

Systematic Review

Advancements in Molecular Biomarkers as Prognostic Predictors for Patients with Glioblastoma: A Systematic Review

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Abstract

Objectives: Glioblastoma (GBM) is a highly aggressive tumor with a median survival of 14-15 months with specific genetic expression. With advances in technology, molecular biomarkers are currently used as predictors to determine the prognosis of patients with GBM.

Methods: We collected literature through PubMed, SCOPUS, and Google scholar, from 2014-2024. The study designs that met the inclusion criteria were cohort, cross-sectional, systematic reviews, and meta-analyses. The studies will be graded according to the risk of bias they represent using Quality of Prognosis Studies (QUIPS) Tool Ratings.

Results: Twelve articles with six different biomarkers (MGMT, IDH, PTEN, EGFR, EGFRvIII, and TP53) met the inclusion criteria and were considered eligible for this systematic review. Prognosis was measured using OS, and the data were compared using univariate analysis of each biomolecule for OS. Methylation of MGMT and IDH mutations was a good prognostic predictor, and amplification of EGFR, EGFRvIII, PTEN, and TP53 mutations was not statistically significant for OS.

Conclusion: Several biomarkers can be used as predictors alone or in combination with one another. Advances in technology and biomolecular science are expected to help predict the prognosis and provide new insights into the management of GBM.

Keywords: Glioblastoma, Biomolecular Markers, Prognosis

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Glioblastoma (GBM) is a primary brain tumor that originates from glial cells. Glioblastoma is an aggressive, invasive, and undifferentiated type of tumor, so based on the World Health Organization (WHO) criteria, glioblastoma is categorized as a grade IV glioma, a malignant tumor.^[1] This tumor has an average incidence of 3.19 per 100,000 people, and the incidence increases across the age range 55-60, and more in men.^[2]

Some of the symptoms and complaints experienced by patients with glioblastoma tumors are the direct effect of the destruction of the cerebral tissue, which leads to necrosis in the tumor and peritumoral areas.^[3] Focal neurological symptoms appear according to the location of the tumor in the brain. While the indirect effect is the space-occupying effect of the tumor due to the progressive increase in tumor size and peritumoral edema, causing an

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increase in intracranial pressure, which occurs in 30-50% of patients with glioblastoma.^[3] Intracranial pressure is characterized by unilateral chronic progressive headache, without a pattern, possibly accompanied by projectile vomiting.^[3]

As modern therapies develop to treat glioblastoma, the median survival of patients with glioblastoma ranges from to 14-15 months after diagnosis, making glioblastoma one of the most challenging tumors to handle.^[2] Developments in surgical approaches and surgical techniques, radiotherapy, and adjuvant chemotherapy can slowly improve the quality of life and decrease the survival of patients with glioblastoma, but the prognosis remains poor.^[2] The main challenge in managing glioblastoma is the complex biological nature of the tumor. Researchers are currently exploring the biological properties of glioblastoma and looking for molecular markers that can distinguish glioblastoma subtypes, with the hope of comparing the prognosis of each glioblastoma subtype and developing a more specific treatment (targeted therapy) for the subtype in the future.

In this systematic review, we discuss the molecular biomarkers of glioblastoma that can distinguish glioblastoma subtypes and determine their role in the prognosis of patients with glioblastoma. The authors limited their study to five main biomarkers that play a role in the prognosis of glioblastoma: methylation of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter, mutation of isocitrate dehydrogenase enzyme 1/2 (IDH1/2), overexpression and amplification of epidermal growth factor (EGFR) receptors, mutation of p53, and mutation of phosphatase and tensin homolog (PTEN).

Methods

Search Strategy

A systematic review written based on English-language articles were collected, selected, and assessed via electronic searches in Google Scholar, PubMed, and Scopus, crossing keywords of "Biomarker," "MGMT," "PTEN," "IDH," "TP53," "EGFR," and "Glioblastoma." Finally, we searched the reference lists of the articles identified and selected those that were judged as relevant. Studies will also be graded according to the risk of bias.

Inclusion and Exclusion Criteria

The inclusion criteria of the studies that will be included in this systematic review are articles published in the last seven years (2014 to 2024), which is a cohort, cross-sectional, systematic review or meta-analysis that analyzes overall survival (OS) based on biomarker results, and includes

patients over 18 years of age. The exclusion criteria were studies other than English studies, radiological diagnosis of glioblastoma without pathological anatomical examination, lack of univariate analysis, and animal studies. The article selection process is shown in the PRISMA 2009 flow diagram in Figure 1.^[4]

Risk of Bias Assessment

To assess the risk of bias in any of the studies included in this systematic review, the authors will use the QUIPS Tool Ratings (Quality in Prognosis Studies)⁵ for cohort studies and AMSTAR-2 Tool Ratings (Assessing the Methodological Quality of Systematic Reviews).^[6]

Results

Twelve retrospective cohort studies were obtained from keyword and reference search results. Table 1 describes the study design, types of biomarkers, number of study subjects, age range, biomolecular characteristics, and study results. Table 2 describes the risks of bias of included studies using the QUIPS Tool Ratings.^[5] Table 3 describes the risks of bias of included systematic review using the AMSTAR-2 Tool Ratings.^[6]

Discussion

This review aimed to explore the benefits of biomarkers in predicting the prognosis of patients with GBM. Twelve studies matched the eligibility criteria and included six biomarkers that were frequently studied as prognostic predictors in patients with GBM.

MGMT

Six studies, conducted by Lee et al., Pinson et al., Christians et al., Wang et al., Gomes et al., and Sareen et al., have investigated the role of MGMT methylation as a prognostic pre-

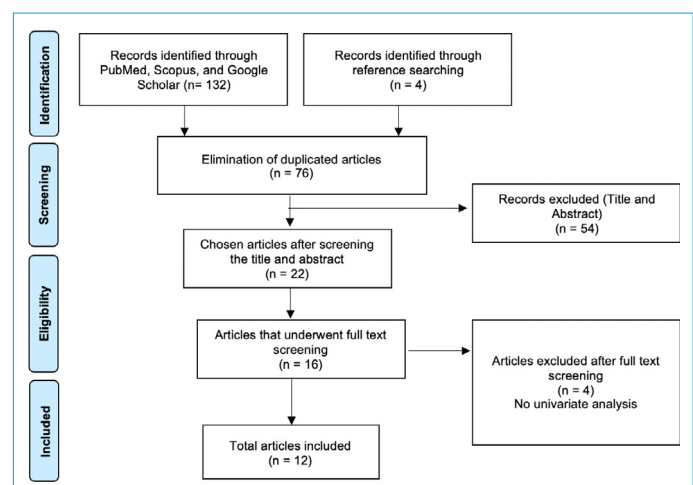


Figure 1. Schematic of PRISMA for systematic selection of articles.^[4]

Table 1. Characteristics of Included Studies					
Author	Biomarker	Design	Sample Size	Age	Overall Survival
Lee et al., ^[7] (2017)	MGMT methylation	Retrospective cohort	12,725	Median 61 (53-69)	MGMT+ had better OS than MGMT- (20 months OS with a CI of 18.5-21.6 months, HR 0.71 p <0,001)
Pinson et al., ^[8] (2019)	MGMT methylation	Retrospective cohort	181	Mean 61,6	MGMT+ had a better median OS than MGMT- 19.7 months (p <0,001)
Christians et al., ^[9] (2019)	IDH1/2 mutation, MGMT methylation, and EGFR amplification	Retrospective cohort	116	Median 65	MGMT+ had a median OS of 15 months, compared with MGMT- with a median of 12 months, univariate analysis was not statistically significant.
					IDH mutation (IDH+) OS median 11 months Wild Type (IDH-) 13 months, univariate analysis was not statistically significant.
					The 14-month median EGFR (+) OS amplification, compared with the 12-month median EGFR (-) OS amplification, was not statistically significant.
Stanceva et al., ^[10] (2014)	TP53 and IDH1/2 mutations	Retrospective cohort	106	Median 56	Multivariate analysis combined IDH+ / MGMT+ had OS 46.5 months, and IDH- / MGMT+ 15 months (p <0,001)
					IDH+ had a median OS of 309 months, compared to IDH- with an OS of 6.2 months. (HR0,274 CI 0,124-0,604, p <0,001).
					TP53 mutations had a median OS of 9.1 months compared to non-mutations with a median of 7.6 months, TP53 mutations versus non-mutations had an HR of 0.764, with a CI 0.489-1.196, which not statistically significant.
Wang et al., ^[11] (2014)	TP53 mutation, IDH1/2, and MGMT amplification	Retrospective cohort	78	Median 45	TP53 mutation (HR 0.545 CI 0.261-1.142, p> 0.05) IDH1+ (HR 0.021 CI 0.136-0.881, p <0.05)
					MGMT+ (HR 0.368 CI 0.172-0.865, p <0.05)
					IDH1+ with MGMT+ Median OS 25 months, MGMT- Median OS 11 months (p <0.05)
Armocida et al., ^[12] (2019)	EGFR amplification	Retrospective cohort	146	Young adults (18-45): mean 38,6 Adults (>45): mean 65	IDH- with TP53 mutation + 17-month median OS, TP53- 7-month median OS (p <0.05)
					EGFR- young adults median OS 21.7 months EGFR+ young adults median OS 16 months
					EGFR- adults median OS 12 months EGFR+ adults median OS 15.8 months (p <0.05)
Weller et al., ^[13] (2014)	EGFR VIII	Retrospective cohort	179	>60 : 98 18-60 : 81	Univariate analysis of EGFR amplification did not have any statistical significance in predicting OS. EGFRVIII amplification was not statistically significant for OS.
	PTEN	Retrospective cohort	60	59.53 (SD10,93)	Loss of heterozygosity in the PTEN gene had a worse OS, with 287 days of OS, compared to 478 days in patients without the PTEN gene disorder (OR 2.557, 95% CI 1.374-4.758)

Table 1. Characteristics of Included Studies (CONT.)

Author	Biomarker	Design	Sample Size	Age	Overall Survival
Gomes et al., ^[15] (2021)	MGMT, IDH1/2 mutation	Retrospective cohort	112	Median 42 (25-60)	MGMT+ (HR 0.39 CI 0.21-0.75, p = 0.005) MGMT+ combined with low mRNA expression (HR 0.56 CI 0.35-0.9) IDH1+ median OS 35.4 months (p<0.001) IDH1- median OS 15.5 months TP53 mutation (HR 2.03, CI 1.14-3.61, p= 0.02) EGFR+ median OS 4 (CI 2-6, p= 0.009) EGFR- median OS 15 (CI 9-21) IDH1+ median OS 5 (CI 2-8, p= 0.97) IDH1- median OS 11 (CI 2-20) IDH+ median OS 14.1 months, CI 8.2-20.0, p<0.01 IDH- median OS 8.1 months, CI 6.1-10.1 TP53+ (HR 1.38, CI 1.83-3.16, CI, p=0.08) Combined TP53, IDH, and Ki-67 mutation (HR 1.86, CI 1.03-3.36, p= 0.04)
Ali et al., ^[16] (2022)	TP53, EGFR amplification, IDH 1	Retrospective cohort	90	<40: 66 >40: 24	
Kucukarda et al., ^[17] (2023)	IDH 1/2, TP53	Retrospective cohort	55	Median 59 (50-66)	
Sareen et al., ^[18] (2022)	MGMT, IDH1, EGFR	Systematic review and meta-analysis	1,231	Median 63 (51-83)	MGMT mutation (658 patients, HR 1.66, CI 1.32-2.09, p<0.0001) IDH1 mutation (480 patients, HR 2.37, CI 1.81-3.12, p<0.0001) EGFR mutation (206 patients, HR 1.31, CI 0.97-1.78, p=0.08)

dictor of GBM.^[7-9,11,15,17] Across these studies, a consistent finding emerges: patients with GBM who exhibit methylation of the MGMT gene (MGMT+) tend to have better OS compared to those without MGMT methylation (MGMT-) (HR 0.75; p <0.001).^[7] Notably, Wang et al. also observed that combined MGMT methylation in GBM patients with IDH mutation correlated with a median OS of up to 25 months (p<0.05).^[11] Furthermore, Gomes et al. reported that patients with both methylated MGMT and lower mRNA expression displayed improved outcomes (HR 0.56, p=0.017, CI95% 0.35-0.90 and HR 0.39, p=0.005, CI95% 0.21-0.75).^[15]

In a sub-group analysis by treatment received, Sareen et al. found notable correlations between MGMT methylation and improved OS in various treatment modalities.^[17] In particular, patients who received alkylating agents showed a significant association between MGMT methylation and a combined hazard ratio (HR) of 1.64 (CI95% 1.23–2.18; p=0.0007). Similarly, in a separate subgroup of patients who were treated with TKIs (either alone or in combination with alkylating agents), MGMT methylation was found to be a significant predictor of OS, with a pooled HR of 1.82 (CI95% 1.25–2.64; p=0.002). Immunotherapy was found to produce comparable results in patients when administered either alone or in combination with alkylating agents, as indicated by a pooled hazard ratio of 2.22 (CI95%: 1.21–4.06; p=0.01).^[17]

The enzyme MGMT plays a crucial role in DNA repair, particularly in protecting cells against alkylating agents and preventing G:C → A:T mutations.^[18] In tumors where MGMT is unmethylated, it interferes with the cells' ability to repair DNA, thus affecting treatment outcomes. Clinical trials targeting the MGMT promoter as a chemotherapy route have consistently shown that tumors with MGMT+ exhibit a survival benefit when treated with Temozolomide (TMZ) and radiotherapy. Conversely, patients without MGMT methylation do not experience the same survival benefit from chemotherapy, posing challenges in selecting additional therapy for them.^[19]

EGFR, EGFRvIII, and PTEN

Five studies discussed EGFR amplification, namely Christians et al., Weller et al., Armocida et al, Sareen et al., and Ali et al.^[9,12,15-17] Four studies reported that EGFR amplification was not significantly associated with OS in GBM patients.^[9,12,15,17] One study reported that EGFR overexpression was a worse prognostic factor for patients with GBM.^[16]

EGFR is a member of the Tyrosine Kinase Receptor (RTK) family.^[19,20] RTK play a role in coordinating complex signaling that regulates various cellular processes. There

Table 2. Risk of Bias Assessment of Included Cohort Studies^[9]

Author	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Lee et al., ^[7] (2017)	Low Bias	N/A	Low Bias	Low Bias	N/A	Low Bias
Pinson et al., ^[8] (2019)	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias	Low Bias
Christians et al., ^[9] (2019)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Stanceva et al., ^[10] (2014)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Wang et al., ^[11] (2014)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Armocida et al., ^[12] (2019)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Weller et al., ^[13] (2014)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Idoate et al., ^[14] (2014)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Gomes et al., ^[15] (2021)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Ali et al., ^[16] (2022)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias
Kucukarda et al., ^[17] (2023)	Low Bias	Low Bias	Low Bias	Low Bias	N/A	Low Bias

N/A: there is no information in the study.

Table 3. Risk of Bias Assessment of Systematic Review and Meta-Analysis^[6]

Criteria	Sareen et al., ^[18] (2022)
PICO components	+
Protocol	+
Study design explanation	+
Comprehensive search strategy	+
Duplicate study selection	+
Duplicate data extraction	+
Details of excluded studies	+
Description of included studies	+
Risk of Bias (RoB) assessments	?
Funding sources	+
Heterogeneity	-
Publication bias	-
Reports conflict of interests	+
Overall rating quality	Good quality

are two types of signaling pathways utilized by RTK, namely the RAS/RAF/MAPK pathway and the PI3K / ALT / mTOR pathway.^[20] The RAS / RAF / MAPK pathway play a role in cell proliferation, differentiation, and migration, while the PI3K / ALT / mTOR pathway plays a role in apoptosis inhibition and survival in the cell cycle.^[17] The amplification of EGFR can lead to regulation of these pathways, resulting in increased cell proliferation, differentiation, and apoptosis inhibition.^[20] However, to date, there has not been much of the role and benefits of EGFR in glioblastoma. Several studies have also discussed the effects of EGFR on OS that have not been statistically significant.^[19] A meta-analysis of five studies involving 575 GBM patients who either had amplification or high expression of the epidermal growth

factor receptor (EGFR) gene did not reveal any prognostic significance. The combined hazard ratio was 1.31 (CI95%, 0.96–1.79; p=0.08).^[20]

Various clinical trials specifically targeting EGFR amplification (EGFR inhibitors, such as gefitinib and erlotinib) have shown no significant effect on OS in patients with glioblastoma. However, it is estimated that crossing the blood-brain barrier is one of the complicating factors. As many as 50% of glioblastoma patients with EGFR amplification have mutations in EGFRvIII.^[21] Previous studies have had controversial results on the role of EGFRvIII as a predictor of OS.^[19,21] Weller et al. explained that there is no significant role of EGFRvIII in predicting OS of patients with glioblastoma.^[13] Univariate analysis revealed that EGFRvIII was not statistically significant, but combined multivariate analysis of patients without EGFR amplification with mutations in higher Ki67 proliferation index, normal PTEN, and MGMT methylation may form a new subgroup of glioblastoma patients with a better prognosis.^[22] Additionally, within this systematic review, one study demonstrated a notably worse prognostic factor for EGFR+ (p=0.009). However, it is essential to interpret this result cautiously because the population with EGFR+ status in this study was associated with advanced age compared to that with EGFR-status. The correlation between age and EGFR status is noteworthy, indicating that EGFR is overexpressed with advancing age. Moreover, the number of subjects is relatively small compared to other studies, with 45 subjects on each arm.^[16]

PI3K activity is regulated by PTEN, a tumor suppressor gene that regulates PI3K activity. The presence of mutations in PTEN (loss of heterozygosity) causes upregulation of the PI3K pathway, increasing inhibition of glioma cells to apoptosis.^[23]

IDH (isocitrate dehydrogenase)

Seven studies have discussed the role of IDH mutations as prognostic predictors, and all seven studies suggest that IDH mutations indicate that patients are more likely to have a longer median OS than patients with glioblastoma without IDH (wild-type IDH) mutations.^[9-11,15-18] Two types of mutations in the IDH gene that exist in glioblastoma, namely, IDH1 and IDH2. IDH1 / IDH2, play a role in oxidative carboxylation from isocitrate to alpha-ketoglutarate, which produces NADPH in the Krebs cycle. Mutations of the IDH gene can increase the reaction to the formation of oncometabolite D-2-hydroxyglutarate (2-HG), a carcinogenetic compound.^[24]

IDH1 and IDH2 mutations are most often found in glioblastoma, increasing 2-HG production to change genetic transcription in various cell types.^[24,25] This makes IDH1 / 2 a crucial component in the development of glioblastoma. IDH1 plays a vital role in glioblastoma cell adaptation. Increased IDH1 activity is an essential factor that causes glioblastoma to grow in an inadequate metabolic environment.^[21,22] IDH1/2 mutation, although it is an oncogenic compound, causes inhibition of survival and proliferation ability of glioblastoma.^[24,25]

In light of these findings, targeted therapy has become a key focus in the management of glioblastoma.^[24] Notable advancements include the development of oral small-molecule inhibitors like Ivosidenib and Enasidenib, which specifically target mutant forms of IDH1 and IDH2, respectively. These inhibitors work by effectively suppressing the enzymatic activity of the mutated proteins, leading to a reduction in the production of 2-HG.^[26] Vorasidenib, another promising agent, functions as a dual inhibitor of mutant IDH1 and IDH2, showing potential based on preclinical studies.^[26] Ongoing clinical trials are also evaluating the effectiveness of Olutasidenib, a selective inhibitor of mutant IDH1, in various solid tumors with IDH1 mutations, including glioblastoma.^[28] Additionally, indirect approaches such as Pevonedistat, which targets the NEDD8-activating enzyme, demonstrate potential in enhancing the effects of IDH1/2 inhibitors by regulating proteins involved in cell cycle control and DNA damage response.^[29]

TP53

Three studies conducted by Stanceva et al., Wang et al., and Ali et al. collectively concluded that TP53 alone is not a statistically significant independent predictor of overall survival (OS) in patients with glioblastoma.^[10,11,16] Despite its role as a tumor suppressor gene, TP53 cannot solely determine prognosis in glioblastoma due to the intricate TP53 signaling pathway and the heterogeneity of TP53 mu-

tations.^[11,30] The diverse effects of mutations and their various types contribute to the complexity of TP53's predictive capacity.^[26]

This complexity is exemplified in the study by Wang et al., where univariate analysis revealed that patients with IDH- and the TP53 mutation had a median OS of 17 months, compared to 7 months for patients with IDH- but lacking the TP53 mutation ($p < 0.05$).^[11] Despite the generally poor prognosis associated with IDH-, the combination of IDH- and TP53 mutations significantly improved OS in glioblastoma patients.^[11] Similarly, Kucukarda et al. reported analogous findings, demonstrating that combined markers of TP53, IDH, and Ki-67 were significant predictors for both progression-free survival (PFS) and OS (HR 2.03, CI95% 1.14-3.61, $p = 0.02$; and OS HR 1.86, CI95% 1.03-3.36, $p = 0.04$).^[18] However, TP53 alone did not emerge as a significant predictor in multivariate analysis.¹⁸ These studies underscore the importance of considering TP53 in conjunction with other molecular markers to comprehensively evaluate its prognostic implications in glioblastoma.

Conclusion

Glioblastoma is a particularly challenging tumor to cure, with a short OS rate. Despite advancements in scientific and technological breakthroughs, there has been considerable progress in comprehending the pathophysiology and molecular behavior of glioblastoma. Furthermore, identifying potential treatment options that can modestly enhance patient outcomes has also been made possible.

This systematic review revealed several molecular biomarkers with substantial prognostic significance for glioblastoma patients, notably methylated MGMT and IDH mutations. Patients with methylated MGMT exhibit improved outcomes, particularly when combined with other biomarkers, such as IDH mutations and lower mRNA expression. Moreover, patients with methylated MGMT have shown enhanced OS rates when undergoing immunotherapy, TKI, and alkylating agents. Furthermore, IDH mutations have consistently emerged as pivotal prognostic factors for superior OS and PFS in multiple studies.

Interestingly, when assessed independently, mutated TP53 failed to demonstrate a significantly worse prognosis. However, when analysed in combination with IDH and high Ki-67 expression, TP53 mutations were significantly associated with poorer prognosis. Conversely, EGFR amplification did not exhibit a consistent significant association with OS across most studies, although it tended to be a worse prognostic predictor in glioblastoma patients.

In the future, the integration of biomolecular diagnostics with targeted therapies is expected to enhance the ef-

fectiveness of glioblastoma treatments. We hope that the benefits of this biomarker will be utilized in healthcare institutions to support diagnosis, treatment, and patient education. Successful therapy and extended OS may bring new hope to patients, their families, and healthcare providers, potentially transforming glioblastoma from a terrifying to manageable condition.

Disclosures

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