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Review

Prognostic factors and survival of recurrent glioblastoma: a systematic review

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Abstract

Introduction: Glioblastoma is a highly aggressive brain cancer with poor prognosis. Recurrence is common, and survival post-recurrence is limited. Identifying prognostic factors for recurrent glioblastoma can optimize treatment and improve outcomes.

Aim: This systematic review analyzed the clinical, molecular, and treatment-related variables that influence survival in patients with recurrent glioblastoma.

Materials and methods: A comprehensive search of PubMed, Scopus, and ProQuest databases included studies from the past decade, assessed using the Newcastle-Ottawa Scale (NOS).

Results: Sixteen studies were analyzed, highlighting age, Karnofsky Performance Status (KPS), molecular markers (MGMT promoter methylation, IDH mutations, TERT promoter mutations, TP53 alterations, ATRX loss, and Ki-67 expression), and surgical resection extent as key prognostic factors. Younger patients with higher KPS scores and favorable molecular markers had better survival. Molecular profiling and maximal resection correlated with improved overall survival (OS). Salvage therapies like chemotherapy and re-resection provided marginal benefits, with variability based on patient demographics and tumor genetics.

Conclusion: Age, KPS, molecular markers, and surgical resection extent significantly predict survival in recurrent glioblastoma. The review underscores the importance of molecular profiling for personalized treatment, though current salvage therapies show limited effectiveness. Innovative approaches are needed to enhance outcomes for this aggressive disease.

Abbreviations used in the article: BSC: best supportive care; **CRE:** complete resection of enhancing tumor; **DFS:** disease-free survival; **GBM:** glioblastoma; **GTR:** gross total resection; **KPS:** Karnofsky Performance Status; **NOS:** Newcastle-Ottawa Scale; **OS:** overall survival; **PFS:** progression-free survival; **rGBM:** recurrent glioblastoma multiforme; **RTOG–RPA:** Radiation Therapy Oncology Group – Recursive Partitioning Analysis; **TTF:** tumor-treating fields

Keywords

glioblastoma, recurrent glioblastoma, prognostic factors, survival, molecular markers

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Introduction

Glioblastoma is one of the most aggressive and lethal forms of brain cancer and is characterized by rapid proliferation and invasive behavior. Despite advances in medical treatments, the prognosis for patients diagnosed with glioblastoma is dismal, with a median survival of 12 to 15 months.[1] Even with surgery, radiation therapy, and chemotherapy, recurrence is nearly inevitable, further complicating disease management. The challenge of recurrent glioblastoma highlights the urgent need to identify factors that can improve patient outcomes and guide personalized treatment strategies.[2]

Recurrent glioblastoma refers to the return of the tumor after the initial therapy and often exhibits greater resistance to standard treatments. By identifying these factors, clinicians can tailor their therapeutic approaches to enhance patient survival and quality of life.[1] Several prognostic variables have been proposed in the context of recurrent glioblastoma, including patient demographics (age), Karnofsky Performance Status (KPS), tumor genetics (MGMT promoter methylation, IDH mutations), extent of resection, response to salvage therapies, and the time between initial treatment and recurrence (progression-free survival). Each of these factors plays a critical role in determining patient outcomes and in guiding treatment decisions.[2]

Prognostic variables play a crucial role in assessing outcomes for patients with recurrent glioblastoma. Patient demographics, particularly age, are significant, as younger individuals generally exhibit better survival outcomes. Karnofsky Performance Status (KPS) is another critical factor, with higher scores correlating with improved prognosis and better tolerance of salvage therapies.[3] Additionally, tumor genetics, such as MGMT promoter methylation and IDH mutations, have been extensively studied. MGMT methylation is associated with a more favorable response to alkylating agents like temozolomide, whereas IDH mutations are indicative of a better overall prognosis, despite being less common in recurrent GBM cases.[4,5] Tumor proliferation markers, such as Ki-67, further refine prognosis, as higher Ki-67 labeling indices are associated with increased tumor aggressiveness and lower survival rates.[6] Additionally, TERT promoter mutations are linked to worse prognosis and more aggressive tumor phenotypes, often in combination with ATRX and TP53 mutations, which further impact tumor biology and therapeutic resistance.[7]

The extent of resection at the time of recurrence significantly influences survival outcomes, with maximum resection typically leading to longer progression-free and overall survival compared to subtotal resection.[8] However, repeated surgical interventions must be weighed against potential morbidity. Additionally, the response to salvage therapies, including re-irradiation, bevacizumab, and targeted molecular therapies, varies among patients based on genetic and clinical factors. Studies indicate that MGMT-methylated and IDH-mutant tumors respond better to salvage treatments, further underlining the importance of genetic profiling in treatment selection.[9]

Another essential prognostic factor is the time between initial treatment and recurrence, also known as progression-free survival (PFS). A longer PFS before recurrence often suggests a more indolent tumor biology and better response to subsequent therapies.[10] In contrast, patients with early recurrence tend to have a more aggressive disease course and poorer survival outcomes. Given the complex interplay of these variables, personalized treatment approaches incorporating patient-specific genetic and clinical characteristics are essential to optimizing outcomes for recurrent GBM patients.[11]

In summary, recurrent glioblastoma presents a formidable challenge in terms of both prognosis and treatment. Understanding the complex interplay between clinical, molecular, and therapeutic factors is essential to improve patient outcomes and guide treatment decisions. Although significant progress has been made, more research is needed to clarify these relationships and to develop personalized and effective treatment strategies. Ongoing advancements in molecular profiling and the development of novel therapies offer hope for the better management of this devastating disease.

Materials and methods

Methods

In this systematic review, a comprehensive literature search was performed using the PubMed, Scopus, and ProQuest databases to gather studies on prognostic factors and survival outcomes in recurrent glioblastoma published in the last decade. Studies were included on the basis of specific criteria that focused on the role of clinical, molecular, and treatment-related prognostic factors in recurrent GBM. Two independent reviewers performed data extraction to ensure consistency and mitigate bias. The quality and risk of bias of each study were assessed using standardized tools such as the Newcastle-Ottawa Scale, ensuring rigorous evaluation.

Search strategy

The search strategy for this systematic review of prognostic factors and survival of patients with recurrent glioblastoma was designed to ensure thorough and comprehensive identification of relevant literature. A structured query was applied across multiple electronic databases including PubMed, Scopus, and ProQuest. To optimize the search, a combination of keywords and Medical Subject Headings (MeSH) terms, such as "recurrent glioblastoma," "prognostic factors," "survival," and "outcome," were used. Boolean operators (AND, OR) helped to refine the search scope. The review was restricted to English-language articles published in the last 10 years to maintain relevance and timeliness.

Inclusion and exclusion criteria

The inclusion criteria for this systematic review of prognostic factors and survival of patients with recurrent glioblastoma were carefully defined to focus on studies that specifically explored the clinical, molecular, and treatment-related prognostic factors in adult patients (18 years and older) with recurrent glioblastoma. To maintain relevance and rigor, eligible studies had to be published in peer-reviewed journals within the last 10 years and written in English. Additionally, they reported survival outcomes such as overall survival (OS) and progression-free survival (PFS), ensuring that the review captured meaningful clinical data on patient outcomes.

Studies were excluded based on criteria such as failing to meet scientific and methodological standards, case reports or reviews, lacking survival data, involving non-human subjects, or focusing solely on primary glioblastoma without recurrence. Additionally, studies with insufficient sample sizes or methodological rigor were excluded. These criteria ensured that the review included only high-quality studies relevant to the analysis of the prognostic factors for recurrent glioblastoma.

Study selections

This systematic review of prognostic factors and survival in patients with recurrent glioblastoma employed a two-stage screening process to ensure unbiased study inclusion. Initially, two researchers independently reviewed titles and abstracts by applying predefined criteria to filter out ineligible studies. Subsequently, the full text of the remaining articles was evaluated to confirm their eligibility. Discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer. This method ensured a comprehensive and unbiased selection, minimized the risk of overlooking relevant studies, and enhanced the reliability of the review.

Results

List of article publication

The flowchart illustrates the process of study identification, screening, eligibility assessment, and inclusion in a systematic review of the prognostic factors and survival of patients with recurrent glioblastoma. It begins with the identification phase, in which 1,128 records were sourced from three databases: PubMed (1,095), Scopus (29), and ProQuest (4). Of these, 1,102 duplicate or ineligible records were removed before screening. Next, 26 records were screened for relevance, and 14 were excluded based on the predefined criteria. The remaining 12 reports were sought for retrieval, although one was not. Of the 13 reports assessed for eligibility, one was excluded because it was a book review, and the other was excluded as a non-scientific review **(Fig. 1)**.

Finally, 11 studies were deemed eligible and were included in the systematic review. These studies provided a basis for analyzing the prognostic factors and survival outcomes in patients with recurrent glioblastoma. This process ensured rigorous selection of relevant studies, enhancing the reliability and accuracy of the findings of the systematic review.

Fu et al.[2], in their retrospective cohort study of 126 patients with recurrent glioma and radionecrosis, show that the two most significant prognostic factors influencing overall survival were the World Health Organization (WHO) grade of the tumor and the percentage of gliosis. Using a nomogram prediction model, they demonstrated that patients with lower WHO grades and higher gliosis percentage had better survival outcomes. The model effectively stratified patients into high- and low-risk groups based on these factors, providing a tool for predicting 2- and 3-year survival probabilities. These findings align with broader research on recurrent glioblastoma, in which factors such as tumor grade and gliosis have been associated with survival, underscoring their relevance in clinical prognosis.[2]

Van Linde et al.[12] conducted a retrospective multicenter analysis of 299 patients with recurrent glioblastoma multiforme (rGBM) from two Dutch centers to evaluate the efficacy of different treatment strategies. They compared systemic treatment (SYST), re-resection (SURG), re-irradiation (RT), and best supportive care (BSC). Their findings indicated that patients receiving SYST or SURG had significantly longer overall survival compared to those receiving BSC. The median survival was 6.5 months for all patients, with better outcomes in the SYST and SURG groups. This analysis aligns with broader research on prognostic factors and survival in recurrent glioblastoma, underscoring the importance of treatment modality, age, and performance status as key factors influencing survival.[12]

Audureau et al.[13] conducted a retrospective multicenter study to evaluate prognostic factors for survival in adult patients with recurrent glioblastoma using decision-tree-based models. They analyzed data from 407 patients in the training set and 370 in the validation set. Key factors affecting survival include age, Karnofsky Performance Status, Radiation Therapy Oncology Group – Recursive Partitioning Analysis (RTOG–RPA) class, surgical resection, and chemotherapy at progression. The study highlighted that KPS at progression was the strongest predictor of overall survival, with higher KPS scores correlating with better outcomes. These findings align with broader research on prognostic factors in recurrent glioblastoma, emphasizing the importance of patient performance status and timely surgical and chemotherapy interventions for prolonging survival.[13]

Jilla et al.[14] conducted a retrospective study of 46 patients with glioblastoma treated at a tertiary care hospital to assess the impact of various prognostic factors on survival outcomes. The study identified that younger age at presentation (≤45 years) and administration of six or more cycles of adjuvant temozolomide chemotherapy were associated with improved overall survival and disease-free survival (DFS).

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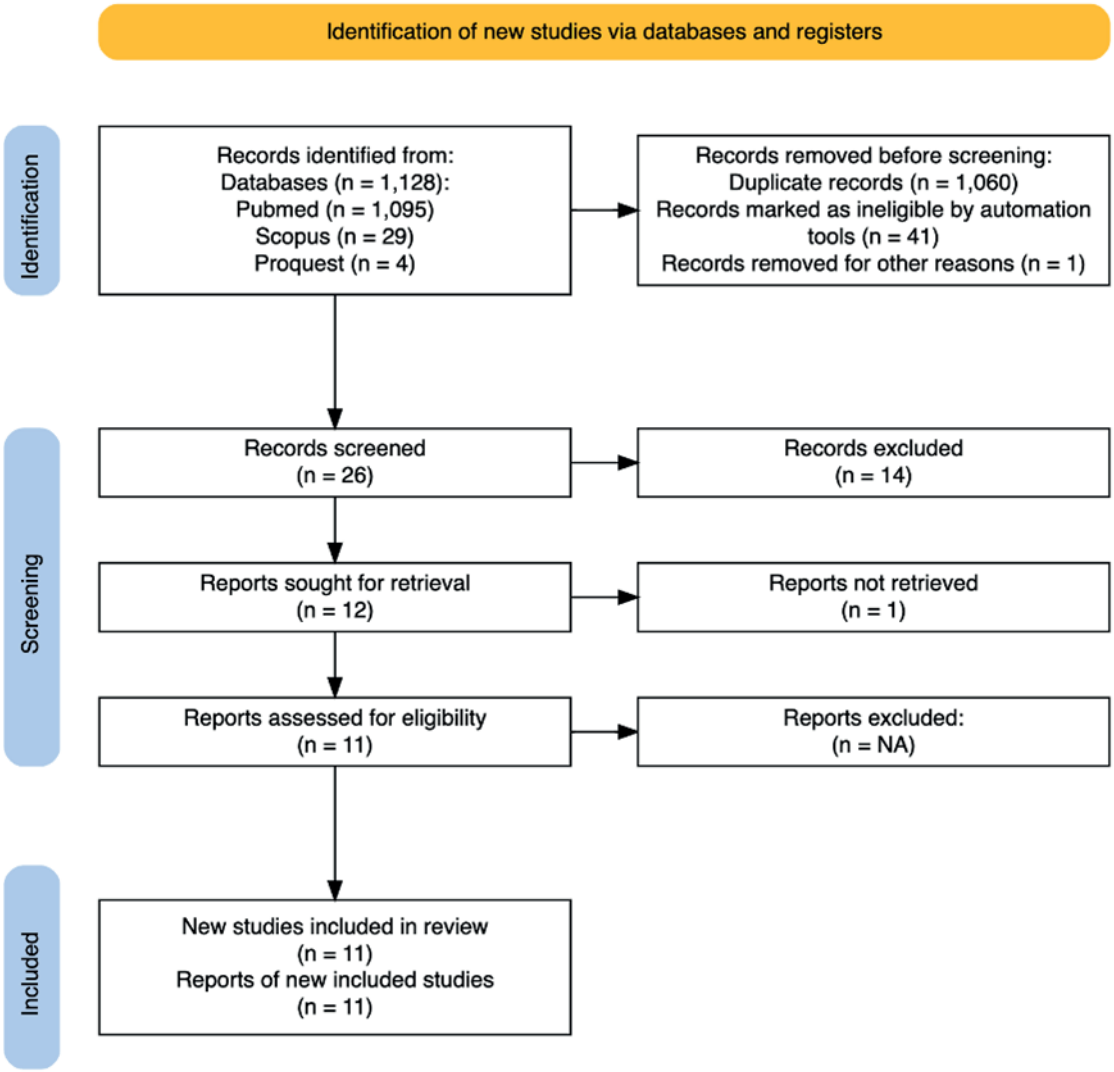

Figure 1. Prisma flow diagram.

Additionally, the use of the antiepileptic drug levetiracetam had a statistically significant positive effect on DFS. These findings align with the broader body of research on prognostic factors for recurrent glioblastoma, particularly emphasizing the importance of age, chemotherapy cycles, and specific supportive treatments for enhancing survival.[14]

Brown et al.[15] showed that their retrospective cohort study of 490 patients with glioblastoma revealed key prognostic factors associated with longer survival. This study found that younger age, MGMT promoter methylation, and debulking surgery are independently associated with improved survival outcomes. Patients who received standard chemoradiotherapy after surgery had a median survival of 16.9 months compared to 9.2 months for non-standard therapies and only 2.0 months for those who received no further therapy. These findings align with research on prognostic factors in recurrent glioblastoma, where factors such as age, molecular markers, and the extent of surgical resection play significant roles in determining patient survival.[15]

Vaz-Salgado et al.[16] reviewed the treatment options for recurrent glioblastoma and highlighted the complexity and lack of a standardized treatment approach in this challenging clinical scenario. This study discusses multiple treatment modalities, including surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapies such as bevacizumab, emphasizing that factors such as patient age, Karnofsky Performance Status, tumor size, and extent of resection significantly impact survival outcomes. This review aligns with a broader understanding of prognostic factors in recurrent glioblastoma, in which individualized treatment plans based on these factors are critical for optimizing survival and quality of life.[16]

Fekete et al.[17] conducted a population-based study of 222 glioblastoma patients treated at Sahlgrenska Univer-

sity Hospital and identified several key prognostic factors influencing survival outcomes. These included age, MGMT promoter methylation, WHO performance status, and the extent of tumor resection (CRET). Patients with hypermethylated MGMT and a better performance status showed longer overall survival, with a median survival of 1.07 years (12.8 months). These findings align with broader research on prognostic factors in recurrent glioblastoma, where tumor genetics, patient condition, and completeness of tumor removal are consistently highlighted as critical determinants of survival.[17]

In their retrospective cohort study of 66 patients with recurrent glioblastoma, Hansen et al.[18] identified several prognostic factors that had a substantial impact on postoperative survival following repeat surgery. Key factors included KPS <70, tumor volume ≥50 cm^3, ependymal involvement, age, and Ki-67 proliferation index. These factors were strongly associated with decreased survival, with a KPS of <70 being particularly impactful. This study also validated a New Scale for Recurrent Glioblastoma Surgery (NSGS) to stratify patients into prognostic groups, reinforcing the importance of these clinical variables for predicting survival. These findings align with broader research on prognostic factors in recurrent glioblastoma, in which patient performance status and tumor characteristics are critical determinants of survival.[18]

Karschnia et al.[19] showed that in a retrospective cohort study of 681 patients with recurrent glioblastoma, re-resection was significantly associated with improved survival outcomes, particularly when the residual contrast-enhancing (CE) tumor volume was ≤1 cm^3. Using the RANO classification, the patients were stratified into prognostic groups based on the extent of resection. Patients with maximal CE resection had a median overall survival (OS) of 12 months compared to 9 months for those with submaximal resection. These findings align with research on prognostic factors in recurrent glioblastoma, highlighting that maximally safe resection and postoperative chemoradiation are the key determinants of survival.[19]

Blakstad et al.[20] showed that several prognostic factors were significantly associated with OS in a retrospective cohort study of 467 glioblastoma patients. Key factors included age, MGMT promoter methylation, tumor location, and extent of surgical resection. Patients younger than 60 years with hypermethylated MGMT, left-hemispheric tumors, and those who underwent gross total resection (GTR) had longer survival outcomes. The study found that median overall survival (OS) was 12.1 months, with patients who received the Stupp regimen having a median OS of 16.1 months. These findings align with existing research on recurrent glioblastoma, in which factors such as patient age, genetic markers, and tumor location are critical determinants of survival.[20]

Schaub et al.[21] conducted a retrospective cohort study of 174 patients with recurrent glioblastoma treated with bevacizumab evaluating the key prognostic factors influencing survival. Karnofsky Performance Status, number of prior recurrences, and number of prior chemotherapies were found to significantly impact the overall survival of patients. The combination of BEV with irinotecan was associated with better outcomes, with patients achieving a median OS of 11.3 months compared to 7.0 months for BEV monotherapy. These findings align with research on prognostic factors in recurrent glioblastoma, highlighting the critical role of KPS and treatment combinations in determining survival outcomes.[21]

Study characteristics

Clinical studies on recurrent glioblastoma, summarized in **Table 1**, have highlighted a range of prognostic factors and treatment outcomes across diverse patient populations. Common variables identified as significant predictors of survival include age, Karnofsky Performance Status, tumor grade, extent of surgical resection, and molecular markers such as MGMT promoter methylation and IDH mutations.

Fu et al.[2] and Wong et al.[32] emphasized the importance of tumor histology and patient performance status in predicting the overall survival. Their findings indicated that younger patients, those with higher KPS scores, and those who underwent more aggressive surgical resection tended to have better outcomes. These observations align with broader research, reinforcing the need for personalized treatment approaches based on both clinical and genetic characteristics.[2]

Several other studies, including those by Van Linde et al.[12] and Hansen et al.[18], have focused on the effectiveness of different treatment modalities such as systemic chemotherapy, re-resection, and re-irradiation. These studies demonstrate that patients who undergo more extensive surgical resections or receive combined therapies often experience improved OS compared to those treated with best supportive care or less aggressive interventions.[12,18]

Moreover, studies by Brown et al.[15] and Schaub et al.[21] revealed that molecular markers (e.g., MGMT methylation) and the use of advanced therapies, such as bevacizumab, significantly influence survival outcomes. These findings underscore the growing role of precision medicine in the management of recurrent glioblastoma, as treatments tailored to the molecular profiles of patients increasingly show promise in extending survival and improving quality of life.[15,21]

Impact of patient demographics and performance status on survival

In studies on recurrent glioblastoma, patient demographics, particularly age and Karnofsky Performance Status, are consistently identified as critical factors influencing survival outcomes. For instance, Fu et al. underscore the importance of these variables, showing that younger patients and those with higher KPS scores typically experience longer overall survival. Fu et al. also highlighted the prognostic value of additional factors such as tumor grade and gliosis

Table 1. Characteristics of the clinical studies

Author (year, country)	Study design	Sample size, age range	Intervention/ Procedure	Follow-up duration	Outcome measures	Main findings
Fu et al.[2], (2024, China)	Retrospective cohort study	126 patients, median age: 49.27 years	WHO grade, gliosis percentage, MGMT methylation status	Surgery, radiotherapy, chemotherapy	Median OS: 838.36 days (approx. 2.3 years)	At least 2 years
Van Linde et al.[12], (2017, Netherlands)	Retrospective multicenter study	299 patients, median age: 59 years (range: 19-77)	Age, tumor extent, extent of initial resection, steroid use, KPS	Systemic treatment, re-resection, re-irradiation, BSC	Median OS: 6.5 months (overall), 11 months for SURG	10 years
Audureau et al.[13], (2017, France)	Retrospective multicenter study	407 patients (training set), median age: 58 years	Age, KPS, RTOG–RPA classes, surgical resection, chemotherapy	Surgical resection, chemotherapy, radiotherapy, best supportive care	Median OS from progression: 7.6 months	Not specified
Jilla et al.[14], (2022, India)	Retrospective, single-institutional study	46 patients, mean age: 48.5 years (range: 21–76)	Age, adjuvant chemotherapy, anti-epileptic drugs	Surgery, radiotherapy, chemotherapy (temozolomide)	1-year OS: 36.9%, 2-year OS: 10.8%, Median OS: 8 months	Not specified
Brown et al.[15], (2022, UK)	Retrospective cohort study	490 patients, median age: 59 years	Age, MGMT promotor methylation, IDH mutation	Surgery, radiotherapy, chemotherapy (temozolomide)	Median OS: 9.2 months (range: 7.9–10.3 months)	Not specified
Vaz-Salgado et al.[16], (2023, Spain)	Retrospective review	Not specified, median age: > 65 years	Age, KPS, tumor size, extent of resection	Surgery, radiotherapy, chemotherapy, immunotherapy, bevacizumab	Median OS: 14 months (initial treatment); <1 year (recurrence)	Not specified
Fekete et al.[17], (2023, Sweden)	Retrospective cohort study	222 patients, median age: 64 years	Age, MGMT promoter methylation, WHO performance status	Surgery (CRET), Radiotherapy, Chemotherapy (TMZ)	Median OS: 1.07 years (12.8 months)	Until June 2018
Hansen et al.[18], (2024, Denmark)	Retrospective cohort study	66 patients, median age: 62 years	KPS <70, Ki-67, ependymal involvement, tumor volume ≧50 cm^3	Surgery, chemotherapy, radiotherapy	Median OS: 335 days after second surgery	Until November 2020
Karschnia et al.[19], (2023, USA & Germany)	Retrospective cohort study	681 patients, median age: 58.8 years	Age, KPS, MGMT methylation, tumor volume	Surgery (re-resection), chemotherapy, radiotherapy	Median OS: 11 months (re-resection), 7 months (no re-resection)	Until death or loss to follow-up
Blakstad et al.[20], (2023, Norway)	Retrospective cohort study	467 patients, median age: 61.8 years	Age, MGMT promoter methylation, tumor location, extent of resection	Surgery, radiotherapy, chemotherapy, stereotactic radiosurgery	Median OS: 12.1 months	Until death or loss to follow-up
Schaub et al.[21], (2016, Germany)	Retrospective cohort study	174 patients, median age: 54 years	KPS, number of prior recurrences, number of prior chemotherapies, MGMT status	Bevacizumab alone or with irinotecan	Median OS: 7.0 months for BEV alone; 11.3 months for BEV + IRI	Until death or loss to follow-up

KPS: Karnofsky Performance Status

percentage, which further underscores the need for personalized treatment strategies tailored to individual patient characteristics.[2]

According to a study by Kim et al.[22], the incidence of glioblastoma is higher in the elderly population (those over 65). Immunological factors associated with aging, GBM progression, and/or resistance to treatment.[22]

Similarly, Van Linde et al. found that age and KPS significantly influenced the efficacy of treatments such as re-resection and systemic therapies, with better outcomes observed in younger patients and those with higher functional status.[12] These findings are consistent with broader research on glioblastoma, in which patient demographics and performance status played a pivotal role in guiding treatment decisions. Understanding these factors will help clinicians to select the most appropriate interventions and improve the survival rates of patients with recurrent glioblastoma.

Role of molecular and genetic markers

The role of molecular and genetic markers in recurrent glioblastoma is pivotal for predicting survival outcomes and guiding personalized treatments. Studies by Fu et al. and Brown et al. underscore the importance of key markers, such as MGMT promoter methylation and IDH mutations, both of which have been associated with improved overall survival.[15]

Fu et al. highlighted that MGMT methylation status, when combined with factors such as tumor grade and gliosis percentage, enables the stratification of patients into high- and low-risk groups. This stratification allows for more tailored treatment strategies that align with the individual patient profiles. Brown et al. also demonstrated that patients with MGMT promoter methylation who received standard chemoradiotherapy had a significantly longer OS than those who did not undergo methylation or received less aggressive treatment.[2]

These findings emphasize the growing role of molecular markers in recurrent glioblastoma, particularly as they help identify patients who might benefit from more targeted or experimental therapies. The integration of these markers into clinical trials exploring novel therapies, such as immunotherapy or gene therapy, offers promise for more personalized and effective treatment plans aiming to extend survival and improve the quality of life of patients with recurrent glioblastoma.

Challenges of salvage therapies and recurrence management

Managing recurrent glioblastoma poses formidable challenges, particularly with respect to salvage therapy. Van Linde et al. shed light on the limitations of treatment options in this context, where survival outcomes often remain poor despite interventions. Wong et al.[32] highlighted the modest effectiveness of salvage therapies, such as chemotherapy, reporting a median survival of only 30 weeks, which underscores the aggressive nature and resistance of recurrent glioblastoma to conventional treatments.

Similarly, Van Linde et al. provided a comparative analysis of re-resection, systemic therapies, and best supportive care (BSC), illustrating that while surgical resection and systemic therapies may extend survival modestly, the overall prognosis remains poor, with a median survival of 6.5 months. This reflects the limited efficacy of available treatments in the face of tumor resistance and aggressiveness.[15]

These studies highlight the delicate balance that clinicians must navigate when deciding between aggressive treatment and supportive care. Factors such as tumor aggressiveness, patient performance status, and response or resistance to prior treatments heavily influence decision making. Ultimately, recurrence management of glioblastoma requires careful consideration of both the potential benefits of extending survival and the importance of maintaining the quality of life of patients.

Methodological quality

In the systematic review of prognostic factors and survival of patients with recurrent glioblastoma, the Newcastle-Ottawa score **(Table 2)** was used to assess the methodological rigor of the included studies. This scale examines selection, comparability, and exposure/outcome criteria. Many investigations have displayed exceptional quality, with several reaching a maximum 9/9 score. Notable examples include studies by Jilla et al.[14] and Audureau et al.[13], which excelled in terms of patient selection, criteria definition, and follow-up protocols. Brown et al.[15] and Fekete et al.[17] scored 8/9 with minor limitations in covariate adjustment. The predominantly high methodological quality of the included studies bolsters the credibility of the findings on prognostic factors and survival outcomes in patients with recurrent glioblastoma.

Discussion

Recurrent glioblastoma (GBM) presents a formidable challenge in terms of prognosis and survival as evidenced by its persistent resistance to conventional therapies. A systematic analysis identified several crucial prognostic factors that significantly affect patient outcomes, including age, extent of surgical resection, molecular markers, and progression-free survival. Age has emerged as a critical determinant, with younger patients generally exhibiting more favorable treatment responses, potentially due to their enhanced ability to withstand aggressive interventions. In contrast, older individuals (classified as those aged 65 and above) often face limited treatment options, primarily because of age-related health complications and reduced tolerance for intensive therapeutic approaches.

The degree of surgical tumor removal consistently correlates with improved survival rates, with maximal resection offering distinct advantages. However, the tumor loca-

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Table 2. NOS (Newcastle-Ottawa Scale) assessment

Study	Selection	Comparability	Exposure/Outcome	Overall rating (NOS)
Jilla et al.[14] (2022, India)	++++ Clear patient selection, well-defined criteria, large sample size (n=46)	++ Comparison by treatment groups	+++ Accurate follow-up for outcomes	9/9
Brown et al.[15] (2022, UK)	++++ Consecutive series of 490 patients, clear inclusion/exclusion	++ Adjusted for key covariates	++ OS and survival predictors assessed with robust methods	8/9
Vaz-Salgado et al.[16] (2023, Spain)	+++ Comprehensive selection but small sample size (n=90)	++ Comparability of treatment modalities	++ Detailed outcomes including OS and PFS	7/9
Fekete et al.[17] (2023, Sweden)	++++ Clear selection criteria, large cohort (n=222)	++ Adjusted for covariates	++ Accurate follow-up, survival analyzed with robust methods	8/9
Hansen et al.[18] (2024, Denmark)	+++ Small sample size (n=66), clear criteria	++ Adjusted by prognostic scale	+++ Detailed follow-up, survival data collected	7/9
Fu et al.[2] (2024, China)	++++ Large sample (n=126), well-defined selection	++ Adjusted for key variables	++ Clear reporting of survival and risk groups	8/9
Van Linde et al.[12] (2017, Netherlands)	++++ Clear selection, large cohort (n=299)	++ Adjusted for multiple clinical variables	++ Detailed follow-up, clear outcomes measured	9/9
Audureau et al.[13] (2017, France)	++++ Comprehensive selection (n=407), multicenter	++ Adjusted for clinical and treatment factors	+++ Decision tree and survival outcomes tracked	9/9
Karschnia et al.[19] (2023, USA/Germany)	++++ Large sample size (681), robust selection, detailed clinical data	++ Stratification by RANO classification and other key clinical variables	+++ Accurate survival and progression tracking	9/9
Blakstad et al.[20] (2023, Norway)	++++ Consecutive series of 467 patients, comprehensive data	++ Adjusted for age, MGMT methylation, extent of resection	++ Detailed survival outcomes, clear follow-up	8/9
Schaub et al.[21] (2016, Germany)	+++ Well-defined cohort (174), detailed inclusion criteria	++ Comparison by treatment with or without irinotecan	++ Clear follow-up, OS and PFS tracked	8/9

Key:
- **Selection**: (+ up to 4) Based on patient selection, inclusion/exclusion criteria, and sample size;
- **Comparability**: (+ up to 2) Adjustments for confounding factors or appropriate comparison ns between groups;
- **Exposure/Outcome**: (+ up to 3) Measurement of outcomes, follow-up duration, and data completeness;
- **Overall rating (NOS)**: total score based on the Newcastle-Ottawa Scale (NOS).

tion and complexity frequently constrain the feasibility of extensive surgical interventions, limiting the potential for aggressive surgical strategies.

Molecular markers such as IDH1 mutations and MGMT promoter methylation have emerged as significant prognostic factors, providing insights into tumor behavior and guiding personalized treatment strategies. These markers not only aid in predicting treatment response but also open up the potential for more targeted therapies. Beyond MGMT and IDH, other molecular markers, including TERT promoter mutations, TP53, ATRX loss, and Ki-67, have also been identified as key prognostic indicators in recurrent GBM and will be discussed in this review. This review also highlights PFS and salvage therapies as critical elements in recurrent GBM management. A longer PFS generally suggests a less aggressive tumor and better outcomes with subsequent therapies, while the effectiveness of salvage treatments such as re-irradiation, chemotherapy, and novel approaches such as tumor-treating fields (TTF) or immunotherapy depends largely on factors such as the patient's performance status and tumor molecular characteristics.

Additionally, this review emphasizes the importance of clinical trials in exploring emerging therapies, such as gene therapy and immunotherapy, which show promise in improving outcomes. Beyond survival, the discussion highlights the need for a holistic approach that integrates

palliative care and measures to improve the quality of life. Managing recurrent glioblastoma requires addressing not only survival but also the broader physical and emotional needs of patients as they navigate this aggressive and challenging disease. The studies summarized in **Table 1** collectively highlight the significant factors that influence survival in patients with recurrent glioblastoma. Common prognostic factors identified across these studies include age, Karnofsky Performance Status, tumor grade, extent of surgical resection, and molecular markers such as MGMT promoter methylation and IDH mutations. These factors play a crucial role in determining treatment response and overall survival (OS), underlining the complexity of managing recurrent glioblastoma. Research has consistently highlighted the need for individualized treatment plans tailored to both clinical and genetic factors.

Age and KPS score have emerged as the most consistent predictors of survival in multiple studies. Fu et al.[2] demonstrated that younger patients with higher KPS scores tended to have better outcomes, a finding echoed by Wong et al.[32], who also emphasized the role of tumor histology in shaping prognosis. Similarly, Van Linde et al. found that age and KPS significantly influenced the efficacy of treatments, such as re-resection and systemic therapies. These findings reinforce the importance of evaluating patient demographics and performance status to effectively guide treatment decisions. Understanding these variables allows clinicians to make more informed choices regarding surgical intervention, chemotherapy, or supportive care, maximizing the potential for extended survival and quality of life. A study by Kim et al.[22] also stated that an older population older than 65 years of age increases the incidence of glioblastoma. Immunological factors associated with aging, GBM progression, and/or resistance to treatment.

Molecular and genetic markers play critical roles in the management of recurrent glioblastomas. Studies by Fu et al. and Brown et al. underlined the significance of MGMT promoter methylation and IDH mutations as key prognostic markers. Patients with MGMT methylation generally showed a better response to chemoradiotherapy and longer survival outcomes. For instance, Fu et al. used MGMT methylation in combination with tumor grade and gliosis percentage to stratify patients into high- and low-risk groups, thereby improving the precision of treatment approaches. These molecular markers are becoming increasingly relevant in designing personalized therapies, as they help identify patients who might benefit from targeted treatments or clinical trials exploring innovative therapies such as immunotherapy or gene therapy.

Recurrent GBM is driven by key molecular alterations, including telomerase reverse transcriptase (TERT) promoter mutations, TP53 and ATRX mutations, and Ki-67 expression. TERT promoter mutations are frequently observed in GBM and are associated with aggressive tumor behavior, poor prognosis, and increased recurrence risk.[23] TP53 mutations, commonly found in secondary GBM, disrupt tumor suppressor functions and promote genetic instability.[24] ATRX mutations are linked to the alternative lengthening of telomeres (ALT) pathway, influencing tumor proliferation and therapy resistance.[25] Additionally, Ki-67, a marker of cellular proliferation, is correlated with increased tumor aggressiveness and recurrence rates, making it a potential prognostic biomarker.[26] These molecular factors collectively contribute to GBM recurrence, influencing treatment responses and patient survival outcomes.

The challenge of managing recurrent glioblastomas is particularly evident in studies focusing on salvage therapies. Van Linde et al. highlighted the limited effectiveness of current salvage treatments, with the median survival rates remaining modest despite aggressive intervention. Wong et al. found that chemotherapy regimens offered only slight improvements in progression-free survival (PFS), whereas Van Linde's analysis demonstrated that even re-resection and systemic therapies yielded only marginal survival benefits. This reflects the overall resistance of recurrent glioblastomas to treatment, necessitating innovative approaches for managing tumor recurrence.[12]

Repeat surgery plays a crucial role in recurrent glioblastoma management, and meta-analyses have highlighted its impact on survival. Lu et al. in World Neurosurgery reviewed multiple studies and concluded that repeat surgery significantly improves overall survival, particularly in patients with good preoperative Karnofsky Performance Status and favorable molecular markers.[27] Gross total resection (GTR) of recurrent glioblastoma is associated with significantly improved progression-free survival compared to subtotal resection, as highlighted in a systematic review by Han et al.[28] Similarly, Jackson et al.[29] found that patients undergoing GTR had longer PFS than those with STR or biopsies, reinforcing the importance of maximal tumor resection for better outcomes. Lu et al.[30], also in World Neurosurgery, reinforced the importance of extent of resection, demonstrating that achieving maximal cytoreduction correlates with longer survival, particularly when combined with adjuvant therapies.[30]

Re-irradiation has emerged as a viable salvage option, particularly for patients ineligible for surgery. Kazmi et al., in the Journal of Neuro-Oncology, analyzed multiple re-irradiation studies and found that fractionated stereotactic radiotherapy offers better local control and survival benefits while minimizing toxicity.[31] More recently, Luo et al. in Clinical Neurology and Neurosurgery confirmed that hypofractionated re-irradiation, especially when combined with systemic therapies such as bevacizumab, improves survival outcomes while reducing treatment-related adverse effects.[32] Bevacizumab, an anti-VEGF monoclonal antibody, has been extensively studied as a salvage therapy, often used in combination with chemotherapy. While it provides symptomatic relief and prolongs PFS, meta-analyses suggest its impact on overall survival remains limited.

Moreover, the timing and type of intervention significantly affected patient outcomes. Van Linde et al. showed that patients who underwent re-resection experienced longer survival than those who only received supportive care,

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indicating the potential value of surgery in select cases. However, the feasibility of aggressive interventions such as surgery is often limited by factors such as tumor location and patient performance status. For instance, Audureau et al. emphasized the importance of KPS at the time of progression as a key determinant of overall survival.[13] Patients with higher KPS scores were more likely to tolerate surgery and chemotherapy, leading to better outcomes than those with poorer performance status.

The complexity of glioblastoma recurrence management is further compounded by the inherent resistance of tumors to conventional therapies. Schaub et al. and Brown et al. highlighted the role of advanced therapies such as bevacizumab in extending survival.[15,21] Schaub et al. reported that bevacizumab, either alone or in combination with irinotecan, was associated with improved survival, particularly in patients who had already undergone multiple lines of chemotherapy. Similarly, Brown et al. emphasized the importance of combining debulking surgery with chemoradiotherapy in patients with favorable molecular profiles, such as MGMT promoter methylation, to maximize treatment efficacy.[15,21]

The recurrence patterns and molecular characteristics of glioblastomas also play pivotal roles in determining patient survival. Karschnia et al.[19] showed that patients who underwent maximal resection of contrast-enhancing tumor volume had significantly longer survival than those with residual tumors.[19] This is consistent with broader research on the importance of surgical intervention in glioblastoma management, particularly when combined with postoperative chemoradiation. Additionally, patients with molecular markers, such as IDH mutations or MGMT methylation, are more likely to benefit from aggressive surgical approaches, further emphasizing the importance of personalized treatment strategies based on both clinical and genetic factors.

As illustrated by Vaz-Salgado et al., age remains a critical factor in determining the success of treatment interventions. Older patients generally exhibit lower survival rates due to comorbidities and reduced tolerance to aggressive therapies. This is particularly evident in studies focusing on bevacizumab and other immunotherapies, where younger patients with a good performance status tend to derive greater benefits from these treatments. Vaz-Salgado et al. also highlighted the complexity of managing recurrent glioblastoma in older populations, as these patients often require more conservative treatment approaches, balancing the quality of life with potential survival benefits.[16]

The importance of molecular profiling in determining treatment outcomes is further highlighted in studies by Fekete et al. They demonstrated that patients with hypermethylated MGMT and a better performance status showed significantly longer survival than those without these genetic markers. These findings underscore the growing role of precision medicine in recurrent glioblastoma, where personalized treatment plans based on molecular characteristics offer the best chance of improving patient outcomes. The integration of genetic testing into routine clinical practice is becoming increasingly important for guiding treatment decisions in this patient population.[17]

Additionally, the extent of surgical resection continues to be a crucial factor in determining patient survival. Studies by Blakstad et al.[20] emphasized the survival benefits of gross total resection (GTR) compared with partial or no resection. Blakstad et al. found that patients who underwent GTR had significantly longer survival, particularly those with MGMT methylation, and younger age. This finding supports the notion that maximal safe resection, when feasible, should be considered in the management of recurrent glioblastoma to optimize the survival outcomes.[20]

In contrast, the role of supportive care in patients with a poor performance status or advanced disease has been highlighted in several studies. Van Linde et al. and Audureau et al. noted that, for patients with low KPS scores, aggressive interventions may not be appropriate because of the risks and limited benefits. Instead, the best supportive care (BSC) focuses on symptom management and quality of life. These studies underscore the importance of individualized care plans that consider both patients' overall health and likelihood of treatment success.[12,13]

The overall prognosis for recurrent glioblastoma remains poor, as reflected in the studies highlighting the aggressive nature of this tumor and the limited effectiveness of current treatment strategies. Despite advances in surgical techniques, radiotherapy, and chemotherapy, recurrent glioblastomas remain incurable. The prognosis remains dismal, with median overall survival post-recurrence ranging between 6 to 10 months.[6]

This systematic review highlights the complex management of recurrent glioblastoma, emphasizing critical prognostic factors such as age, KPS, tumor grade, molecular markers, and resection extent. Advances in neuro-oncology, including molecular profiling and personalized treatments, have shown promise for better survival and quality of life. Nonetheless, optimizing salvage therapies, managing recurrences, and overcoming treatment resistance remain significant challenges that necessitate ongoing research and innovation.

Limitations

Studies on recurrent glioblastoma often face limitations in study design, sample size, and treatment protocols, which complicate direct comparisons. Jilla et al. had small sample sizes, which limits generalizability. The retrospective nature of most studies introduces a bias in patient selection and data collection. Variations in treatment modalities and salvage therapies across institutions further complicate the interpretation of the survival outcomes. Although molecular markers, such as MGMT methylation, are crucial, not all patients undergo genetic profiling, limiting personalized treatment applicability. Additionally, varying follow-up periods, with some lacking long-term data, hinder the assessment of the impact of treatment on overall survival and disease progression.

Conclusion

The prognosis and survival outcomes of patients with recurrent glioblastoma remain poor despite advancements in surgery, chemotherapy, and radiotherapy. Key prognostic factors identified included age, Karnofsky Performance Status (KPS), molecular markers such as MGMT promoter methylation, and the extent of surgical resection. Younger patients and those with higher KPS scores showed better survival outcomes, with molecular markers increasingly guiding personalized treatment. The limited efficacy of salvage therapies and the resistance of tumors to conventional treatments underscores the need for ongoing research and innovative therapies. Advances in neuro-oncology, including molecular profiling and individualized treatments, offer the best hope for improving the survival and quality of life of patients with this aggressive disease.

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Author contributions

R.A.A., F.D., and I.R.A contributed to the design and implementation of the research; R.A.A., A.R.L, and I.R.A - to the analysis of the results and to the writing of the manuscript; R.A.A. conceived the original and supervised the project.

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