radiological, and molecular variables. The key findings for consideration were as follows: 1) age, volumetric tumor MRI pattern (expressed by the preoperative T1/T2 MRI index), EOR, and *MGMT* methylation status were confirmed as independent survival predictors on multivariate Cox regression analysis; 2) a novel prognostic score for EGBM surgical patients was assessed by CART analysis; and 3) surgery can be considered as a first therapeutic option in the workflow of EGBM patients, especially when the preoperative estimated EOR is greater than 80%.

TABLE 1. Clinical, radiological, molecular, surgical, and follow-up characteristics of the study population

Parameter	Value
No. of pts	322
Mean age ± SD, yrs	72.28 ± 4.86
Sex, n (%)	
Female	137 (42.55)
Male	185 (57.45)
Side, n (%)	
Lt	170 (52.79)
Rt	152 (47.21)
Tumor site, n (%)	
Precentral	112 (34.78)
Postcentral	100 (31.06)
Temporal + insular	110 (34.16)
Clinical presentation, n (%)	
No deficits	14 (4.35)
Nonspecific symptoms (headache, nausea, vomiting, disorientation)	108 (33.54)
Motor deficits	76 (23.6)
Sensory deficits	7 (2.17)
Visual/speech deficits	64 (19.88)
Seizures	53 (16.46)
Median preop KPS score (range)	90 (60–100)
Preop, n (%)	
Diabetes	32 (9.94)
Solid tumor	25 (7.77)
Chronic pulmonary disease	24 (7.45)
Peptic ulcer disease	15 (4.66)
Previous myocardial infarction	12 (3.73)
Chronic kidney disease	9 (2.79)
Cerebrovascular disease	8 (2.48)
Mild liver disease	6 (1.86)
Lymphoma/leukemia	5 (1.55)
Connective tissue disease	3 (0.93)
Metastatic tumor in recent history	2 (0.62)
Preop CCI, n (%)*	
0	150 (50.17)
1	82 (27.42)
2	52 (17.39)
≥3	15 (5.01)
Radiological features	
Ependymal involvement, yes vs no	114 (35.4%) vs 208 (64.6%)
Corpus callosum involvement, yes vs no	96 (29.81%) vs 226 (70.19%)
Necrotic-cystic component, yes vs no	248 (77.02%) vs 74 (22.98%)
Midline shift, yes vs no	151 (46.89%) vs 171 (53.11%)
Median preop tumor volume on postcontrast T1-weighted images (range), cm^3	31.45 (0.39–197.7)
Median preop tumor volume on T2-weighted images (range), cm^3	56.5 (0.52–231)

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TABLE 1. Clinical, radiological, molecular, surgical, and follow-up characteristics of the study population

Parameter	Value
Preop T1/T2 MRI index, n (%)	
<0.73	185 (57.45)
≥0.73	137 (42.55)
Median residual tumor (range), cm^3	1.344 (0–191)
Median EOR (range), continuous variable	95 (35–100)
EOR, n (%), categorical variable	
100%	125 (38.82)
90%–99%	92 (28.57)
80%–89%	43 (13.35)
≤79%	62 (19.25)
Biological features	
MGMT met (yes vs no)†	155 (54.96%) vs 127 (45.04%)
IDH1/2 mutation (yes vs no)‡	11 (3.62%) vs 293 (96.38%)
Median Ki-67 % (range)	25 (3–90)
Two-gene model, n (%)§	
MGMT met & *IDH1/2* mutation	6 (2.16)
MGMT met & *IDH1/2* wt	149 (53.60)
MGMT unmet & *IDH1/2* mutation	5 (1.80)
MGMT unmet & *IDH1/2* wt	118 (42.45)
Median hospitalization (range), days	8 (5–14)
Postop course, n (%)	
No deficits	152 (47.2)
Nonspecific postop symptoms (headache, nausea, vomiting, disorientation)	44 (13.66)
Motor deficits	73 (22.67)
Sensory deficits	3 (0.93)
Visual/speech deficits	46 (14.29)
Seizures	4 (1.24)
Postop protocol, n (%)	
Stupp protocol	250 (77.64)
CT or RT alone	50 (15.53)
No adjuvant treatment	22 (6.83)
6-month follow-up, n (%)¶	
No deficits	176 (73.64)
Motor deficits	35 (14.64)
Sensory deficits	8 (3.35)
Visual/speech deficits	18 (7.53)
Seizures	2 (0.84)
Median preop KPS score (range)	90 (60–100)
OS (alive vs dead)	77 (23.91%) vs 245 (76.09%)
OS at 1-yr follow-up	42.07%
OS at 2-yr follow-up	14.89%
PFS (no recurrence vs recurrence)	52 (16.15%) vs 270 (83.85%)
PFS at 1-year follow-up	24.8%
PFS at 2-year follow-up	9.64%

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TABLE 1. Clinical, radiological, molecular, surgical, and follow-up characteristics of the study population

Parameter	Value
OS assessed by age	
65–69 yrs	44.20%
70–74 yrs	46.16%
≥75 yrs	28.57%
OS assessed by EOR	
100%	55.03%
90%–99%	44.96%
80%–89%	35.32%
≤79%	16.44%

CT = chemotherapy; met = methylation; pts = patients; RT = radiation therapy; wt = wild-type.
* Cohort = 299 patients.
† Cohort = 282 patients.
‡ Cohort = 304 patients.
§ Cohort = 278 patients.
¶ Cohort = 239 patients.

GBM in the Elderly

In the last decade, the role of surgery has been shown to be the primary option in GBM management, especially in light of recent literature demonstrating a survival benefit associated with a greater EOR.[8,21,25,28–36] The incidence of intracranial tumors in elderly individuals is increasing due to aging of the population and increasing life expectancy.[37]

In 2017, according to Eurostat, the European Union population over the age of 65 years has an additional 20 years of life expectancy, and the percentage of people older than 80 years is expected to more than double in the coming decades, thus unavoidably changing the shape of the age pyramid. These age-associated demographic trends are already having a significant impact with regard to modifications in the disease epidemiology and management of neurosurgical care. Unfortunately, EGBM patients tend to have a drastically reduced survival compared with their younger counterparts.[1,38,39] This could partially be explained by unfavorable tumor biology, performance status, comorbidities, treatment toxicity, trend toward less aggressive treatment, etc. Taking into account the poor prognosis and progressive increase in the incidence of GBM in the elderly population, investigation of treatment efficiency is of significant interest in the management of these patients[10,11,13–19] (Table 5, Fig. 3).

Survival Analysis in EGBM

This retrospective investigation supports the widely known role of age, tumor preoperative MRI index, EOR, and *MGMT* methylation status as independent predictors of survival. Our results confirmed the poorer prognosis for EGBM patients with increasing age.[1,6,40] When stratifying the survival results according to age intervals, we found that 1-year OSs in subgroups of patients who were 65–69, 70–74, 75–79, and ≥ 80 years old were 42.20%, 46.16%, 28.57%, and 4.26%, respectively.

Although several investigations have found that extensive resection is associated with longer survival in EGBM patients, aggressive surgery remains a controversial issue, mainly due to concerns over the balance between treatment benefits and side effects based on age, comorbidity conditions, and supposed different tumor biologies.[10,11,13,14,16,17,19] With regard to the role of EOR, several retrospective investigations showed that greater EOR appears to correlate with an incremental OS benefit in the elderly population, similar to younger patients.[10,11,13,14,16,17,19]

Despite previous investigations recognizing EOR as an independent survival predictor, volumetric data were analyzed as qualitative and not quantitative variables. In this study, we reported the quantitative data and identified a threshold value capable of discriminating the survival benefit. The volumetric analysis showed 1-year survival rates of 55.03%, 44.96%, 35.32%, and 16.44%, when the EOR was 100%, 90%–99%, 80%–89%, and ≤ 79%, respectively. In addition, infiltration of the corpus callosum caused a worse prognosis ($p = 0.023$) as an indirect measure of the possibility of obtaining radical resection in consideration of the vast tumor infiltration.

Our study also noted the role of *MGMT* even among EGBM patients ($p = 0.002$), which was consistent with other investigations.[16,17] Concerning the radiological data, our results confirmed the prognostic survival value of the preoperative T1/T2 MRI index, clarifying its role in predicting a more aggressive biological behavior in those cases with a value close to 1 ($p = 0.002$). In view of the wide heterogeneity of GBM, combining next-generation sequence analysis and assessments of MRI texture analysis parameters could further clarify the role of this volumetric index.[21,41]

Interestingly, unlike other studies, no correlation between KPS score ($p = 0.254$) and CCI score ($p = 0.574$) and OS was found.[1,37] This could be explained by the fact that in the present investigation, patients treated surgically had

TABLE 2. Predictors of OS in univariate and multivariate analyses

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age, yrs	1.028	1.001–1.055	**0.035**	1.040	1.006–1.075	**0.018**
Sex						
Male	1					
Female	1.161	0.901–1.497	0.247			
Side						
Lt	1					
Rt	1.169	0.908–1.506	0.224			
Tumor site						
Precentral	1					
Retrocentral	0.987	0.723–1.348	0.938			
Temporal + insular	1.026	0.758–1.389	0.866			
Preop CCI (0 vs ≥1)	0.862	0.664–1.119	0.265			
Preop KPS score	1.112	0.905–1.110	0.574			
Radiological features						
Ependymal involvement (yes vs no)	1.132	0.900–1.425	0.286			
Corpus callosum involvement (yes vs no)	1.308	0.998–1.713	**0.040**	1.449	1.051–1.998	**0.023**
Necrotic-cystic component (yes vs no)	0.980	0.727–1.322	0.897			
Midline shift (yes vs no)	1.057	0.822–1.360	0.664			
Preop tumor volume on postcontrast T1-weighted images, cm^3	1.000	0.998–1.002	0.500			
Preop tumor volume on T2-weighted images, cm^3	0.994	0.992–0.997	**<0.0001**	0.997	0.993–1.000	0.123
Preop T1/T2 MRI index	5.408	3.144–9.301	**<0.0001**	3.206	1.537–6.685	**0.002**
Residual tumor, cm^3	1.016	1.009–1.022	**<0.0001**	1.018	0.997–1.040	0.081
EOR (continuous variable)	0.983	0.978–0.987	**<0.0001**	0.985	0.977–0.994	**0.002**
EOR (categorical variable)						
100%	1					
90%–99%	1.296	0.944–1.799	0.108			
80%–89%	1.774	1.190–2.644	**0.005**			
≤79%	3.424	2.412–4.861	**<0.0001**			
Biological features						
MGMT methylation (yes vs no)	0.645	0.490–0.849	**0.002**	0.678	0.500–0.919	**0.012**
IDH1/2 mutation (yes vs no)	0.476	0.223–1.014	0.055	0.658	0.287–1.512	0.325
Ki-67	1.002	0.995–1.010	0.456			
Two-gene model						
MGMT met & *IDH1/2* mut	1					
MGMT met & *IDH1/2* wt	1.740	0.639–4.736	0.278			
MGMT unmet & *IDH1/2* mut	1.183	0.264–5.298	0.826			
MGMT unmet & *IDH1/2* wt	2.788	1.020–7.618	**0.045**			

Boldface type represents statistically significant results ($p < 0.05$).

high KPS scores with chronic yet stabilized comorbidities, while those with relevant morbidities were excluded in the preoperative anesthesiological evaluation. Patients with a preoperative KPS score < 60 or chronic uncontrolled diseases underwent only needle biopsy and, consequently, were excluded from this investigation.

Flanigan et al.[1] reported that patients with a CCI score ≥ 1 were associated with decreased survival ($p = 0.018$). The difference obtained in identifying CCI score as a survival prognostic factor in EGBM patients could be due to the presence or absence of chronic comorbidities in addition to the specific therapeutic controls and treatments. This suggests the need for more adequate scales to assess the severity of comorbidities, in addition to other chronic pathologies, in patients with GBM.

Overall, these results emphasize the importance of a multidisciplinary approach for a careful evaluation of surgical options in EGBM patients.

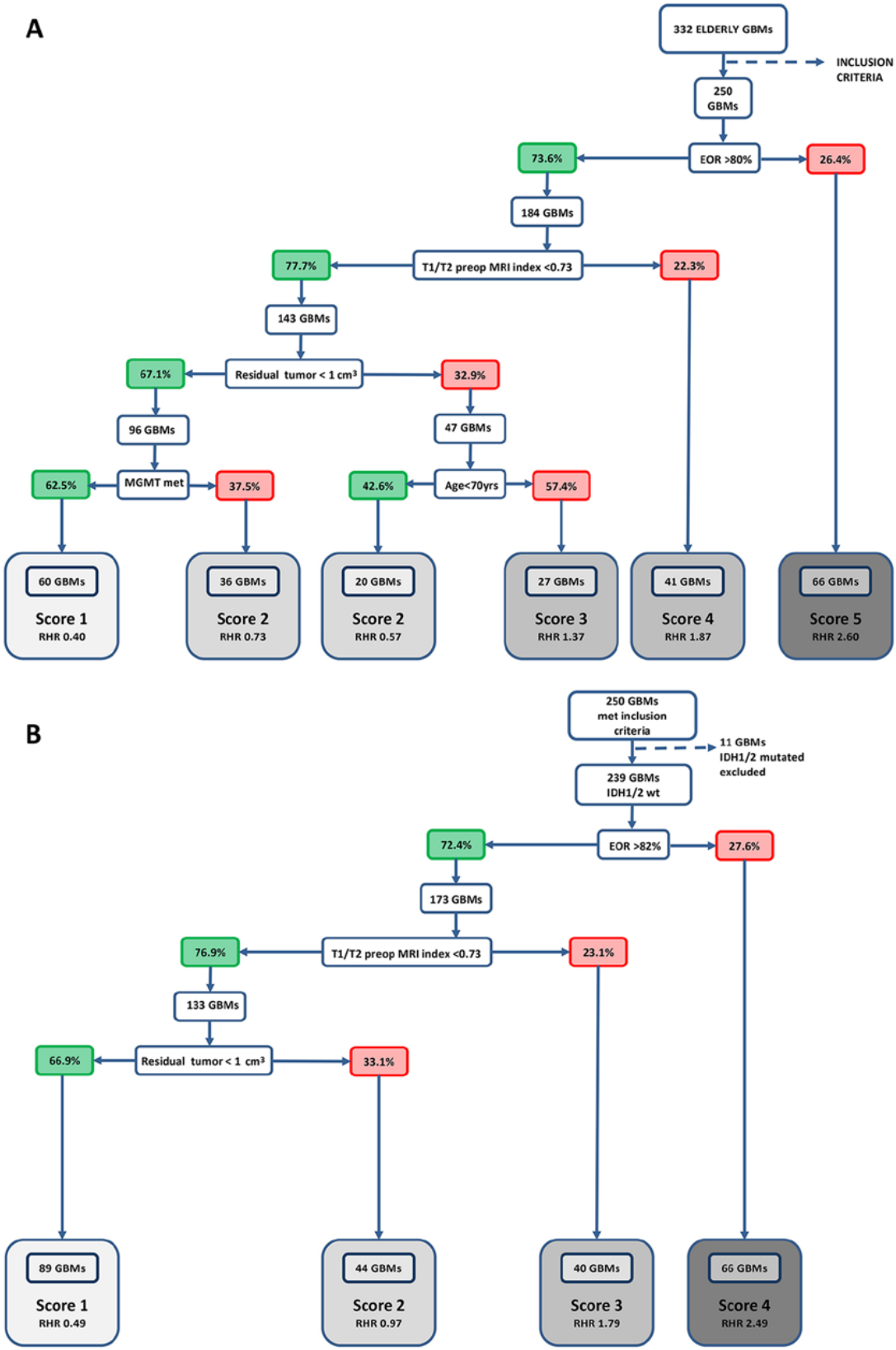

FIG. 1. Random forest, CART algorithm. The CART algorithm provides a graphic visualization of the interaction between risk factors detected by Cox survival analysis. In each hierarchical node, the study population is split according to the presence (*green*) or not (*red*) of the variable able to influence prognosis. **A:** CART model performed on 250 EGBM cases that met all the selection criteria. A score from 1 to 5 was assigned to the 6 terminal nodes thus defined based on the RHR. Patients belonging to the subgroup with RHR = 0.73 and to the subgroup with RHR = 0.55 were joined to create a single group, labeled "score 2." This was done considering the small sample size of each subgroup and similarities in RHR values. **B:** CART model applied to *IDH1/2* wild-type EGBM patients (239 cases). A score from 1 to 4 was obtained from the 4 terminal nodes.

TABLE 3. Estimated OS at 12, 18, and 24 months in EGBM patients (n = 250) according to the CART score

Score*	Variable	HR	95% CI	p Value	Estimated OS (%)		
					12 mos	18 mos	24 mos
1	EOR >80%, preop T1/T2 MRI index <0.73, residual tumor <1 cm^3, *MGMT* met	1	—	—	76.73	56.30	44.45
2	EOR >80%, preop T1/T2 MRI index <0.73, residual tumor <1 cm^3, *MGMT* unmet	1.626	0.985–2.685	**0.058**	69.00	48.53	15.25
	EOR >80%, preop T1/T2 MRI index <0.73, residual tumor >1 cm^3, age <70 yrs						
3	EOR >80%, preop T1/T2 MRI index <0.73, residual tumor >1 cm^3, age >70 yrs	3.290	1.875–5.775	**0.000**	40.74	12.07	6.04
4	EOR >80%, preop T1/T2 MRI index >0.73	4.743	2.829–7.954	**0.000**	15.80	3.95	—
5	EOR <80%	7.529	4.712–12.031	**0.000**	15.21	3.04	—

Boldface type represents statistically significant results ($p < 0.05$).
* A survival score from 1 to 5 was defined based on CART analysis.

TABLE 4. Estimated OS at 12, 18, and 24 months in EGBM patients with *IDH1/2* wild-type (n = 239) according to the CART score

Score*	Variable	HR	95% CI	p Value	Estimated OS (%)		
					12 mos	18 mos	24 mos
1	EOR >82%, preop T1/T2 MRI index <0.73, residual tumor <1 cm^3	1	—	—	72.90	53.38	32.52
2	EOR >82%, preop T1/T2 MRI index <0.73, residual tumor >1 cm^3	1.914	1.216–3.013	**0.005**	49.72	22.90	11.45
3	EOR >82%, preop T1/T2 MRI index >0.73	3.622	2.300–5.703	**<0.0001**	16.25	4.06	—
4	EOR <82%	5.772	3.875–8.596	**<0.0001**	15.21	—	—

Boldface type represents statistically significant results ($p < 0.05$).
* A survival score from 1 to 4 was defined based on CART analysis.

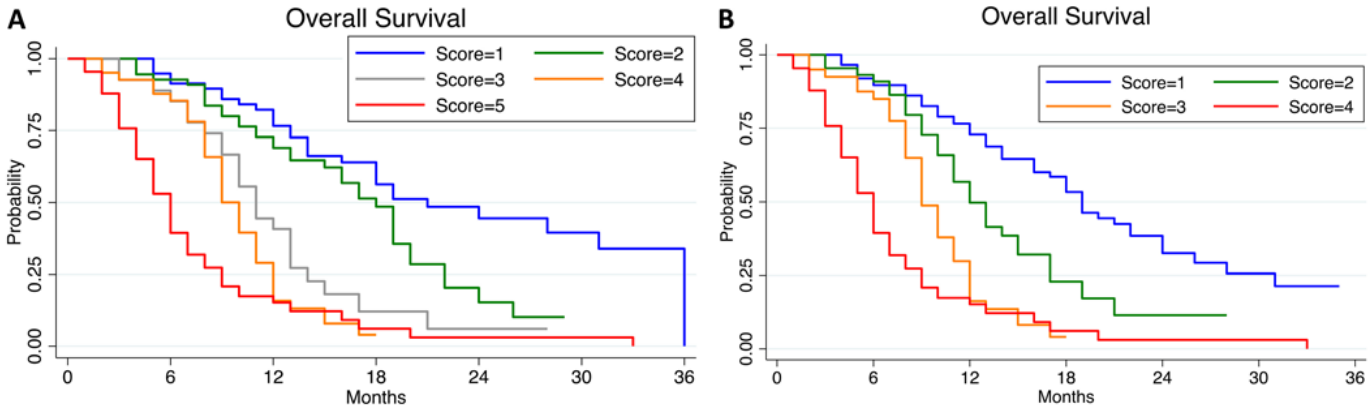

FIG. 2. OS stratified by CART analysis prognostic score. Kaplan-Meier curves display the OS of EGBM patients according to the prognostic scores elaborated by the CART model. **A:** Survival stratified by the score from 250 EGBM cases that met the selection criteria. **B:** Survival stratified by the score from 239 EGBM *IDH1/2* wild-type cases.

TABLE 5. Review of the literature in elderly patients with GBM

Authors & Year	No. of Pts	Age (yrs)	Results	Conclusions
Han et al., 2020[14]				
Metanalysis including retrospective observational studies	10,815	>60	GTR associated w/ a significant improvement in OS compared w/ STR (HR 0.70, 95% CI 0.64–0.77); elderly pts who underwent GTR showed lower risk of 3-mo (OR 0.47, 95% CI 0.24–0.93), 6-mo (OR 0.38, 95% CI 0.26–0.56), 9-mo (OR 0.35, 95% CI 0.25–0.49), & 1-yr (OR 0.40, 95% CI 0.29–0.56) mortality	GTR seems to be more effective than STR in achieving longer survival in elderly pts w/ high-grade glioma
Lombardi et al., 2019[16]				
Retrospective cohort study	113	>65	According to CGA, 35% of pts were classified as fit, 30% as vulnerable, & 35% as frail; median OS was 16.5 mos (95% CI 14.6–18.2 mos), 12.1 mos (95% CI 8.1–16.1 mos), & 10.3 mos (95% CI 8.8–11.8 mos) for fit, vulnerable, & frail pts, respectively (p = 0.1); median PFS was 11.2 mos (95% CI 6.07–16.4 mos), 7.7 mos (95% CI 4.6–10.7 mos), & 7.1 mos (95% CI 5.7–8.4 mos) for fit, vulnerable, & frail pts, respectively (p = 0.2)	CGA held prognostic significance in elderly pts w/ GBM; it is likely that CGA fit pts are those who would benefit from combined treatment w/ RT-CT
Cohen-Inbar, 2019[19]				
Cohort study	20,705	>75	A stepwise decrease in GTR attained as a function of age (36% at 18–44 yrs vs 24% at 75 yrs, p < 0.001)	EGBM pts who undergo a GTR rather than biopsy alone have improved PFS & OS; a greater EOR appears to correlate w/ an incremental OS benefit in the elderly population, similar to younger pts
Prospective study	30	>65	GTR carries reduced risks for mortality & a modest benefit in terms of functional independence & OS (171 vs 85 days, p = 0.035)	
Retrospective study	80	>65	Negative prognostic factors for EGBM pts undergoing GTR, including a preop KPS score <80, COPD, presenting motor/ language/cognitive deficit, & tumor largest diameter >4 cm	
Minniti et al., 2019[17]				
Systematic review & meta-analysis	12,607	>60	OS was 5.71 mos (95% CI 5.04–6.36 mos) in biopsy, 8.68 mos (95% CI 7.87–9.48 mos) in STR, & 14.04 mos (95% CI 12.8–15.2 mos) in GTR	Maximal degrees of tumor removal when the operative option is indicated, regardless of age, preventing new permanent neurological deficits & maintaining good quality of life
RCT	30	>65	Median survival times of 171 & 85 days after resection or biopsy, respectively (p = 0.035)	
Asmaa et al., 2018[10]				
Cohort study	20,705	>75	GTR decreased in a stepwise manner as a function of pt age (from 36% [18–44 yrs] to 24% [>75 yrs], p < 0.001); GTR had a 2- to 3-fold increase in OS	A continuous linear increase in survival after combination of different modalities w/ best outcomes observed in pts undergoing aggressive resection followed by adjuvant CRT combined w/ TMZ; molecular stratification & analysis of *MGMT* methylation may help to identify pts who may particularly benefit from CT
Retrospective cohort study	274	>65	21.9% complications after resection, w/ a rate of neurological complications of 7.7%	
Retrospective cohort study	124	>65	KPS score <80 was of negative prognostic value (p < 0.006), STR or GTR was associated w/ significantly improved OS (median 11.0 & 15.0 mos, p < 0.02) compared w/ partial resection or biopsy (both 4.0 mos)	
RCT	30	>65	Pts undergoing resection had significantly longer survival time (171 vs 85 days, p = 0.03) compared w/ those having biopsy	
Systematic review & meta-analysis	12,607	>60	Increase in PFS & OS among pts who had undergone either STR or GTR compared w/ biopsy; no change in mortality & morbidity & improvements in KPS score in pts undergoing GTR compared w/ STR	

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TABLE 5. Review of the literature in elderly patients with GBM

Authors & Year	No. of Pts	Age (yrs)	Results	Conclusions
Okada et al., 2017[18]				
RCT	30	>65	Surgical removal of the tumor prolonged survival by 2.8 times more than biopsy (median OS 171 days after the craniotomy vs 85 days after the biopsy)	Surgery is aimed at achieving maximal cytoreduction of the tumor; resection as much as possible is associated w/ favorable prognosis even in elderly pts w/ GBM; in addition to histological diagnosis, information regarding molecular markers, such as *IDH* mutation & *MGMT* methylation status, is necessary to develop a treatment strategy
Systematic review & meta-analysis	12,607	>60	Resection was superior to biopsy in OS (mean difference 3.88 mos, 95% CI 2.14–5.62 mos, p < 0.001), PFS, postoperative KPS score, & mortality; GTR was significantly superior to STR in terms of OS (mean difference 3.77 mos, 95% CI 2.26–5.29 mos, p < 0.001), PFS, & postop KPS score	
Retrospective cohort study	206	>70	Survival advantage of GTR compared w/ the biopsy (OS 10.7 vs 2.8 mos)	
Retrospective cohort study	124	>65	Survival advantage of GTR compared w/ the biopsy (OS 15 vs 5.6 mos)	
Retrospective cohort study	237	>65	Survival advantage of GTR compared w/ STR (OS 17.7 vs 16.1 mos)	
Retrospective cohort study	120	>65	Survival advantage of GTR compared w/ STR (OS 14.1 vs 9.6 mos)	
Braun & Ahluwalia, 2017[11]				
Retrospective study	80	>65	Median OS of 5.7 mos in the surgery group vs 4.0 mos in the biopsy group	A maximal safe resection is recommended, after stratifying for periop risk factors including performance status & medical comorbidities
Retrospective study	146	>65	Improved median OS of 17.7 mos in GTR compared w/ 4.0 mos in the biopsy group	
Cohort study	20,705	>75	GTR in the group of pts ≥75 yrs was associated w/ an OR of 0.5 compared w/ pts 18–44 yrs old; GTR had a longer OS than those who underwent STR	
Halani et al., 2017[13]				
Retrospective study	146	>65	Improved median OS of 17.7 mos in GTR compared w/ 4.0 mos in the biopsy group	Treatment options available that not only improve OS, but also do not necessarily compromise quality of life; aim for GTR of tumor in elderly pts, regardless of age; if GTR is not possible, STR results in improved OS compared w/ those pts who undergo operative biopsy alone (median OS: GTR 15 mos vs STR 9 mos vs biopsy 4 mos); pts >65 yrs have an added benefit from combined TMZ & RT after GTR (median OS: no adjuvant treatment 2.0 mos vs RT alone 4.0 mos vs CMT 5.0 mos vs CT alone 8.0 mos vs Stupp protocol 18.0 mos)
Retrospective cohort study	120	>65	Survival advantage of GTR compared w/ STR (OS 14.1 vs 9.6 mos)	
Retrospective cohort study	124	>65	Survival advantage of GTR compared w/ the biopsy (OS 15 vs 4 mos)	
Retrospective cohort study	237	>65	Survival advantage of GTR compared w/ STR (OS 17.7 vs 16.1 mos)	
Retrospective cohort study	120	>65	GTR had longer survival compared w/ STR (14.1 vs 9.6 mos, p = 0.038); pts >75 yrs had worse survival than younger (median OS: 7.9 vs 15.1 mos, p < 0.0001); for EOR, age >75 yrs (HR 1.06, 95% CI 1.02–1.10) was associated w/ worse outcomes, & greater KPS scores (HR 0.97, 95% CI 0.95–0.99) were associated w/ better prognosis	
Retrospective study	58	>80	Median OS was 4.2 mos; factors associated w/ greater OS included KPS score >90 (p < 0.05)	

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TABLE 5. Review of the literature in elderly patients with GBM

Authors & Year	No. of Pts	Age (yrs)	Results	Conclusions
Jordan et al., 2016[15]				
Retrospective study	80	>65	Median OS of 5.7 mos in the surgery group vs 4.0 mos in the biopsy group	With acceptable perioperative risk stratification according to overall health & performance status, greater EOR may allow for prolonged survival as well as larger samples of tissue for genetic & molecular markers; involved-field RT is also an effective modality of therapy for elderly pts; TMZ given either alone or adjuvant to RT is associated w/ improved survival in elderly pts
Retrospective cohort study	168	>60	GTR + RT & re-resection of recurrent tumor each provided independent prognostic benefits in older group	
RCT	30	>65	Pts undergoing resection had significantly longer survival time (171 vs 85 days, p = 0.03) compared w/ those having biopsy	
Retrospective cohort study	124	>65	Survival advantage of GTR compared w/ the biopsy (OS 15 vs 4 mos)	
Retrospective study	103	>65	PFS & OS improved w/ increasing EOR; RT & TMZ after surgery were also associated w/ improved PFS & OS	

CGA = comprehensive geriatric assessment; CMT = combined modality radiochemotherapy; COPD = chronic obstructive pulmonary disease; CRT = chemo- and radiotherapy; GTR = gross-total resection; RCT = randomized controlled trial; STR = subtotal resection; TMZ = temozolomide.
Articles are grouped according to the final results that our review research included (Fig. 3). The 9 review studies reported are based on a total of 34 studies.

CART Analysis

The principal novelty of this study is the elaboration of a prognostic and integrated score based on the CART analysis. This approach identifies the strongest prognostic variables and generates a creative and integrative visualization chart that illustrates the results in an easily interpretable tree structure from a large number of data. The model is based on the influence of interactions of various parameters and not on single ones, which permits the creation of a model that closely reflects the disease complexity. In this investigation, the CART analysis based on the 250 cases provided 6 terminal nodes, the RHRs of which were used to generate the prognostic score with the purpose of facilitating the survival stratification before patients were discharged postoperatively.

Patients belonging to the subgroups with RHR = 0.73 and RHR = 0.55 were joined to create a single group labeled "score 2." This was done because of the small sample size of each subgroup and similarities in RHR values. Patients with scores of 1 or 2 had better survival, with 1-year estimated OSs of 76.73% and 69.00%, respectively. The worst survival was for patients with scores from 3 to 5, with 1-year estimated OS after surgery ranging between 40.74% and 15.21% after surgery.

It is important to highlight that the EOR was the most robust influencing factor in the algorithm hierarchy, while age appeared at the third node of the CART algorithm, thus strengthening the role of surgery also in EGBM and performing patients (who have a high preoperative KPS score), when surgical planning allowed us to preoperatively estimate an EOR > 80%.[6,17,42] In a previous investigation, Flanigan et al. elaborated a risk prognostic score in EGBM patients based on variables identified using the multivariate stepwise analysis (age, EOR, preoperative weakness, tumor size, and CCI).[1] A point designation was then given to each factor and points were totaled for each patient, considering only the presence of the variables and ruling out their interactions. Our model thus provides for a rapid and accurate assessment of survival prognosis after surgery and relies on concrete parameters rather than on a subjective metric.

It is widely reported in the literature that the *IDH1/2* mutation is associated with a better prognosis in GBM patients in terms of disease-free survival and progression. *IDH1/2* mutant GBMs represent less than 10% of all GBMs and show different genetic, epigenetic, and clinical features compared with the 1/2 wild-type counterpart.[43] In this investigation, the *IDH1/2* mutation was detected in only 3.4% of cases (11 patients), with a similar distribution within each score class identified by CART analysis (3, 1, 2, 3, and 2 *IDH1/2* EGBM patients for scores 1, 2, 3, 4, and 5, respectively). The equal portioning of the *IDH1/2* mutation may determine that its positive survival impact is equally distributed within the different score groups identified by CART analysis.

Analyzing only *IDH1/2* wild-type EGBM patients, we excluded age and *MGMT* methylation status from the model, while the EOR, residual tumor, and preoperative neuroradiological tumor growth pattern, expressed by the preoperative T1/T2 MRI index, were confirmed as the fundamental nodes in the prognostic model. Generally,

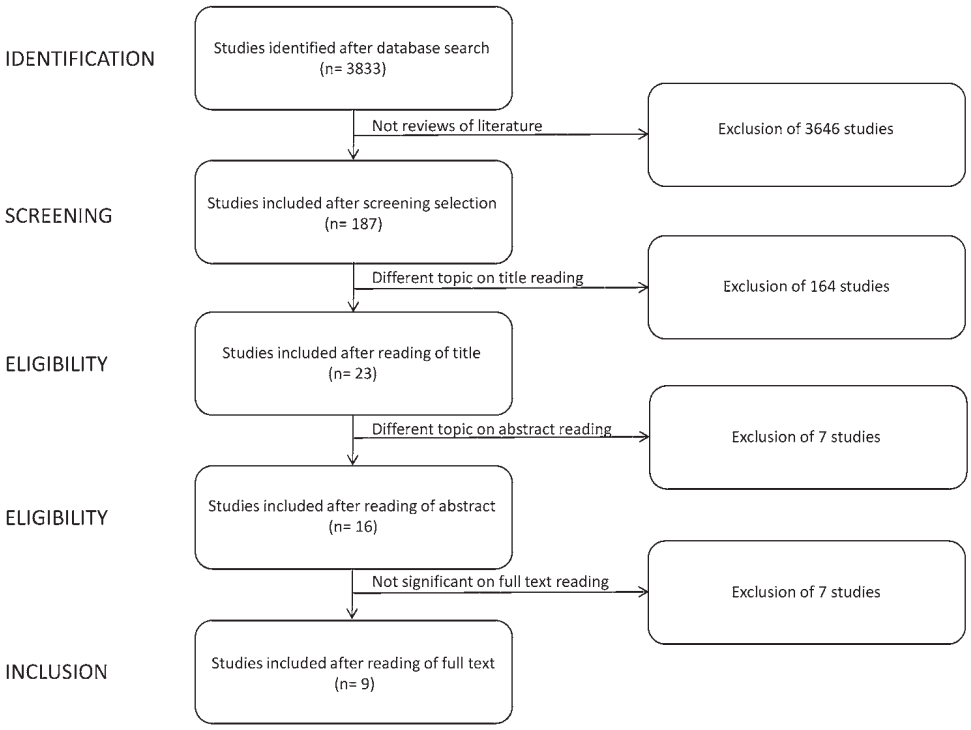

FIG. 3. Systematic review and meta-analysis flowchart. The figure shows the different decisional phases regarding the inclusion and exclusion of the papers reviewed in the studies based on the role of surgery in EGBM patients.

IDH-mutant gliomas are younger, and in these patients GBM is more likely to derive from a low-grade glioma and therefore also carries the *IDH* mutation.[44] This investigation highlights that EOR is the main prognostic factor in EGBM patients, giving rise to the first split node in both generated CART models (Fig. 1). This may suggest that the OS is influenced by other numerous mutations, such as mutations in *ATRX*, *CIC*, *EGFR*, *FUBP1*, *NOTCH1*, *PTEN*, *H3F3A*, *IDH1/2*, *PIK3CA*, and *BRAF*, and amplifications in *EGFR* or *MDM2*; copy number alterations of chromosomes 1p, 7, 10, and 19q are involved in glioma genesis and tumor progression.[41,45]

Limitations and Future Directions

A limitation of our study is that we included only patients with resectable GBM based on clinical and radiological criteria (high preoperative KPS score, controlled comorbidities, and/or high chances of achieving a large EOR). Patients who underwent needle biopsy, who did not undergo resection, were thus excluded. An additional limitation is that comorbidities were not adequately discussed (heart disease, cancer, anticoagulation, etc.), because only patients with controlled mild or moderate comorbidities were considered for surgery. It is thus important to have stringent clinical selection criteria in EGBM patients to select which may benefit from surgery so that underlying comorbidities do not have a direct impact on surgical outcomes.

Despite the inherent limitations of the retrospective nature of this study, the prognostic score elaborated for EGBMs could be useful in a day-to-day clinical environment. It could also prove to be useful after surgery and previous oncological treatments, to discuss prognosis and draw future prospective clinical trials. Patients with better OS showed a better PFS and lower score.[21,45] The prognostic survival score assessed in this investigation can thus be considered an indirect measure of tumor progression.

An additional limitation is represented by the heterogeneous treatment at tumor recurrence. Each patient underwent individualized management at tumor progression. It is well known that to improve the prediction models, salvage treatment information should be updated in the analysis at the time of tumor progression. Moreover, the study lacks details about functional recovery time and neurocognitive outcomes according to variable levels of resection. To overcome this drawback, future prospective multicenter studies based on larger cohorts with longer follow-up periods need to include time-dependent analysis.

Future studies are needed to further assess the numerous molecular and genomic markers that may prove to be of clinical interest in GBM. In addition, radiological features should be included in prospective future clinical studies considering the growing importance of radiogenomics. Considering the heterogeneity of GBM, texture features from multiparametric MRI and next-generation sequence analysis could prove to be of assistance in managing these patients. Computed prognostic scores may prove to be useful in a day-to-day clinical setting and in research to provide more thorough assessments in future prospective clinical trials. In conclusion, the survival score could be useful when deciding and discussing prognosis to better address the entire management of EGBM patients.

Conclusions

Elderly patients with GBM typically carry a poor prognosis. There are no gold standards or widespread guidelines to be applied to this group of patients, and optimal strategy and management remain debatable. Advanced age alone should not necessarily preclude optimal resection followed by adjuvant radiation and chemotherapy. Our study showed that prediction models can be used to generate a promising, thorough, and new clinical prognostic score for EGBM surgical patients to guide clinicians in the decision-making process. Thorough evaluation and selection of EGBM patients may lead to favorable survival benefit.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ius, Sabatino. Acquisition of data: Ius, Somma, Altieri, Angileri, Certo, Cofano, Della Pepa, La Rocca, Panciani, Pignotti, Spena, Sabatino. Analysis and interpretation of data: Ius, Pignotti, Sabatino, Somma. Drafting the article: Ius, Somma, Pignotti, Sabatino. Critically revising the article: all authors. Reviewed submitted version of manuscript: Ius, Somma, Altieri, Angileri, Barbagallo, Cappabianca, Certo, Cofano, D'Elia, Della Pepa, Fontanella, Germanò, Garbossa, Isola, La Rocca, Maiuri, Olivi, Panciani, Pignotti, Skrap, Spena, Sabatino. Approved the final version of the manuscript on behalf of all authors: Ius. Statistical analysis: Ius, Isola. Administrative/technical/material support: Ius, Pignotti. Study supervision: Ius, Angileri, Barbagallo, Cappabianca, Esposito, Fontanella, Germanò, Garbossa, Olivi, Skrap, Sabatino.

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