Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 26; 10(F):345-354.
https://doi.org/10.3889/oamjms.2022.8970
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Meta-analytic Review Article*

The Impact of Extent of Resection on the Prognosis of Glioblastoma Multiforme: A Systematic Review and Meta-analysis

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Edited by: https://publons.com/researcher/391987/mirko-spiroski
Citation: Chaulagain D, Smolanka V, Smolanka A, Munakomi S. The Impact of Extent of Resection on the Prognosis of Glioblastoma Multiforme: A Systematic Review and Meta-analysis. Open Access Maced J Med Sci. 2022 May 26; 10(F):345-354. https://doi.org/10.3889/oamjms.2022.8970
Keywords: Predictor factors; Glioblastoma multiforme; Extent of resection
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Received: 11-Feb-2022
Revised: 18-Apr-2022
Accepted: 16-May-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The aim of the study was to investigate the predictor factors of mortality describing the prognosis of primary surgical resection of glioblastoma multiforme (GBM).

MATERIALS AND METHODS: A systemic search was conducted from electronic databases (PubMed/Medline, Cochrane Library, and Google Scholar) from inception to September 12, 2021. All statistical analysis was conducted in Review Manager 5.4.1. Studies meeting inclusion criteria were selected. A random-effect model was used when heterogeneity was seen to pool the studies, and the result was reported in the hazards ratio (HR) and corresponding 95% confidence interval.

RESULTS: Twenty-three cohort studies were selected for meta-analysis. There was a statistically significant effect of extent of resection (EOR) on prognosis of surgery in GBM patients (HR = 0.90 [0.86, 0.95]; $p < 0.0001$; $I^2 = 96\%$), male gender (HR= 1.19 [1.06, 1.34]; $p = 0.002$; $I^2 = 0\%$), and decrease Karnofsky Performance Status (HR= 0.97 [0.95, 0.99]; $p = 0.003$; $I^2 = 90\%$). Age and tumor volume were also analyzed in the study.

CONCLUSION: The results of our meta-analysis suggested that age, gender, pre-operative KPS score, and EOR have significant effects on the post-surgical mortality rate; therefore, these factors can be used significant predictor of mortality in GBM patients.

Introduction

Malignant gliomas (MG) are an invasive group of tumors, which are believed to be derived from glial cells and account for 75% of malignant brain tumors [1]. The most common (60%–70%) and aggressive subtype of MG is a glioblastoma (GBM), with an annual incidence of 3–5/100,000 people [2], [3]. Ionizing radiations and familial cancer syndromes such as neurofibromatosis Types 1 and 2, and Li-Fraumeni syndrome are risk factors for <1% of GBM and males are more commonly affected [4], [5]. GBM can develop through different genetic pathways and is classified into primary and secondary GBM [5]. Primary (*de novo*) GBM is associated with EGFR amplification (36%) and PTEN mutations (25%), with a mean age of presentation of 62 years [5]. Secondary glioblastomas are associated with TP53 mutations (65%) and may develop through a progression from low-grade MG, presenting at a mean age of 45 years [5]. Sensorimotor deficits, epilepsy, headache, and nausea are common presenting symptoms of GBM, and radiographic features include an irregularly increasing mass with associated edema and mass effect, seen with either magnetic resonance imaging (MRI) or computed tomography scan [1]. Population-based studies have shown that the median survival rate is 42.4 % at 6 months and 17.7 % at 1 year [6].

Palliative therapy for GBM includes prophylactic antiepileptic drugs for seizures, corticosteroids for the peritumoral edema, and anticoagulants for venous thromboembolism, which have an incidence of 20%–30% in this disorder. Survival with palliative therapy ranges from 3 to 4 months [7]. Surgery plus radiation therapy and concomitant temozolomide are the standard therapy offered to patients with newly diagnosed GBM. Median survival is increased to 6 months with surgical resection alone, while surgical resection plus radiation therapy offers a better mean survival of 12 months [7], [8]. GBM is a highly infiltrative tumor and the addition of radiation therapy plus concomitant chemotherapy offers better chances of survival. The addition of concomitant chemotherapy with temozolomide to surgical resection plus radiation therapy improves survival to 14.6 months [8].

There are several prognostic factors that affect survival in GBM patients. In a recursive partitioning analysis, Lamborn *et al*. showed that younger age (≤40), higher Karnofsky Performance

Scale (KPS) score (≥70), adjuvant chemotherapy, and greater extent of resection (EOR) were all linked with improved survival after the treatment with surgery in GBM patients [9]. Another study performed univariate and multivariate analysis on several prognostic factors affecting survival in newly diagnosed GBM patients treated with surgery and found that lower age (<65), higher KPS score (≥90) and greater extend of tumor resection (EOR) (≥98) were significantly associated with improved survival [10]. A systematic review and meta-analysis also showed that gross total resection (GTR) significantly ($p < 0.001$) increased survival at 1 year when compared with subtotal resection (STR) [11].

However, no previous meta-analysis has evaluated the effectiveness of factors that predict the mortality in patients. We evaluate the significance of age, gender, EOR, tumor volume, and pre-operative KPS score for predicting the mortality in post-surgical GBM patients.

Methods

Data sources and search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta analyses guidelines [12]. An electronic search from PubMed/Medline, Cochrane Library, and Google Scholar was conducted from their inception to September 12, 2021 (detailed strategy provided in Supplement Table 1), with only English language-based literature, using the search string: (Astrocytoma OR Cystic astrocytoma OR Glioblastoma multiforme OR Grade IV astrocytoma) AND (resection OR surgical process OR operation) AND (extent). In addition, we manually screened the cited articles of the previous meta-analyses, cohort studies, and review articles to identify any relevant studies.

Study selection

All studies were included if they met the following eligibility criteria which can be described as PICOS: (1) P (Patients): Glioblastoma multiforme (GBM); (2) I (Intervention): Any type of surgical resection of GBM; (3) C (Control): None; (4) O (Outcome): Predictive factors of mortality using Univariate/Multivariate analysis of age, gender, tumor volume, EOR and KPS; (5) S (Studies): Cross-sectional studies, cohort studies, and human-based, randomized, and controlled trials published in English only.

Data extraction and quality assessment of studies

Two reviewers independently searched electronic databases. Studies searched were exported to the EndNote Reference Library software version 20.0.1 (Clarivate Analytics), and duplicates were screened and removed.

Data extraction and quality assessment of included studies were done simultaneously and independently by two reviewers. Newcastle-Ottawa Scale (NOS) was used to assess the quality of the cross-sectional studies. NOS score 1–5 was considered high risk for bias, 6–7 was moderate, and score >7 was considered low risk of bias (details of scoring provided in Supplement Table 2).

Statistical analysis

Review Manager (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020) was used for all statistical analyses. The data from studies were pooled using a random-effects model. Analysis of results was done by hazards ratio (HR) with respective 95% confidence intervals. The Chi-square test was performed to assess any differences between the subgroups. Sensitivity analysis was done to see if any individual study was driving the results and to implore reasons of high heterogeneity. As per Higgins *et al*, scale for heterogeneity was considered as follows: I^2 = 25–60% – moderate; 50%–90% – substantial; 75%–100% – considerable heterogeneity, and $p < 0.1$ indicated significant heterogeneity [13]. $p < 0.05$ was considered significant for all analyses.

Results

Literature search results

The initial search of the three electronic databases yielded 1861 potential studies. After exclusions based on titles and abstracts, the full texts of 286 studies were read for possible inclusion. A total of 23 studies remained for quantitate analysis. Figure 1 summarizes the results of our literature search.

Study characteristics

Table 1 provides the basic characteristics of included studies [14], [15]. Our analysis included 23 published studies. All are cohort studies. A total of 137,406 GBM patients were included in these studies. Ten studies are from USA, three are from Korea, two are from Germany, two from France, one from Italy, one from Spain, one from Canada, one from China,

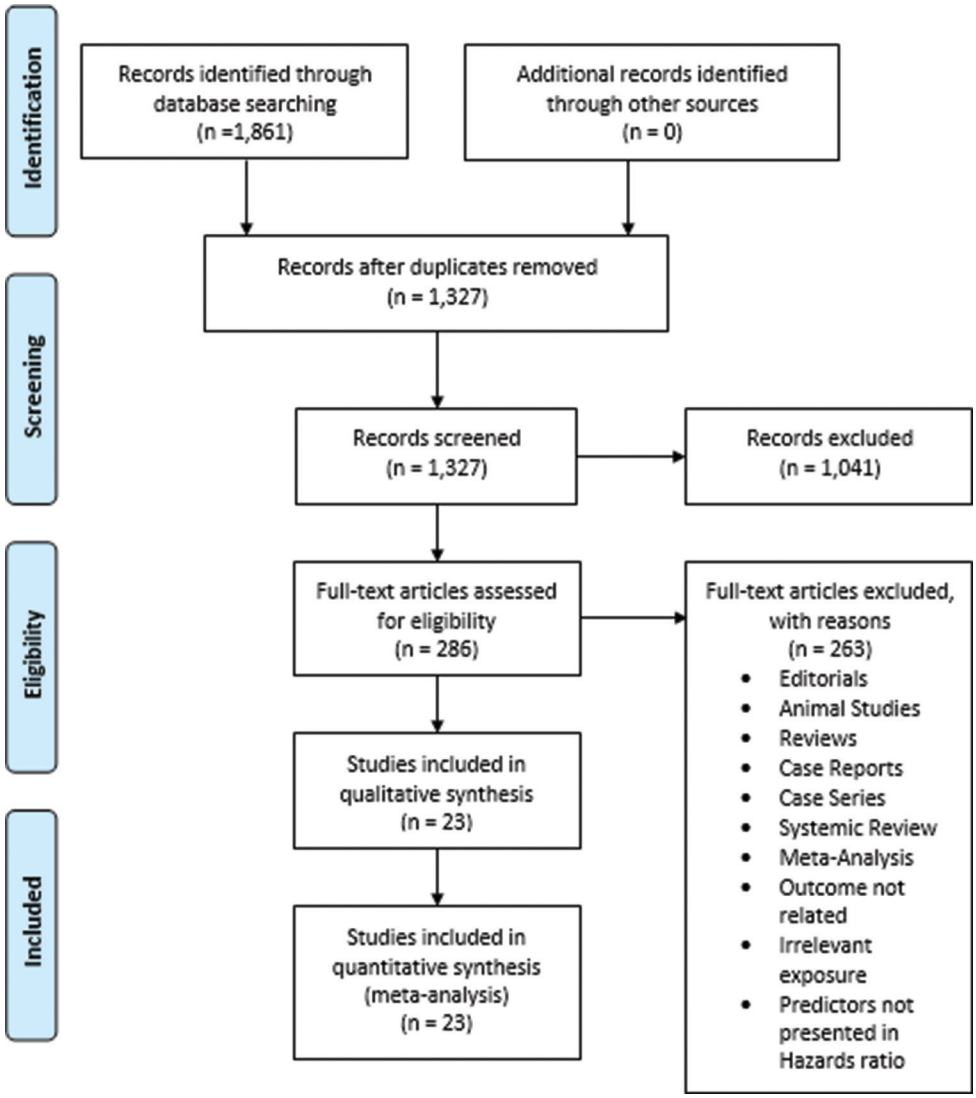

Figure 1: Prisma Flow chart

and one from Iran. Average age from these studies was 50.31 years.

Publication bias and quality assessment

As a symmetric funnel plot is seen so there is no publication bias (Figure 2). All studies have low risk of bias.

Results of meta-analysis

Detailed forest plot outlining the effect size of extension of resection (Figure 3), age (Figure 4), gender (Figure 5), pre-operative KPS (Figure 6), and tumor volume (Figure 7) is provided in the manuscript.

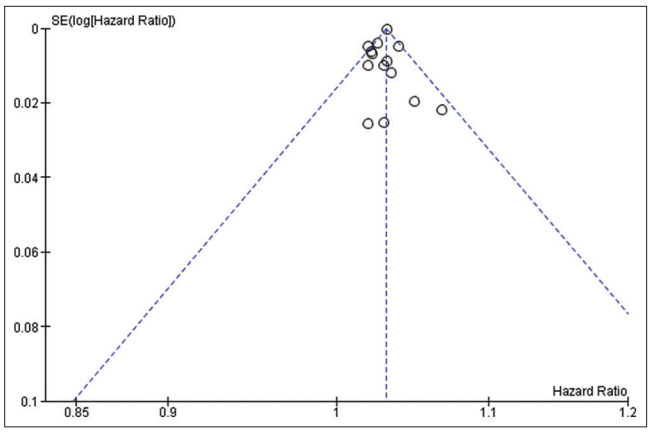

Figure 2: Funnel plot

Effect of extent of resection of surgery in prognosis of glioblastoma multiforme patients

The pooled results from ten studies [16], [17], [18], [19], [20], [21], [22], [23], [24], [25] showed statistically significant ratio of survival when there was increase in EOR (HR= 0.90 [0.86, 0.95]; p< 0.0001; I^2= 96%).

Effect of age in prognosis of glioblastoma multiforme patients after surgery

The pooled results from 14 studies [14], [15], [16], [17], [18], [19], [20], [21], [23] [26], [27], [28], [29],

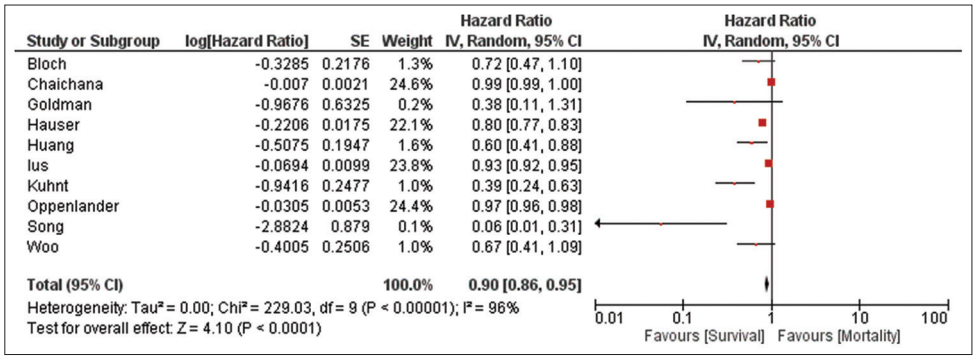

Figure 3: Forest plot outlining effect size of extent of resection

[30], showed a statistically significant ratio of mortality when there was increase in age (HR= 1.03 [1.03, 1.03]; p < 0.00001; I^2 = 30%).

Effect of gender in prognosis of glioblastoma multiforme patients after surgery

The pooled results from four studies [14], [28], [31], [32] showed a statistically significant ratio of mortality in female as compared to males (HR= 1.19 [1.06, 1.34]; p = 0.002; I^2= 0%).

Effect of pre-operative KPS in prognosis of glioblastoma multiforme patients after surgery

The pooled results from 11 studies [14], [15], [16], [17], [18], [23], [27], [31], [33], [34], [35] showed statistically significant ratio of survival with decreased pre-operative KPS (HR = 0.97 [0.95, 0.99]; p = 0.003; I^2 = 90%).

Effect of tumor volume in prognosis of glioblastoma multiforme patients after surgery

The pooled results for effect of tumor volume in prognosis of GBM patients after surgery were taken from three studies [30], [34], [36]. Subgroup analysis was done based on the pre-operative or post-operative readings. Pooled analysis of pre-operative tumor volume showed statistically non-significant relation with prognosis of GBM patient (HR= 1.01 [0.85, 1.20]; p = 0.91; I^2= 9%). Statistically non-significant relation with prognosis of GBM patient was seen in post-operative tumor volume as well (HR= 1.14 [0.93, 1.39]; p = 0.20; I^2 = 73%). Overall, the result showed statistically non-significant relation of tumor volume with prognosis (HR= 1.05 [1.00, 1.10]; p = 0.05; I^2= 55%).

Sensitivity analysis

A sensitivity analysis was conducted to assess the influence of each study on the overall effect by excluding one study at a time, followed by the generation of pooled Hazard Ratio (HR) for the rest of the studies. No significant change was observed after the exclusion of any individual study, suggesting the results were robust.

Discussion

Despite the low incidence in the general population, GBM is challenging to manage for health care systems around the world. Even with the best current multidisciplinary treatment, GBM owes an ominous prognosis, the average survival

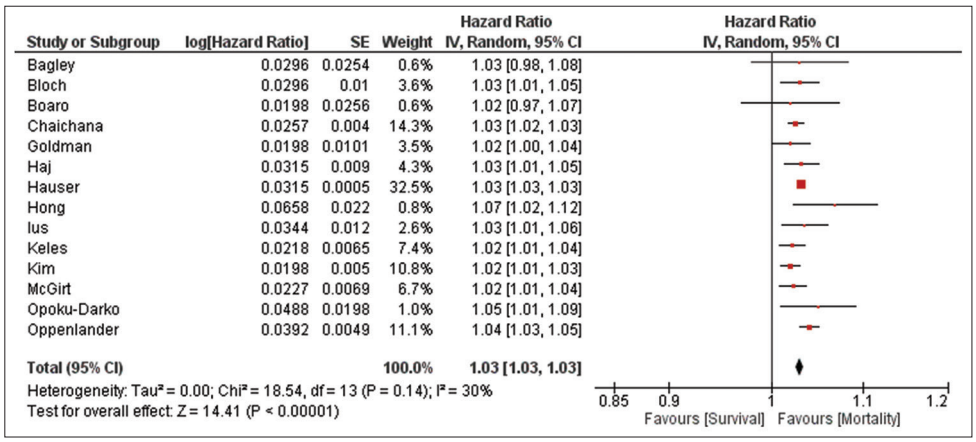

Figure 4: Forest plot outlining effect size of age

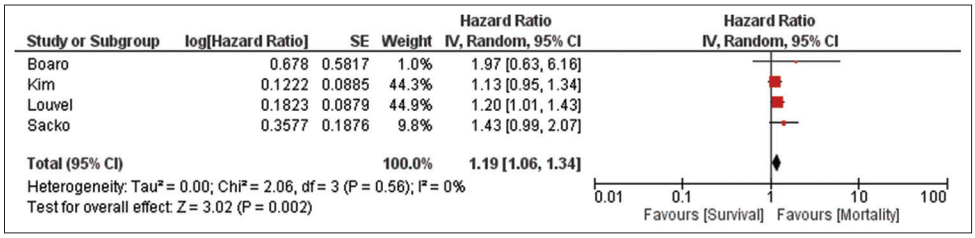

Figure 5: Forest plot outlining effect size of gender

after diagnosis is only 14 months [37]. The standard treatment for GBM is multidisciplinary evaluation, and surgical intervention with maximal safe resection, followed by radiation therapy and concomitant adjuvant chemotherapy [38].

Brown *et al*. found the effects on survival after tumor resection, reported that gross total resection improves overall and progression-free survival more significantly than subtotal resection [11]. Similar results for survival were reported by Li *et al*. [39]. However, no meta-analysis reported results regarding predictor factors of post-surgical effects on survival and mortality in GBM patients. The results of our meta-analysis suggested that post-resection mortality is associated with age, EOR, gender, and KPS score. However, the volume of the tumor does not affect mortality.

Age is a negative prognostic indicator, therefore, an important consideration in GBM treatment. A surveillance epidemiology and end result population analytic study reported a statistically significant decrease in survival with every year increase in patient age [40]. Brodbelt *et al*. found median survival rate dropping from 12 to 18 months to 3 to 6 months, from a younger age to older age groups [41]. Results of our analysis suggested that increasing age is responsible for the high rate of mortality. Out of 14 studies reporting data on age, only two studies showed non-significant effects on mortality. According to Bagley *et al*., the reason for the non-significant effects of age and extent of surgical resection on mortality was related to their limited sample size or inherent differences in the patient population. In contrast, other included studies showed a significant effects of age on mortality. Hong *et al*. found that 51 years of age is the cutoff value for overall survival and 55 years of age is cutoff for progression-free survival. The results of our analysis showed that even after the tumor resection, the increasing age is still a significant cause of mortality.

Unlike advancing age, the EOR plays an important role in improving survival. The purpose of the surgical resection is to remove the tumor as much as possible, alleviating the mass effect, to obtain brain tissue for the analysis of the pathology [42]. However, in 90% of cases, the tumor recurrence can occur within a 2-cm margin of the primary site [43]. A combination of techniques such as intraoperative MRI, ultrasonography, neuronavigation, and fluorescence-guided surgery enabled a safe and maximal resection. According to Manrique-Guzmán *et al*., despite after the maximal resection and chemoradiation, tumor recurrence can occur within 10 months, mediated by resident cancer stem cells [44]. However, Woo *et al*. concluded that since is not possible to achieve gross total resection in most cases, resulting in non-significant survival predicting properties of EOR, reducing the residual tumor volume with a cutoff threshold of 3.50 cc can improve overall survival, and therefore, can be a superior predictor than EOR. Song *et al*. showed results of GBM resection in children, they found that complete resection was the most significant prognostic factor; however, radial resection with temozolomide should be used as the initial treatment choice. On contrary to Woo *et al*., Kuhnt *et al*. found significant effects of EOR on survival, they postulated that the significant results were attained because of preservation of neurological function. In our study, the assessment of evidence from 11 cohorts showed a significant effect of EOR on predicting survival in GBM patients. Complete resection showed more significant survival. However, unlike EOR the tumor volume has no significant effect on predicting the mortality in GBM.

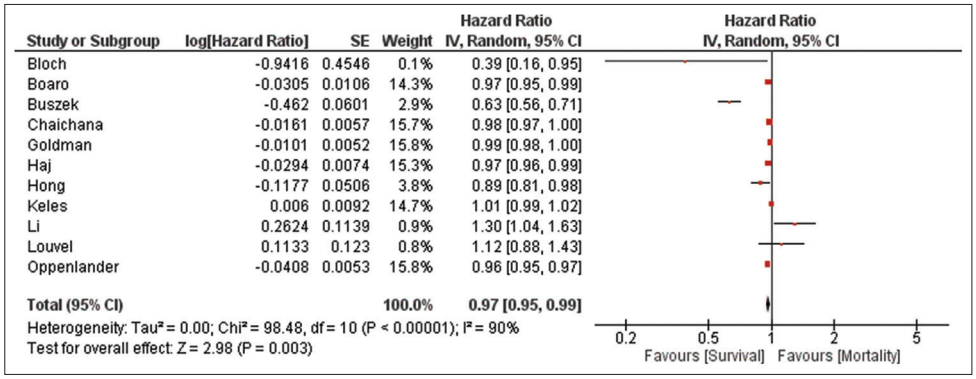

Figure 6: Forest plot outlining effect size of preoperative KPS

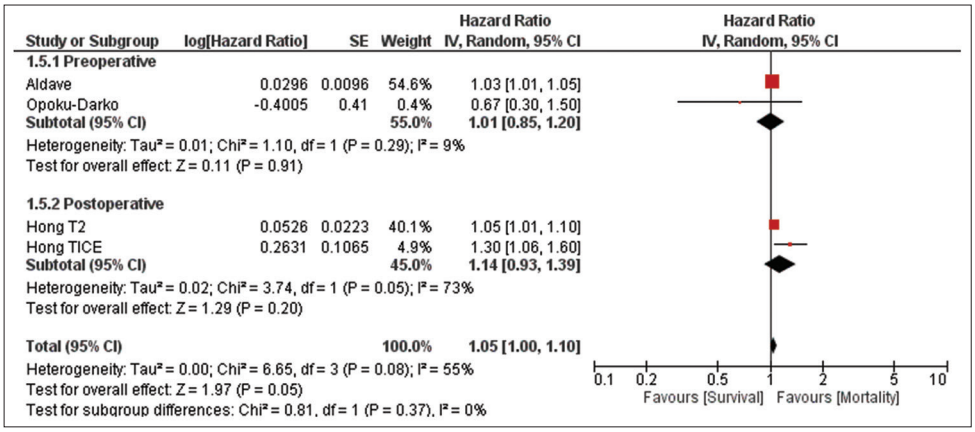

Figure 7: Forest plot outlining effect size of tumor volume

In several studies, a higher percentage of GBM in males is reported, with female to male ratio of 1 to 1.9 [45], [46]. However, the reason for sex disparities and the involvement of sex hormones in the pathophysiology of GBM is not well verified. Barone *et al*. found that the estrogen increased survival in an orthotopic model of glioblastoma, therefore, the estradiol-based study may be beneficial in treating GBM [47]. The high frequency of estrogen receptor methylation was observed in GBM, indicating that estrogen has protective effects on GBM [48]. Yu *et al*. discovered androgen receptor signaling can promote tumorigenesis of GBM in adult men through inhibiting transforming growth factor β receptor signaling [49]. A large study conducted by Tian *et al*. that gender influences GBM prognosis, compared to male patients they found that female patients have better post-surgical survival [50]. Similar results were established after the analysis of four studies, we found that male patients have a higher mortality risk than female patients.

The Karnofsky Performance Scale (KPS) score is a commonly used system to distinguish the patient prognosis and to determine the appropriate management in GBM [51], [52]. The low pre-operative KPS value is associated with shorter overall survival. Chambless *et al*. found that post-operative KPS score is a reliable predictor of survival in GBM patients [37]. The significant pre-operative KPS score suggested the reliability of the KPS score to predict survival.

Limitation

Our study is limited in several ways. First, there was one study that had patients of adolescent age. Second, all studies were cohort, and no randomized and controlled trials were found. Finally, high heterogeneity was observed in EOR and pre-operative KPS. These studies were pivotal in forming analysis, but more studies should be conducted.

Table 1: Basic characteristics of selected studies

Study	Year	Study design	Duration	Country	Total GBM patients (*n*)	Male (%)	Mean age (years)	Factors present	New Ottawa scale score
Keles *et al*., 2006	2006	Cohort	1994–2001	USA	102	53	51.67	Age and pre-operative KPS	8
Mcgirt *et al*., 2009	2009	Cohort	1996–2007	USA	949	59.3	50.3	Age	8
Song *et al*., 2010	2010	Cohort	1985–2007	Korea	27	51.8	8.33	Extent of resection	8
Kunht *et al*., 2011	2011	Cohort	2002–2008	Germany	135	57.7	59.3	Extent of resection	8
Bloch *et al*., 2012	2012	Cohort	2005–2009	USA	107	47.2	53.6	Age, extent of resection, and pre-operative KPS	9
Ius *et al*., 2012	2012	Cohort	June 1998–May 2011	Italy	190	58.4	N/A*	Age and extent of resection	8
Aldave *et al*., 2013	2013	Cohort	August 2007–December 2011	Spain	52	55.6	58.7	Tumor volume	9
Oppenlander *et al*., 2014	2014	Cohort	2001–2011	USA	170	61.8	55.2	Age, extent of resection, and pre-operative KPS	9
Chaichana *et al*., 2014	2014	Cohort	January 2007–July 2012	USA	336	61	60.5	Age, extent of resection, and pre-operative KPS	9
Li *et al*., 2016	2016	Cohort	June 1993–December 2012	USA	1229	62	55.7	Pre-operative KPS	9
Louvel *et al*., 2016	2016	Cohort	2005–2011	France	692	33.3	N/A*	Gender and pre-operative KPS	8
Opoku-darko *et al*., 2017	2017	Cohort	2004–2016	Canada	29	62	59.8	Age and tumor volume	9
Haj *et al*., 2017	2017	Cohort	2005–2013	Germany	149	55.1	61.8	Age and pre-operative KPS	9
Hauser *et al*., 2018	2018	Cohort	2004–2013	USA	89,839	57.3	N/A*	Age and extent of resection	9
Goldman *et al*., 2018	2018	Cohort	January 2005–December 2014	USA	163	68	55.13	Age, extent of resection, and pre-operative KPS	8
Bagley *et al*., 2019	2019	Cohort	January 2013–December 2016	USA	37	68	61	Age	8
Woo *et al*., 2019	2019	Cohort	January 2009–December 2014	China	147	61	53	Extent of resection	8
Buszek *et al*., 2020	2020	Cohort	2004–2015	USA	45942	59	56.33	Pre-operative KPS	9
Kim *et al*., 2020	2020	Cohort	2006–2016	Korea	837	56.5	55.3	Age and gender	9
Hong *et al*., 2020	2020	Cohort	2000–2013	Korea	113	56.6	46.67	Age, pre-operative KPS, and tumor volume	9
Huang *et al*., 2020	2020	Cohort	March 2006–May 2018	Iran	171	66	41.33	Extent of resection	8
Sacko *et al*., 2021	2021	Cohort	January 2008–2013	France	157	65.6	62.5	Gender	9

KPS: Karnofsky Performance Status, GBM: Glioblastoma multiforme, N/A: Not available.

Conclusion

The results of our meta-analysis suggested that age, gender, pre-operative KPS score, and EOR have significant effects on the post-surgical mortality rate; therefore, these factors can be used significant predictor of mortality in GBM patients. Males, elder patients, and with lower pre-operative KPS score have high mortality risk after surgery. Complete resection of tumor decreases the risk of mortality. However, the pre-operative tumor volume has no effects on mortality.

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Supplement Tables

Supplement Table 1: Search string

Search engine	Search strategy
Pubmed/Medline	(“astrocytoma”[MeSH Terms] OR “astrocytoma”[All Fields] OR “astrocytomas”[All Fields] OR ((“cystic””[All Fields] OR “cystical”[All Fields] OR “cystically”[All Fields] OR “cystics”[All Fields]) AND (“astrocytoma”[MeSH Terms] OR “astrocytoma”[All Fields] OR “astrocytomas”[All Fields])) OR (“glioblastoma”[MeSH Terms] OR “glioblastoma”[All Fields] OR (“glioblastoma”[All Fields] AND “multiforme”[All Fields]) OR “glioblastoma multiforme”[All Fields]) OR (“glioblastoma”[MeSH Terms] OR “glioblastoma”[All Fields] OR (“grade”[All Fields] AND “iv”[All Fields] AND “astrocytoma”[All Fields]) OR “Grade IV astrocytoma”[All Fields])) AND (“resect”[All Fields] OR “resectability”[All Fields] OR “resectable”[All Fields] OR “resectates”[All Fields] OR “resected”[All Fields] OR “resecting”[All Fields] OR “resection”[All Fields] OR “resectional”[All Fields] OR “resectioned”[All Fields] OR “resectioning”[All Fields] OR “resections”[All Fields] OR “resective”[All Fields] OR “resects”[All Fields] OR ((“surgical procedures, operative”[MeSH Terms] OR (“surgical”[All Fields] AND “procedures”[All Fields] AND “operative”[All Fields]) OR “operative surgical procedures”[All Fields] OR “surgical”[All Fields] OR “surgically”[All Fields] OR “surgicals”[All Fields]) AND (“process”[All Fields] OR “processe”[All Fields] OR “processed”[All Fields] OR “processes”[All Fields] OR “processing”[All Fields] OR “processings”[All Fields])) OR (“operability”[All Fields] OR “operable”[All Fields] OR “operate”[All Fields] OR “operated”[All Fields] OR “operates”[All Fields] OR “operating”[All Fields] OR “operations”[All Fields] OR “operational”[All Fields] OR “operative”[All Fields] OR “operatively”[All Fields] OR “operatives”[All Fields] OR “operator”[All Fields] OR “operators”[All Fields] OR “operators”[All Fields] OR “surgery”[MeSH Subheading] OR “surgery”[All Fields] OR “operations”[All Fields] OR “surgical procedures, operative”[MeSH Terms] OR (“surgical”[All Fields] AND “procedures”[All Fields] AND “operative”[All Fields]) OR “operative surgical procedures”[All Fields] OR “operation”[All Fields])) AND (“extent”[All Fields] OR “extents”[All Fields])
Google Scholar	(Astrocytoma OR Cystic astrocytoma OR Glioblastoma multiforme OR grade IV astrocytoma) AND (resection OR surgical process OR operation) AND (extent)
Cochrane	(Astrocytoma OR Cystic astrocytoma OR Glioblastoma multiforme OR Grade IV astrocytoma) AND (resection OR surgical process OR operation) AND (extent)

Supplement Table 2: Quality assessment of cohorts using New Ottawa Scale

Studies	Selection (maximum 4)				Comparability (maximum 2)	Outcome (maximum 3)			Total score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Keles *et al*., 2006	1	0	1	1	2	1	1	1	8
Mcgirt *et al*., 2009	1	0	1	1	2	1	1	1	8
Song *et al*., 2010	1	0	1	1	2	1	1	1	8
Kunht *et al*., 2011	1	0	1	1	2	1	1	1	8
Bloch *et al*., 2012	1	1	1	1	2	1	1	1	9
Ius *et al*., 2012	1	0	1	1	2	1	1	1	8
Aldave *et al*., 2013	1	1	1	1	2	1	1	1	9
Oppenlander *et al*., 2014	1	1	1	1	2	1	1	1	9
Chaichana *et al*., 2014	1	1	1	1	2	1	1	1	9
Li *et al*., 2016	1	1	1	1	2	1	1	1	9
Louvel *et al*., 2016	1	0	1	1	2	1	1	1	8
Opoku-darko *et al*., 2017	1	1	1	1	2	1	1	1	9
Haj *et al*., 2017	1	1	1	1	2	1	1	1	9
Hauser *et al*., 2018	1	1	1	1	2	1	1	1	9
Goldman *et al*., 2018	1	0	1	1	2	1	1	1	8
Bagley *et al*., 2019	1	0	1	1	2	1	1	1	8
Woo *et al*., 2019	1	0	1	1	2	1	1	1	8
Buszek *et al*., 2020	1	1	1	1	2	1	1	1	9
Kim *et al*., 2020	1	1	1	1	2	1	1	1	9
Hong *et al*., 2020	1	1	1	1	2	1	1	1	9
Huang *et al*., 2020	1	0	1	1	2	1	1	1	8
Sacko *et al*., 2021	1	1	1	1	2	1	1	1	9
Boaro *et al*., 2021	1	1	1	1	2	1	1	1	9