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The efficacy and safety of poly ADP-ribose polymerase (PARP) inhibitors in patients with high-grade glioma (HGG): A systematic review and meta-analysis

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ABSTRACT

Purpose: While poly ADP-ribose polymerase (PARP) inhibitors represent a promising treatment strategy in early phase trials of patients with high-grade glioma (HGG), the clinical outcomes exhibit variability, mainly due to drug-specific pharmacokinetics and insufficient biological stratification involving MGMT and IDH status. We aimed to investigate the safety and efficacy of PARP inhibitors in grade 3 and 4 gliomas.

Methods: A systematic review and data synthesis were conducted. Records were extracted from PubMed, Scopus, Web of Science, and Embase from inception to May 24th, 2025, and included in accordance with predetermined eligibility criteria.

Results: Twelve studies, including 795 patients, were included. The pooled disease control rate (DCR) among patients with HGG was 27%; however, this estimate was associated with substantial heterogeneity and an extremely wide prediction interval (PI: 0.4–97.1%), indicating that the pooled value should not be interpreted as a stable estimate of expected clinical benefit in future studies or individual patient populations. The pooled grade $\geq$ 3 adverse event rate was 13% with a wide PI (2.2–51.2%), although heterogeneity was also substantial. Fixed-time survival outcomes and molecular/treatment subgroup analyses were summarized descriptively. Several subgroup findings, including those related to IDH status, MGMT promoter methylation, disease setting, and concomitant therapy, should be interpreted as exploratory because of limited study numbers, single-arm trial designs, inconsistent clinical contexts, and substantial between-study heterogeneity.

Conclusion: Available evidence suggests that PARP inhibitors have investigational activity and an overall acceptable safety profile in selected glioma populations, but the certainty of evidence is very low. Because pooled estimates were imprecise and accompanied by wide prediction intervals, these analyses should be regarded as descriptive and hypothesis-generating rather than clinically definitive. Larger randomized, biomarker-stratified

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trials with harmonized outcome definitions are required before PARP inhibitors can be assigned a clear therapeutic role in HGG.

1. Introduction

Gliomas are the most prevalent primary brain cancer (Ostrom et al., 2017). According to the latest 2021 World Health Organization (WHO) classification, adult-type diffuse gliomas, high-grade gliomas, are now categorized into three main groups based on their molecular profile: astrocytoma, Isocitrate dehydrogenase (IDH)-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype (Louis et al., 2021).

The DNA repair system plays a vital role in the survival and stability of cancerous cells (Clementi et al., 2020). Temozolomide disrupts this system and prevents DNA repair by cancer cells, leading to cell arrest and death (Singh et al., 2021). PARP inhibitors have demonstrated efficacy in tumors with deficiencies in DNA repair mechanisms, such as BRCA-mutated breast and ovarian cancers (Ashworth and Lord, 2018). They inhibit DNA repair, a phenomenon known as synthetic lethality, which is highly effective in homologous recombination (HR) DNA repair pathways, such as those harboring BRCA1/2 mutations, and is characterized by a state called "BRCAness" (Cella et al., 2024; Vyas et al., 2013; Lord and Ashworth, 2008). BRCAness is predominantly dependent on single-strand DNA repair mechanisms; when these mechanisms are suppressed, double-strand breaks accumulate, leading to cell death (Murai and Pommier, 2023; Saffhill and Ockey, 1985). Various studies have shown promising results of their efficacy in various tumors, especially those with BRCA1/2 mutations, including breast, ovary, pancreas, and prostate cancers (Bryant et al., 2005; Farmer et al., 2005; Lord and Ashworth, 2017; George et al., 2017; Fong et al., 2009; Mateo et al., 2015; Robson et al., 2017). While gliomas do not typically harbor BRCA mutations, the frequent alterations in other DNA repair pathways, such as methylguanine-DNA methyltransferase (MGMT) promoter methylation and IDH mutations, provide a theoretical basis for the efficacy of PARP inhibitors in this setting (Jiang et al., 2020).

Veliparib and Olaparib are the most advanced PARP inhibitors in clinical testing. Olaparib demonstrates significant penetration into glioma tissue and initial indications of disease stabilization, particularly in IDH-mutant lower-grade tumors; however, its combination with Temozolomide is often challenging, due to hematologic toxicity (Fanucci et al., 2023; Hanna et al., 2020). Veliparib, intended as a brain-penetrant PARP inhibitor, has not demonstrated improvements in progression-free or overall survival in randomized phase II trials for newly diagnosed glioblastoma, irrespective of MGMT methylation status (Sarkaria et al., 2024; Sim et al., 2021). The observed outcomes likely reflect variations in blood-brain barrier permeability, pharmacokinetics, trial design, and molecular context, including MGMT promoter methylation and IDH mutation status.

A systematic synthesis of available evidence is necessary to elucidate the therapeutic potential of PARP inhibition in high-grade gliomas (HGGs) and identify the subgroups most likely to benefit. Given the biological and methodological inconsistencies, the current study aims to systematically review the safety and efficacy of PARP inhibitors in patients with glioma to better clarify outcomes in HGGs, IDH-mutant or wildtype, MGMT promoter methylated or unmethylated, and across different concomitant therapies.

2. Material and methods

This systematic review has been submitted to the International Prospective Register of Systematic Reviews (PROSPERO), registration code CRD42024579472, and it was conceptualized in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021).

2.1. Search strategy

A comprehensive review was conducted across four databases: PubMed (Medline), Web of Science (WoS), Scopus, and Embase, spanning their inception to May 24th, 2025. The databases were thoroughly investigated using stratified search syntax tailored to each database, with relevant terms including "Glioma," "PARP," and "Poly ADP-Ribose Polymerase." The search syntaxes are provided in detail in **Supplementary File 1**.

2.2. Eligibility criteria

Studies reporting outcomes of PARP inhibitors in pediatric and adult patients with glioma were eligible for further analysis. Observational studies (cross-sectional and retrospective or prospective cohorts), clinical trials (regardless of randomization), and case series with 10 or more patients were included in the meta-analyses. Non-English studies, along with the other study designs (case reports, abstracts, posters, chapters, and review articles), were excluded. A distinct PICO framework was designed for this study as follows: P (Population): All patients with a diagnosis of brain glioma were considered. Notably, after the 2021 WHO report (Louis et al., 2021), the classification of CNS tumors changed, and the primary diagnosis of glioma was made regardless of IDH mutation status. However, patients with other types of glial cell tumors, such as gliosarcoma, or with low-grade glioma (grades 1 and 2) were not excluded from the analyses of adverse events (Robins et al., 2016; Su et al., 2014). I (Intervention): PARP inhibitors, including Olaparib, Niraparib, Rucaparib, Talazoparib, or other approved or investigational PARP inhibitors, administered as monotherapy or in combination regimens. In some studies, patients received various concomitant therapies (Kleinberg et al., 2023; Schaff et al., 2022). Of these, only those concomitant therapies that all patients had received were included in the analysis. C (Comparator): Placebo, standard-of-care therapies, alternative systemic anticancer treatments, or no comparator (for single-arm studies where applicable). (Outcomes): Clinical efficacy outcomes (progression-free survival and overall survival), safety outcomes (incidence and severity of adverse events), and treatment-related outcomes relevant to PARP inhibitor therapy. Adverse events were defined based on the Common Terminology Criteria for Adverse Events (CTCAE) (Shah, 2022).

2.3. Screening process and data extraction

The records were loaded into EndNote V.21 and assessed by two reviewers (S. F. T. and M. A. H.) using a process of duplicate removal, followed by title/abstract screening and full-text evaluation. Studies that met the inclusion criteria were selected for data extraction (independently by A. A. and F. R.) and statistical analysis. For studies that did not report exact proportions, we used digitization software (WebPlotDigitizer) to extract data points from published Kaplan-Meier (KM) curves to prevent selection bias (Aydin and Yassikaya, 2022; Drevon et al., 2016).

2.4. Quality assessment

The studies included were evaluated for quality using the Methodological Index for Non-Randomized Studies (MINORS) (Slim et al., 2003). Two independent reviewers scored each study based on 12 criteria, with a maximum score of 24 for comparative studies. Randomized controlled trials were assessed using a revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (JAC et al., 2019). Discrepancies

were resolved through discussion or consultation with the senior author (Supplementary File 2).

2.5. Statistical analysis

Restricted Maximum Likelihood (REML) and a random-effect model were used to compute the pooled rates, with extended 95% confidence intervals (95% CI). Egger's test and funnel plots were used to evaluate publication bias, and $P < 0.05$ was used as the threshold for statistical significance. Due to substantial heterogeneity among the included studies, proportions were pooled on the logit scale using a random-effects model and back-transformed using the inverse logit function for the main outcomes. This method was used to avoid boundary issues and variance instability inherent to raw proportion pooling.

Where applicable, 95% prediction intervals (95% PI) were also calculated to estimate the expected range of true effects in a future comparable study, incorporating between-study heterogeneity. Prediction intervals were calculated on the transformed scale using the estimated between-study variance from the random-effects model and a t-distribution with k-2 degrees of freedom, where k represents the number of contributing studies or estimates. They were then back-transformed to the proportion scale. Therefore, 95%CI and 95%PI were interpreted separately: the 95%CI reflects precision of the pooled estimate, whereas the 95%PI reflects between-study dispersion and expected variability in future settings.

Analyses of efficacy outcomes, including disease control rate, overall survival, and progression-free survival, were primarily confined to HGGs (grades 3 and 4). Initially, all HGGs were pooled, followed by targeted analyses of grade 4 gliomas. In grade 4 disease, we compared glioblastoma (GBM) and diffuse intrinsic pontine glioma (DIPG) when data were available. Outcomes were stratified by key molecular subgroups, specifically MGMT promoter methylation status in GBM (methylated vs unmethylated) and IDH status in HGGs (IDH-wildtype vs IDH-mutant). Furthermore, we assessed outcomes within treatment-related subgroups, comparing PARP inhibitor type (Veliparib versus Olaparib) and concomitant therapy (radiotherapy alone, radiotherapy plus Temozolomide, or Temozolomide alone). Adverse event analyses for safety outcomes encompassed the entire glioma population, including studies that enrolled both pediatric and adult patients and, when reported, lower-grade tumors, to ensure comprehensive capture of toxicity events using the Freeman-Tukey double arcsine transformation. All statistical analyses were carried out using STATA v. 17.

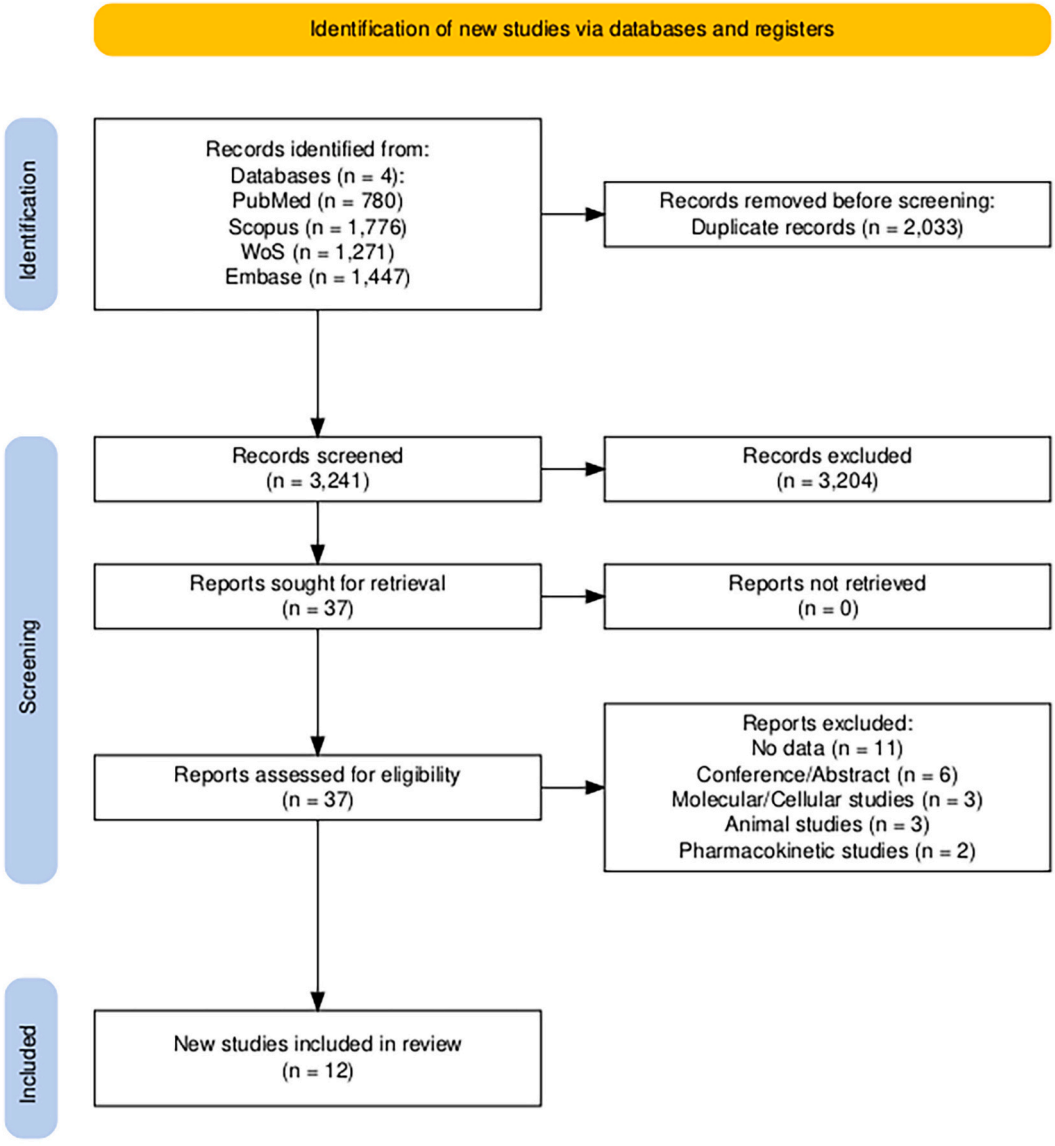

Fig. 1. Study selection process.

3. Results

3.1. Selection process

A total of 5274 records were retrieved; 2033 duplicate records were removed along with an additional 3204 due to irrelevance. The remaining 37 full-texts were reviewed, yielding 12 articles for the systematic review and meta-analysis after meeting the study's inclusion criteria. Fig. 1 illustrates the comprehensive selection procedure for the study.

3.2. Study characteristics

Twelve studies (Fanucci et al., 2023; Sarkaria et al., 2024; Sim et al., 2021; Robins et al., 2016; Su et al., 2014; Kleinberg et al., 2023; Schaff et al., 2022; Stefan et al., 2025; Karajannis et al., 2025; Vazquez I et al., 2024; Derby et al., 2024; Baxter et al., 2020) were eligible and included, of which only one was a case series (Schaff et al., 2022), and the remaining were all clinical trials. The studies comprised 795 patients (299 females, 37.6%), aged 1.8 to 81 years, who were treated with two PARP inhibitors (Olaparib, Veliparib) alone or in combination with

Table 1
Study characteristics.

First Author, Year	Country	N (Female)	Age (years)	Histology [Grade] (N)	Prior Treatments	PARPi Type	PARPi Dosage	Concomitant Therapy	OS (Months)	PFS (Months)
Stefan et al., 2025 (33)	France	30 (10)	58.5 (25–70)	Glioblastoma	Biopsy (8), Partial resection (22), No prior chemotherapy	Olaparib	50, 100, 200 mg BID	RT + TMZ	19.8	6.2
Karajannis et al., 2025 (34)	USA	37 (12)	14.73 (4.53)	Anaplastic Astrocytoma (15), Glioblastoma (18), High-grade astrocytic tumor (4)	Surgery / Corticosteroids	Veliparib	65 mg/m2 BID, 5 days/ week	RT + TMZ	N/A	N/A
Sarkaria et al., 2024 (21)	USA	223 (96)	58.8 (11.55)	Glioblastoma	RT + TMZ	Veliparib	40 mg BID, (7 days)	TMZ	28.1	13.2
Derby et al., 2024 (36)	UK	16 (7)	71.5 (44–78)	Glioblastoma	Resection (10), Biopsy (6)	Olaparib	5 mg D (3), 100 mg D (3), 100 mg BID (7), 200 mg BID (3)	RT (39.9–40.1 Gy in 15 fractions)	10.8	5.5
Vazquez I et al., 2024 (35)	France	35 (9)	48 (25–64)	Astrocytoma, Oligodendroglioma [High-grade Glioma]	Chemotherapy+RT	Olaparib	300 mg BID	N/A	15.9	2.05
Fanucci et al., 2023 (19)	USA	15 (5)	38(23–69)	Astrocytoma, Oligodendroglioma [G2 (6), G3 (4), G4 (5)]	Resection (11), Biopsy (4), RT (14), Chemotherapy (21), Nivo (2)	Olaparib	300 mg BID	N/A	20.7	3.63
Kleinberg et al., 2023 (26)	USA	24 (8)	N/A	Astrocytoma [G4 (24)]	N/A	Veliparib	10 mg BID	TMZ (24), RT (18)	13	N/A
Schaff et al., 2022 (27)	USA	20 (3)	42 (24–75)	Astrocytoma, Oligodendroglioma, DIPG, Glioblastoma	RT + TMZ (19), BEV (7), IDH Inhibitors (3), Veliparib (1)	Olaparib	150 mg Triweekly	TMZ (20), BEV (3), Pembro (1), RT (1)	N/A	N/A
Sim et al., 2021 (22)	Australia	84 (25)	60 (22–78)	Glioblastoma	N/A	Veliparib	200 mg BID	RT + TMZ	12.7	5.7
Baxter et al., 2020 (37)	USA	65 (37)	6.6 (2.2–15.8)	Glioma, Astrocytoma, Glioblastoma	No prior treatment	Veliparib	50 mg/m^2 BID	RT (54 Gy in 30 fractions)	N/A	N/A
Robins et al., 2016 (24)	USA	215 (72)	N/A	High-grade Glioma, Glioblastoma, Gliosarcoma	Resection (193), Biopsy (17)	Veliparib	40 mg BID	TMZ	N/A	N/A
Su et al., 2014 (25)	USA	31 (15)	8.5 (1.8–21)	DIPG, Glioblastoma Multiform, Ependymoma, Astrocytoma, Medulloblastoma, Glioma, Sarcoma	N/A	Veliparib	20 mg/m^2 BID	TMZ	N/A	N/A

Notes: Ages are presented according to the available data as mean (sd), median (range), or (range).
The PARP dosages are presented as simply as possible. In most papers, these dosages were escalated; therefore, the detailed data are omitted from this table.
The numbers and grades in histology were mentioned if only specified in the included papers.
PARPi: PARP inhibitor; OS: Overall Survival (Median); PFS: Progression-free Survival (Median); M: Months; mg: milligram; D: Daily; BID: twice a day; RT: Radiotherapy; Nivo: Nivolumab; DIPG: Diffuse Intrinsic Pontine Glioma (Diffuse Midline Glioma); BEV: Bevacizumab; TMZ: Temozolomide; Pembro: Pembrolizumab; Gy: Gray
Triweekly: Three times a week; Biweekly: Two times a week.

other therapies, including alkylating agents and radiotherapy. Table 1 provides a detailed presentation of the included studies. Among the 12 included studies, 11 (Fanucci et al., 2023; Sarkaria et al., 2024; Sim et al., 2021; Robins et al., 2016; Kleinberg et al., 2023; Schaff et al., 2022; Stefan et al., 2025; Karajannis et al., 2025; Vazquez I et al., 2024; Derby et al., 2024; Baxter et al., 2020) provided separate data on HGGs, enabling distinct analyses of tumor type, IDH mutation, MGMT methylation, treatment regimen, and concomitant therapy.

3.3. Disease control rate (DCR)

The pooled DCR for patients with HGGs was 27% [95%CI:0.09–0.57] in eight studies (Fanucci et al., 2023; Sim et al., 2021; Robins et al., 2016; Kleinberg et al., 2023; Schaff et al., 2022; Vazquez I et al., 2024; Derby et al., 2024; Baxter et al., 2020), with no difference between Olaparib and Veliparib subgroups ($p = 0.19$). The observed heterogeneity was significant ($I^2 = 87.36\%$, $\tau^2 = 3.37$; $P < 0.001$). However, there was no significant publication bias ($p = 0.31$). The predicted DCR interval for Olaparib, Veliparib, and overall was (26.0–65.4)%, (0−100)%, and (0.4–97.1)% (Fig. 2). Additionally, neither MGMT methylation nor IDH status was found to significantly alter DCR in our analysis.

3.4. Overall survival (OS) and progression-free survival (PFS) rates

The six-month, one-, two-, and three-year OS in patients with HGGs were reported to be 87% [95%PI:69.5–94.9], 60% [95%PI:17.6–91.6], 30% [95%PI:2.2–89.2], and 22% [95%PI:0.05–93.7], respectively. There was no significant difference between the Olaparib and Veliparib groups at any time point.

The six-month and one-year PFS rate in patients with HGGs was reported to be 38% [95%PI:4.0–90.3] and 23% [95%PI:2.8–75.1], respectively. There was no significant difference between the Olaparib and Veliparib groups at any time point.

Because the available fixed-time OS and PFS data were predominantly derived from grade 4 glioma cohorts, the overall HGG survival estimates largely reflect outcomes in grade 4 disease rather than an independent grade 3–4 evidence base. Therefore, the overall HGG OS/PFS estimates should be interpreted primarily as descriptive summaries of the grade 4-dominant dataset.

3.5. Severe adverse event rate (Grades 3 and 4)

Adverse events were reported in all studies, with only seven (Fanucci et al., 2023; Sim et al., 2021; Robins et al., 2016; Schaff et al., 2022; Stefan et al., 2025; Vazquez I et al., 2024; Derby et al., 2024) providing the total event counts, along with separate counts for each grade (Ostrom et al., 2017; Louis et al., 2021; Clementi et al., 2020; Singh et al., 2021). A pooled severe adverse event rate analysis was performed, resulting in 13% [95%CI:0.08–0.21]. Subgroup analysis revealed no significant difference between the Olaparib- and Veliparib-treated groups, with pooled severe adverse event rates of 12% [95% CI:0.07–0.18] and 16% [95%CI:0.07–0.31], respectively ($P = 0.50$). The observed heterogeneity was significant ($I^2 = 92.94\%$, $\tau^2 = 0.62$; $P < 0.001$).

In addition, in a subgroup analysis regarding concomitant therapies, a pooled severe adverse event rate of 5% [95%CI: 0.02–0.14], 7% [95% CI: 0.01–0.36], and 21% [95%CI:0.17–0.26] were observed in radiotherapy alone, radiotherapy and Temozolomide, and Temozolomide alone, respectively. A notable difference was observed among the three groups ($P = 0.01$). The observed heterogeneity was significant ($I^2 = 94.94\%$, $\tau^2 = 0.72$; $P < 0.001$). Additionally, publication bias was also

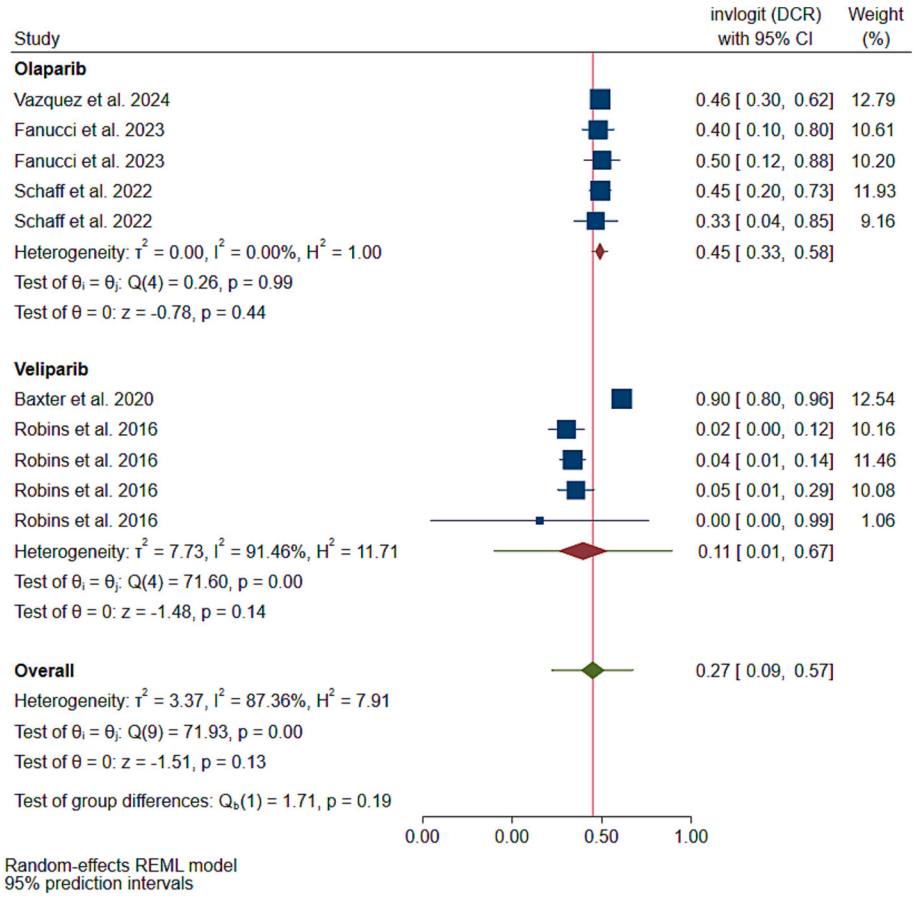

Fig. 2. DCR forest and funnel plots.

significant ($P = 0.03$).

3.6. Subgroup analyses

3.6.1. Grade 4 gliomas; adult GBM and pediatric diffuse intrinsic pontine glioma (DIPG)

A targeted subgroup analysis of grade 4 gliomas was conducted using seven studies (Sarkaria et al., 2024; Sim et al., 2021; Robins et al., 2016; Kleinberg et al., 2023; Stefan et al., 2025; Derby et al., 2024; Baxter et al., 2020). Because nearly all analyzable fixed-time OS and PFS data contributing to the overall HGG survival estimates came from grade 4 cohorts, the pooled grade 4 OS/PFS estimates were numerically identical to the corresponding overall HGG estimates. We therefore present the grade 4 analysis not as an independent corroborative analysis, but as a clarification that the survival evidence base is grade 4-dominant. The six-month, one-, two-, and three-year OS in patients with grade 4 gliomas were reported to be 87% [95%PI:69.5–94.9], 60% [95% PI:17.6–91.6], 30% [95%PI:2.2–89.2], and 22% [95%PI:0.5–93.7], respectively. The six-month and one-year PFS rate in patients with grade 4 glioma was reported to be 38% [95%PI:4.0–90.3] and 23% [95% PI:2.8–75.1], respectively. No significant OS or PFS differences were observed between Veliparib and Olaparib at any time points. Additionally, GBM and DIPG showed no significant differences in OS or PFS at any time point, except for the two-year OS rate, where GBM exhibited higher rates than DIPG ($P = 0.02$). Also, regarding concomitant therapies, patients receiving concomitant TMZ alone had higher six-month and one-year OS than those receiving concomitant radiotherapy alone ($P = 0.02$ and < 0.001, respectively). However, the latter result should be interpreted with caution, since there was only one study on DIPG (by Baxter et al. (Baxter et al., 2020)), and no sensitivity analysis for comparison was possible. It should also be noted that radiotherapy alone was not a concomitant therapy used only in DIPG, but was also a concomitant therapy used in GBM (in the study by Derby et al. (Derby et al., 2024)), which included newly diagnosed GBMs and patients with prior radiotherapy or chemotherapy for CNS tumors, both of which were among their exclusion criteria.

3.6.2. Recurrent and newly diagnosed GBM

Four studies (Sarkaria et al., 2024; Sim et al., 2021; Robins et al., 2016; Stefan et al., 2025) were included in a subgroup analysis comparing recurrent and newly diagnosed GBMs. The data were sufficient only for comparing 6-month PFS, in which recurrent and newly diagnosed GBM had 15% [95%CI:0.10–0.22] and 60% [95% CI:0.40–0.77], respectively ($P < 0.001$). The PI for 6-month PFS recurrent and newly-diagnosed GBM were (5.7–33.1)%, and (0–100)%, respectively. The observed heterogeneity was significant ($I^2 = 95.25\%$, $\tau^2 = 2.01$; $P < 0.001$). Additionally, publication bias was also significant ($P < 0.001$). Given the limited number of studies, the availability of only one comparable time point, substantial heterogeneity, and evidence of publication bias, this subgroup result should be interpreted as exploratory and hypothesis-generating rather than as evidence of a reliable difference between newly diagnosed and recurrent GBM.

3.6.3. MGMT methylation in HGGs

Only five studies (Fanucci et al., 2023; Sarkaria et al., 2024; Sim et al., 2021; Stefan et al., 2025; Derby et al., 2024) reported distinctive data on MGMT methylation in HGGs, of which four included GBMs. HGGs with methylated MGMT had significantly higher two-year OS rate than unmethylated MGMT HGGs ($P < 0.001$). The PFS rate, on the other hand, was significantly higher in methylated HGGs at the one-year follow-up ($P < 0.001$), but not at the six-month follow-up ($P = 0.09$) (Fig. 3).

3.6.4. IDH mutations in HGGs

As shown in Fig. 4, only four studies (Fanucci et al., 2023; Schaff et al., 2022; Karajannis et al., 2025; Vazquez I et al., 2024) reported distinct data on IDH mutations in HGGs. One- and two-year OS rate was significantly higher in the IDH-wildtype HGGs than the mutant ($P = 0.01$ and $P < 0.001$, respectively). Additionally, a similar pattern emerged in six-month and one-year PFS rates ($P = 0.02$ and < 0.001, respectively). Because only a small number of studies contributed to this subgroup analysis, and the statistical significance of the PFS comparison changed after adopting logit-transformed random-effects pooling, these findings should be interpreted cautiously as exploratory and potentially sensitive to the pooling methodology. Unfortunately, unlike the MGMT subgroup analysis, stratification by exact tumor type was not possible due to insufficient data.

3.7. Quality assessment and publication bias

Quality assessment results are presented in **Supplementary File 2**. Among non-randomized or single-arm studies assessed using MINORS, scores ranged from 9/16 to 14/16 for non-comparative studies and from 16/24 to 21/24 for comparative studies. The lowest MINORS score was observed in the retrospective case series by Schaff et al. (Schaff et al., 2022), mainly due to retrospective data collection, limited follow-up reporting, and a lack of prospective sample-size calculation. For randomized trials assessed using RoB 2, Sarkaria et al. (Sarkaria et al., 2024), Sim et al. (Sim et al., 2021), and Robins et al. (Robins et al., 2016) were judged to have an overall low risk of bias. However, each had some concerns regarding the randomization process. Funnel plots and Egger's tests are presented in **Supplementary File 3**. Evidence of publication bias was detected for some outcomes, including newly diagnosed versus recurrent GBM 6-month PFS and severe adverse events.

4. Discussion

This systematic review and meta-analysis provide a comprehensive evaluation of the most recent data on the safety and efficacy of PARP inhibitors in patients with HGG. The summary is shown in Tables 2 and 3. The overall pooled DCR of 27% across the included studies suggests that some patients achieved disease control; however, none of the studies establish a predefined DCR threshold for clinical benefit, necessitating cautious interpretation of the clinical significance of this finding. Our subgroup analysis revealed no significant difference in DCR between Olaparib and Veliparib ($P = 0.19$). However, the prediction interval for the overall DCR was extremely wide (0.4–97.1), indicating that the pooled estimate has limited clinical interpretability and should not be used to predict the expected DCR in a future study or patient population. Accordingly, this estimate is best viewed as a descriptive summary of a heterogeneous evidence base rather than evidence of a consistent treatment effect.

Our findings indicate that IDH mutation does not consistently correlate with PARP sensitivity, suggesting that the interactions among DNA repair mechanisms, therapeutic administration, and tumor microenvironment may be more influential than traditional pathway predictions in vivo. Although IDH mutation is a known favorable predictive marker for response to chemo, radiation, and PARP inhibitors (Karpel-Massler et al., 2019; Li et al., 2013; Shi et al., 2015; Sulkowski et al., 2017), our pooled analysis revealed superior OS in IDH-wildtype patients. This may be because many IDH-mutant gliomas have a more favorable natural history and strong responses to standard chemoradiation, potentially obscuring the incremental benefit of PARP inhibition in non-stratified trials. However, the discrepancy emphasizes the complexity of PARP biology in glioma. Recurrent EGFR amplification induces replication stress and ATR activation, creating a context in which PARP inhibition can cause severe DNA damage (Wu et al., 2020). PTEN loss, a characteristic of IDH-wildtype disease, impairs RAD51-mediated HR and enhances the efficacy of PARP inhibitors in vitro, particularly when combined with topoisomerase I inhibitors such as Indotecan (Kim et al., 2023; McEllin et al., 2010). From a pharmacologic

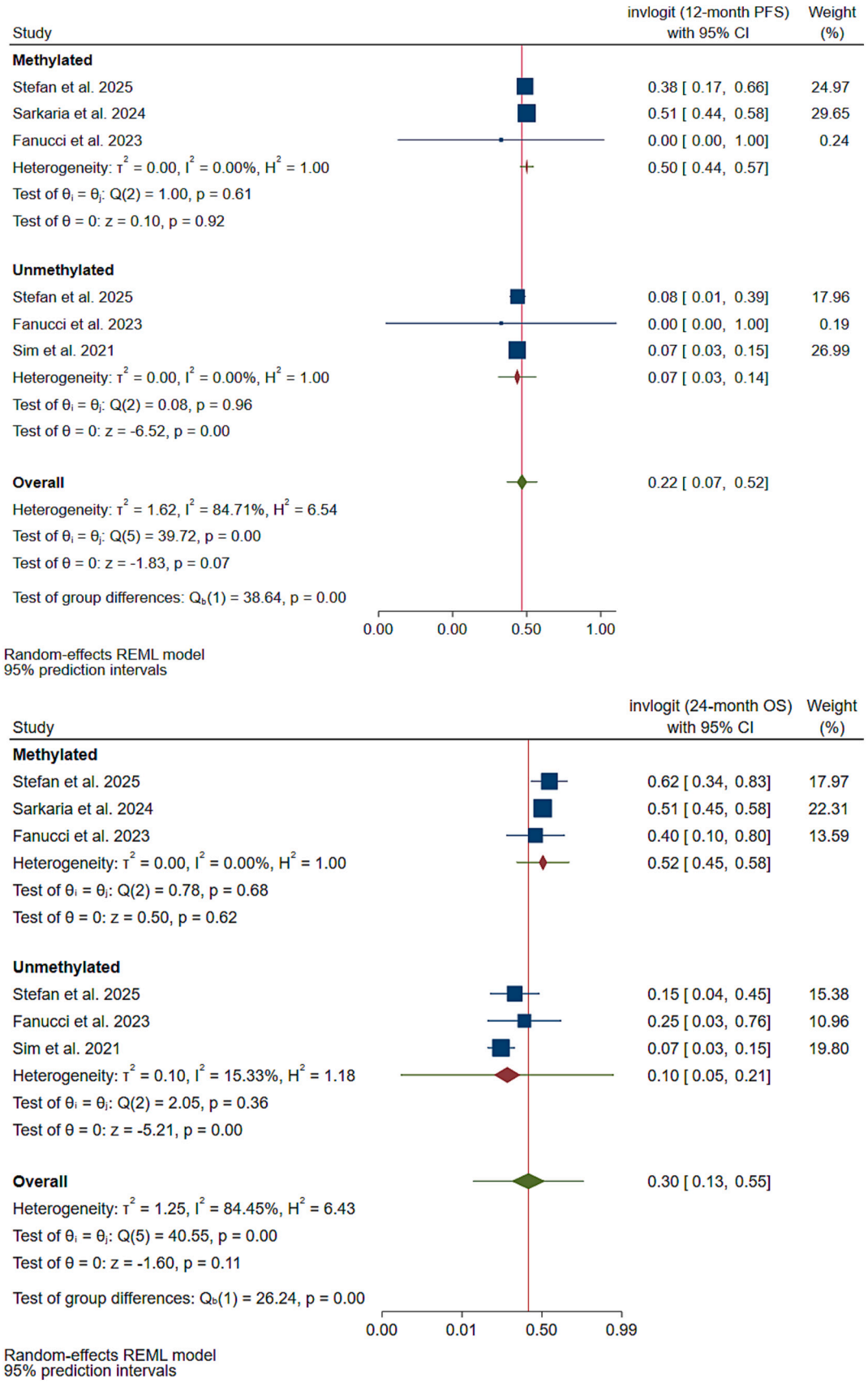

Fig. 3. OS and PFS in HGGs regarding MGMT methylation.

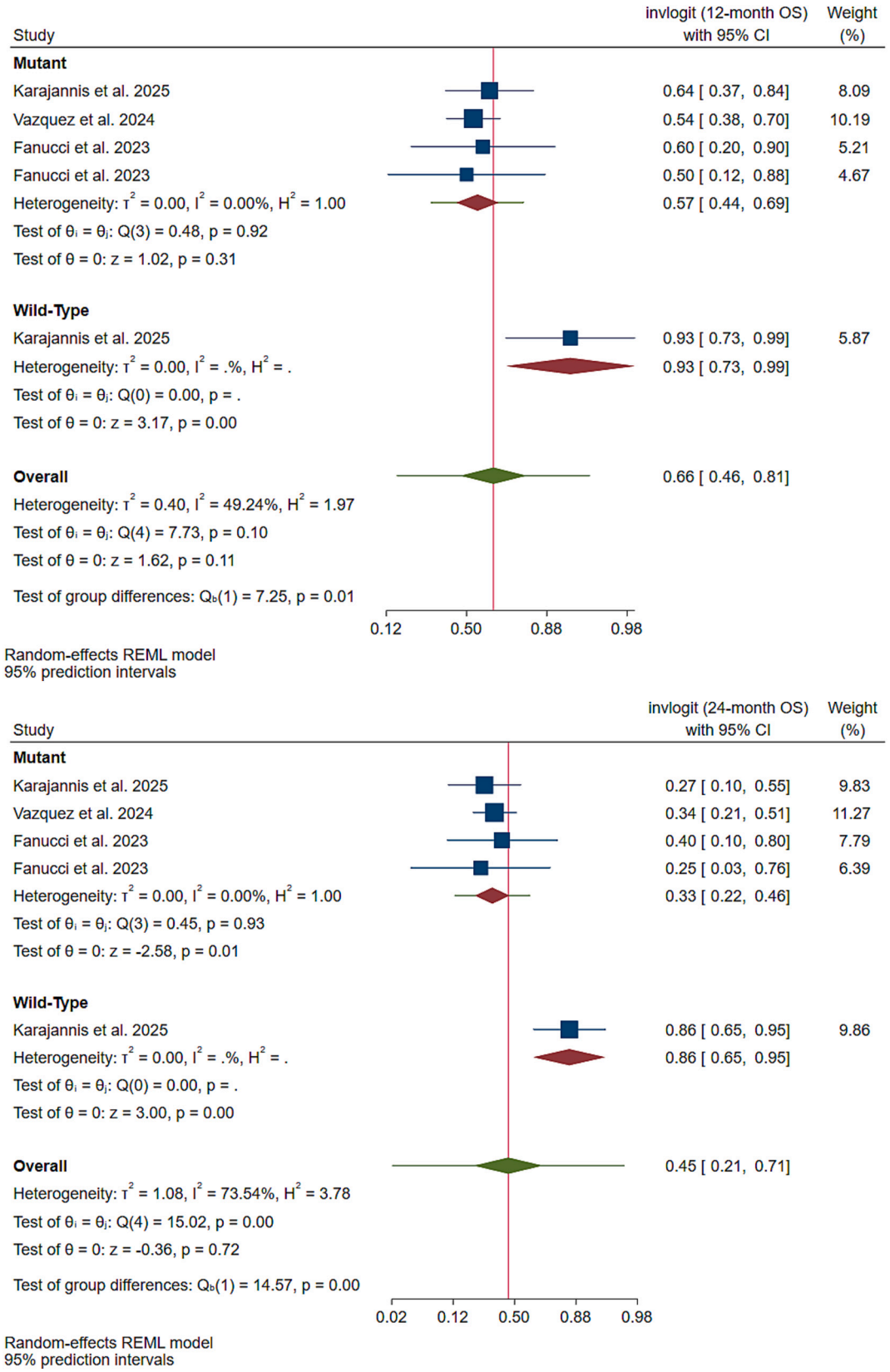

Fig. 4. OS and PFS in HGGs regarding IDH mutation.

perspective, IDH-wildtype gliomas generally demonstrate increased disruption of the blood-tumor barrier, resulting in elevated intratumoral concentrations of Olaparib compared to the relatively preserved blood-brain barrier observed in many IDH-mutant astrocytomas, as indicated by the OPARATIC pharmacokinetic study (Hanna et al., 2020; Bejarano et al., 2025; Waitkus et al., 2018). The interplay of genomic stress, repair

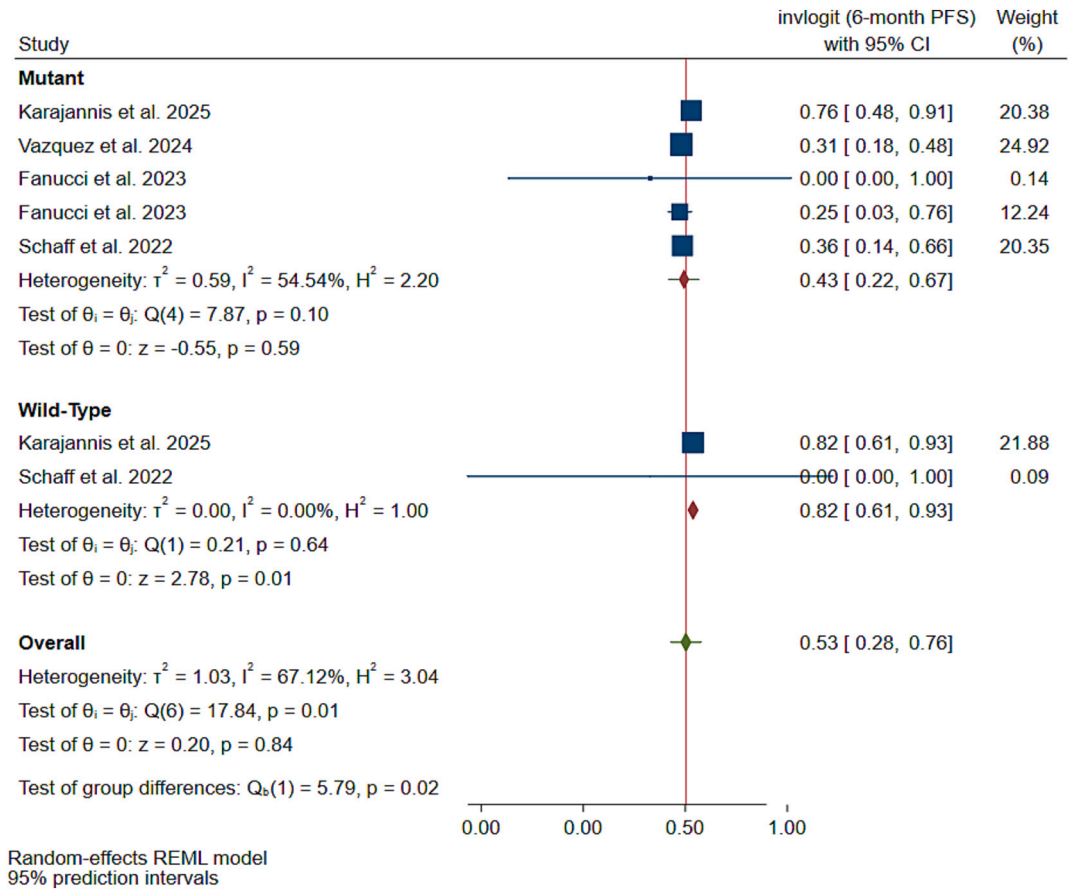

Fig. 4. (*continued*).

Table 2
Main pooled outcomes for PARP inhibitors in HGGs.

Outcome	Number of Studies	Pooled Estimate (%)	95% CI	95% PI	I^2 (%)
DCR	5	27	9–57	0.4–97.1	87.36
6-month OS	8	87	81–91	69.5–94.9	35.5
1-year OS	8	60	46–73	17.6–91.6	82.7
2-year OS	8	30	16–50	2.2–89.2	89.3
3-year OS	5	22	8–48	0.05–93.7	89.5
6-month PFS	9	38	23–56	4.0–90.3	90.8
1-year PFS	8	23	12–38	2.8–75.1	81.9
Severe AE	7	13	8–21	2.2–51.2	92.94

Notes: DCR: Disease control rate; OS: Overall survival; PFS: Progression-free survival; AE: Adverse event; CI: Confidence interval; PI: Prediction interval. Survival estimates are based on high-grade glioma data but are grade 4-dominant because most analyzable fixed-time OS/PFS data came from grade 4 glioma cohorts. Prediction intervals are shown where available. All pooled estimates should be interpreted as descriptive summaries rather than stable estimates of expected clinical effect.

deficits, and enhanced drug delivery offers a biologically plausible rationale for the increased overall survival in IDH-wildtype disease.

The importance of underlying tumor biology in determining PARP inhibitor efficacy is well recognized. For instance, Murnyák et al. reported that PARP1 overexpression was more pronounced in proneural and classical-specific glioblastoma subtypes (ATRX and TP53 mutants). This factor could contribute to varying responses to PARP inhibition (Murnyák et al., 2017). This suggests that while Olaparib and Veliparib may have similar efficacy at a broader population level in our analysis, individual patient responses could still be significantly influenced by molecular characteristics such as PARP1 expression or other subtype-specific factors not fully elucidated in this pooled analysis, and thus, suggesting the application of advanced "omic" strategies for patient selection (Fanucci et al., 2023; Vazquez I et al., 2024). For example, RNA-based profiling also enables the assessment of DNA damage response (DDR) programs, SLFN11 expression (a reproducible biomarker of sensitivity to PARP inhibitors and alkylators), and transcriptomic HR deficiency scores that capture functional DNA repair impairment, even in the absence of canonical BRCA or IDH lesions (Zhou et al., 2025; Lok et al., 2017). Recent studies have shown promising results using genomic and transcriptomic models to predict HR deficiency with precision across various cancer types (Scattolin et al., 2024; Lee et al., 2024). Additionally, emerging machine-learning methodologies that consolidate these molecular layers into cohesive predictive frameworks may facilitate the prospective identification of PARP-sensitive glioma states, thereby minimizing biological noise and enhancing trial efficiency in forthcoming biomarker-enriched studies (Jiang et al., 2024).

Recent evidence suggests that glioma progression and therapeutic response are influenced by regulatory programs that operate alongside traditional oncogenic signaling and DNA damage repair mechanisms. Dysregulation of ion channels, including voltage-gated potassium and calcium channels, as well as chloride conductances, has been associated with glioma proliferation, invasion, metabolic adaptation, and treatment resistance (Elias et al., 2023). In parallel, single-cell and functional studies demonstrate that malignant glioblastoma cells occupy distinct transcriptional cell states and can undergo plastic state transitions, contributing to intratumoral heterogeneity and variable treatment responses (Neftel et al., 2019). Epigenetic regulators, such as chromatin modifiers and noncoding RNAs, are consistently associated with therapy-induced reprogramming and resistance phenotypes

Table 3
Exploratory subgroup comparisons.

Outcome	Veliparib vs Olaparib	MGMT methylated vs unmethylated	Mutant vs wildtype IDH	Adult GBM vs pediatric DIPG	Newly diagnosed vs recurrent GBM	Concomitant therapy
DCR	0.19	NA	0.68	NA	NA	<0.001*
6-month OS	0.47	0.048*	0.43	0.57	NA	0.02*
1-year OS	0.35	0.18	0.01*	0.12	NA	<0.001*
2-year OS	0.64	<0.001*	<0.001*	0.02*	NA	0.01*
3-year OS	0.85	NA	NA	<0.001*	NA	<0.001*
6-month PFS	0.89	0.09	0.02*	0.18	<0.001*	0.05
1-year PFS	0.45	<0.001*	<0.001*	0.4	NA	0.22
Severe AE	0.5	NA	NA	NA	0.06	0.01*

Notes: DCR: Disease control rate; OS: Overall survival; PFS: Progression-free survival; AE: Adverse event; GBM: Glioblastoma; DIPG: Diffuse intrinsic pontine glioma; NA: Not applicable.
Values represent nominal between-group *P* values.
These subgroup analyses were not adjusted for multiple comparisons and should be interpreted as exploratory rather than confirmatory.

(Amirmahani et al., 2025). Various signaling systems that are crucial to GBM aggressiveness and resistance, such as PI3K/AKT and MAPK networks, interact with stress-response pathways. These include DNA damage response pathways and immune-sensing/inflammatory signaling, such as the cGAS/STING pathway, highlighting therapeutic vulnerabilities that depend on context (Pouyan et al., 2025; Low et al., 2024; Ji et al., 2022; Lan et al., 2024). In addition to innate immune sensing, the prognosis and treatment response of glioma are influenced by extensive inflammatory processes, such as macrophage polarization and TGF-β–mediated immunoregulation. These processes can be analyzed through transcriptomic signatures, which may elucidate the varied outcomes observed in biomarker-defined subgroups (Zeng et al., 2022; Duan et al., 2024).

Olaparib monotherapy led to a median PFS of 3.63 months in IDH1/2-mutant gliomas in a multicenter phase II trial by Fanucci et al., with prolonged stable disease in grades 2 and 3 gliomas and in MGMT unmethylated HGGs (Fanucci et al., 2023). Both Fanucci et al. (Fanucci et al., 2023) and Murnyák et al. (Murnyák et al., 2017) reported promising results with Olaparib in IDH-mutant HGGs. This aligns with the concept of synthetic lethality, where PARP inhibition may be particularly effective in tumors with deficiencies in DNA repair mechanisms. This implies that although PARP inhibitors have certain advantages, the manner in which they slow disease progression may vary depending on the type of glioma (Su et al., 2014; Baxter et al., 2020). The pooled severe adverse event rate of 14% suggests that PARP inhibitors are generally well-tolerated in glioma patients, particularly in those with early-onset gliomas (Kleinberg et al., 2023; Derby et al., 2024).

The combination of PARP inhibitors with other treatment modalities, such as radiotherapy and Temozolomide, represents another promising avenue for improving outcomes in glioma patients. Bisht et al. (Bisht et al., 2024) demonstrated that combining Naringin and Temozolomide in vitro can significantly enhance anti-glioma effects by targeting PARP-1 and other DNA repair enzymes. However, the durability of response remains a challenge, similar to those observed with bevacizumab in recurrent low-grade glioma (Habibi et al., 2024). Radiotherapy-alone cohorts showed high DCR and relatively favorable 6-month PFS in exploratory subgroup analyses, but these findings should be interpreted cautiously given limited data and substantial heterogeneity.

However, unlike the survival trends observed in our exploratory analyses, the previous meta-analysis did not find a significant overall survival advantage with the addition of targeted therapies in phase III trials, potentially due to differences in the mechanisms of action and patient populations. Notably, both meta-analyses report that combining targeted therapies with chemoradiotherapy did not result in a statistically significant increase in adverse events, suggesting these combinations can be integrated into glioma management without compromising safety. Still, finding a balance between toxicity and efficacy is a challenge.

Beyond Temozolomide and radiotherapy, PARP inhibitors have been studied in combination with other DDR drugs and, to a lesser extent, immunotherapy. Berzosertib and AZD6738 suppress ATR in glioma models. CRISPR-based chemogenomic screens have shown that PARP and ATR inhibition have considerable synthetic lethality, encouraging the development of PARP-ATR regimens (Niraparib plus Elimusertib) to improve responsiveness and address PARP inhibitor resistance (Walter et al., 2024; Zimmermann et al., 2022; Lin et al., 2025; Wengner et al., 2023). Pre-clinical studies in PTEN-deficient glioblastoma show that PARP inhibitors (Niraparib or Olaparib) and non-camptothecin topoisomerase I inhibitors (LMP400/Indotecan, LMP744) synergistically target PTEN-null cells, supporting biomarker-driven trials in this population (Kim et al., 2023; Kim et al., 2022). Combination evaluations increasingly recommend PARP inhibitors with ATM, CHK1, and WEE1 to leverage replication stress and overcome resistance. Due to PARP inhibitor-induced STING activation and PD-L1 upregulation, they investigate PARP-immune checkpoint inhibitor combinations such PD-1/PD-L1 and CTLA-4. Clinical data on glioma are currently being developed, mostly from solid tumor investigations (Rodriguez et al., 2024; Wang et al., 2025; Chu et al., 2022). Higher-potency and brain-penetrant agents, such as Niraparib, Olaparib, Pamiparib, and the PARP1-selective NMS-293, demonstrated effective intratumoral drug delivery and PARP pathway suppression. Ongoing randomized, biomarker-enriched trials are evaluating the role of PARP inhibition in glioma treatment (Table 4).

4.1. Limitations

While this is the first systematic review and data synthesis of the existing literature on PARP inhibitors in patients with gliomas, several caveats should be considered. The primary drawback of the current study is the limited number of papers and patients, which limits the ability to draw solid conclusions and perform various subgroup analyses, especially since most studies were early-phase and single-arm. Second, of the available PARP inhibitors, only two (Olaparib and Veliparib) were used and reported; therefore, we cannot be certain that the results of this study can be generalized to all PARP inhibitors. In addition, the significant heterogeneity in study designs, patient populations, treatment regimens, tumor types, and, especially, prior treatments across the included studies has a major impact on the generalizability of our results. Furthermore, the long-term outcomes of PARP inhibitors in glioma patients remain uncertain, given the limited follow-up periods in most studies, especially regarding more invasive types such as GBM or DIPG. The potential for late toxicities and the development of resistance mechanisms over time are important considerations that require further investigation.

Table 4
Ongoing trials involving PARP inhibitors in glioma.

PARP inhibitor(s)	NCT	Concomitant therapies	Comparative	Phase & Design	Population & Biomarker Focus	Main Outcomes	Status
Niraparib	NCT06388733	RT	TMZ + RT	Phase III, randomized, parallel-arm, active-controlled	Adults with newly diagnosed, MGMT-unmethylated GBM.	Primary: PFS up to 24 months. Key secondary: OS vs TMZ.	Recruiting
Olaparib	NCT03212742	RT (IMRT) + TMZ	Single-arm	Phase I/IIa, open-label; dose-escalation then expansion.	Unresectable HGGs (including GBM) treated in the upfront setting; no biomarker selection.	Phase I primary: determine RP2D; Phase II primary: 18-month OS in unresectable GBM.	Active, not recruiting
Olaparib	NCT02974621	Cediranib Maleate	Bevacizumab	Randomized phase II, 1:1, active-controlled	Adults with recurrent GBM (first/s recurrence), bevacizumab-naïve after prior RT + TMZ.	Primary: PFS at 6 months (PFS-6). Secondary: OS and safety; exploratory: blood/tissue/imaging biomarkers of response.	Active, not recruiting (closed to accrual and intervention)
NMS-03305293 (NMS-293)	NCT04910022	TMZ	Lomustine	Multi-center, open-label Phase 1/2 dose-escalation and expansion	Phase 1: adult diffuse gliomas at first relapse. Phase 2: adult IDH-wt recurrent GBM at first relapse; sponsor may restrict by MGMT status.	Phase 1 primary: MTD and RP2D; Phase 2 primary: antitumor effectiveness in IDH-wt GBM (RANO, PFS).	Active, not recruiting (closed to accrual)
Pamiparib, Olaparib	NCT04614909	TMZ	NA	Phase 0/2 (early Phase 1), open-label, single-center	Newly diagnosed and recurrent GBM; Phase 2 enrichment based on intratumoral drug exposure (PK).	Phase 0 focuses on intratumoral PK/PD; exploratory Phase 2 focuses on efficacy signals (radiographic response, PFS)	Recruiting (early Phase 1 / Phase 0–2)
Talazoparib	NCT04740190	Carboplatin + RT	Single-arm	Phase II, single-arm "TAC-GReD"	Recurrent HGG with dDDR, including IDH or PTEN mutation, or "BRCAness" signature by NGS profiling.	Primary: PFS-6 by RANO. Secondary: safety/tolerability, OS, and correlation of biomarkers (DDR alterations) with outcomes.	Completed (results analysis ongoing)
Veliparib (ABT-888)	NCT03581292	RT + TMZ after Chemoradiation	NA	Phase II	Newly diagnosed HGG (GBM, anaplastic astrocytoma, malignant glioma) without H3 K27M or BRAFV600 mutations.	Efficacy (PFS and OS), Safety	Active, not recruiting
Olaparib	NCT05188508	Pembro + TMZ	NA	Phase II, open-label, non-randomized	Cohort A: recurrent grade II–III IDH-m glioma. Cohort B: recurrent IDH-wt glioma with deleterious HRR-gene mutations (BRCA1/2, ATM, CHEK2).	Primary: ORR; Secondary: safety, toxicity, PFS, OS, and radiographic response.	Recruiting
Olaparib	NCT05463848	Pembro + TMZ	Pembro	Phase II, open-label, multi-center	Adults with recurrent GBM (IDH-wt GBM, gliosarcoma, HGG) at relapse undergoing re-resection.	Safety and efficacy (toxicity profile, antitumor activity such as response/PFS).	Recruiting

Notes: dDDR: deficiency in DNA damage repair; MTD: Maximum tolerated dose; Pembro: Pembrolizumab; TMZ: Temozolomide; HGG: High-grade glioma; RP2D: Recommended Phase 2 Dose; HRR: Homologous Recombination Repair; IDH-wt: IDH-wildtype; PFS: Progression-free survival; OS: overall survival; ORR: Overall response rate; IDH-m: IDH-mutant; NA: Not available; PK: Pharmacokinetics; PD: Pharmacodynamics

Some methodological limitations also require special attention. Several subgroup analyses were conducted without formal adjustment for multiple comparisons, and the resulting *p*-values should therefore be interpreted as exploratory and hypothesis-generating rather than confirmatory. Moreover, substantial statistical heterogeneity was observed across multiple pooled outcomes, reflecting marked clinical and methodological diversity among included studies. While random-effects models were utilized, pooled estimates in the context of significant heterogeneity should be considered descriptive summaries rather than accurate representations of a common treatment effect. Moreover, harmonizing outcomes based on fixed-time survival milestones fails to adequately account for key differences in disease context, including distinctions between newly diagnosed and recurrent disease, varying response assessment schedules, and differing definitions of disease control across trials.

Although a formal risk-of-bias assessment was performed using MINORS and RoB 2, the overall certainty of evidence should be regarded as very low. Under a GRADE framework, the evidence base would be downgraded because most efficacy data were derived from early-phase, single-arm, or non-randomized studies; several outcomes showed substantial statistical heterogeneity; prediction intervals were wide; subgroup analyses were limited by small numbers of studies and inconsistent clinical contexts; and publication bias was detected for some outcomes. Therefore, the present findings should be interpreted as descriptive and hypothesis-generating rather than as evidence supporting a definitive clinical effect.

Collectively, these factors limit the clinical generalizability of pooled estimates to specific patient subgroups and underscore the need for more homogeneous, biomarker-stratified trials and individual patient-level meta-analyses. Further research with larger sample sizes and various designs is required to investigate this field in greater detail and to evaluate other PARP inhibitors, along with extensive, more specific follow-up data.

5. Conclusion

The available evidence suggests investigational clinical activity of PARP inhibitors in selected high-grade glioma populations, particularly grade 4 glioma cohorts treated with radiotherapy and/or Temozolomide; however, the certainty of evidence is very low because of early-

phase study designs, limited controlled data, substantial heterogeneity, wide prediction intervals, and sparse biomarker-stratified subgroup data. The efficacy data presented in this review predominantly originate from adult HGG cohorts. In contrast, the safety and toxicity outcomes encompass a broader range of glioma populations, including pediatric patients and mixed-grade tumors. Therefore, conclusions about therapeutic benefits should be approached with caution beyond adult HGG populations, particularly in pediatric and lower-grade gliomas, where the evidence is still limited and varied. Additional randomized controlled trials with extended follow-up are needed to determine the efficacy of PARP inhibitors across various glioma subtypes and age groups. Future research must focus on biomarker-driven patient selection, the optimization of combination strategies, and the mechanisms of resistance to clearly define the role of PARP inhibition in glioma treatment as molecular stratification evolves.

CRediT authorship contribution statement

Farhang Rashidi: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mohammadmahdi Sabahi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Ali Allahdadi:** Writing – review & editing, Writing – original draft, Resources, Data curation. **Pouria Delbari:** Writing – review & editing, Writing – original draft, Software, Resources. **Mohammad Amin Habibi:** Methodology, Investigation, Data curation, Conceptualization. **Sahar Fathi Tavani:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation. **Amirhossein Zare:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation. **Shahab Aldin Sattari:** Writing – review & editing, Writing – original draft, Resources, Investigation. **Safwan Alomari:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation. **Mohammad Mofatteh:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources. **Mohammad Sadegh Mashayekhi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Shima Shahjouei:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis. **Surabhi Ranjan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Investigation. **Badih Adada:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Roukoz B. Chamoun:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Hamid Borghei-Razavi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources.

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Informed consent

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Consent for publication

All authors give their consent to the submission of this article to the Journal of Neuroimmunology.

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Declaration of competing interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2026.579021.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

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