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REVIEW

The clinical benefit of adding anlotinib to chemoradiothearpy in high-grade gliomas: a systematic review, meta-analysis, and specific analysis on glioblastoma

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Abstract

Anlotinib, a novel multi-target tyrosine kinase inhibitor, has shown promise in improving survival and managing associated complications. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of Anlotinib in patients with high-grade glioma, specifically glioblastoma (GBM). This study was conducted according to the PRISMA guidelines. A systematic search was conducted on PubMed, Embase, Web of Science, and Scopus up to 9 December 2024. The included studies were appraised and assessed for quality and potential bias and further statistical analyses were performed using STATA v.17. A total of 17 studies with 473 patients were recruited, which included 204 patients with GBM. The pooled analysis resulted in a 6-month OS of 67% (95% CI: 42–92%) and a 1-year OS equal to 50% (95% CI: 36–64%) from the Anlotinib treatment. Progression-free survival at 6 months was 61% (95% CI: 46–75%), and at 1 year was 27% (95% CI: 13–41%), also showing similar promising outcomes. The overall response rate (ORR) and disease control rate (DCR) were reported at 55% (95% CI: 44–67%) and 90% (95% CI: 87–94%), respectively. The sub-group analysis revealed that adding anlotinb to temozolomide (TMZ) and radiotherapy had superior outcomes regarding OS, PFS, and DCR. Moreover, the highest ORR and complete response rate were achieved by Anlotinib plus stereotactic radiosurgery. Anlotinib demonstrates considerable efficacy in extending survival and achieving disease control in high-grade glioma patients when added to radiotherapy and TMZ. These findings can support its inclusion in therapeutic regimens, warranting further investigation in large-scale randomized controlled trials.

Keywords Tyrosine kinase inhibitor · TKI · Glioma · Glioblastoma · GBM

Abbreviations

CR	complete response
PR	partial response
PD	progressive disease
OS	overall survival
PFS	progression-free survival

Introduction

Gliomas are a heterogeneous group of primary brain tumors that present considerable challenges in neuro-oncology [1], Subtypes such as astrocytomas, oligodendrogliomas, ependymomas, and glioblastomas exhibit significant variability in biological behavior and prognosis [2]. Even though multimodal treatment strategies like maximal surgical resection, radiation therapy, and chemotherapy have gotten better, the outlook for people with high-grade gliomas is still not good.

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The median survival time for these patients ranges from 1 to 5 years, depending on the subtype and grade [3]. For lower-grade gliomas, survival may last for several years; however, progression to higher grades frequently occurs [4].

The infiltrative nature of gliomas, in addition to their molecular heterogeneity and resistance to standard therapies, contributes to the overall difficulty in achieving durable outcomes [5]. Current treatment challenges encompass the inability to attain complete surgical resection owing to the diffuse growth patterns of gliomas, the constraints imposed by the blood-brain barrier on systemic therapy delivery, and the tumors' intrinsic resistance to chemotherapy and radiotherapy [6, 7]. These obstacles raise the sense of need for innovative therapeutic approaches targeting glioma-specific pathways while maintaining manageable toxicity profiles [8].

Anlotinib, a novel multi-target tyrosine kinase inhibitor (TKI), has emerged as a promising candidate in glioma therapy [9–11]. Its mode of action entails the suppression of critical pathways integral to tumor angiogenesis and proliferation, encompassing vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors (FGFRs), and platelet-derived growth factor receptors (PDGFRs). After these pathways are disrupted, Anlotinib reduces the vascular support required for tumor growth and progression. This makes it a possible treatment for people with different types of gliomas (Fig. 1) [11].

Preliminary studies have indicated that Anlotinib may improve progression-free survival (PFS) and overall survival (OS) in glioma patients while maintaining a manageable safety profile [9, 10]. Commonly reported adverse events (AE) are known to be hand-foot syndrome and hypertension, being generally mild to moderate in severity, reinforcing its feasibility in clinical practice [10, 11]. However, data remain scattered across small-scale studies with variable methodologies, necessitating a comprehensive evaluation of its efficacy and safety; therefore, in this systematic review and meta-analysis, we aimed to synthesize the available evidence on the role of Anlotinib in high-grade glioma treatment, focusing on survival outcomes, response rates, and adverse event profiles.

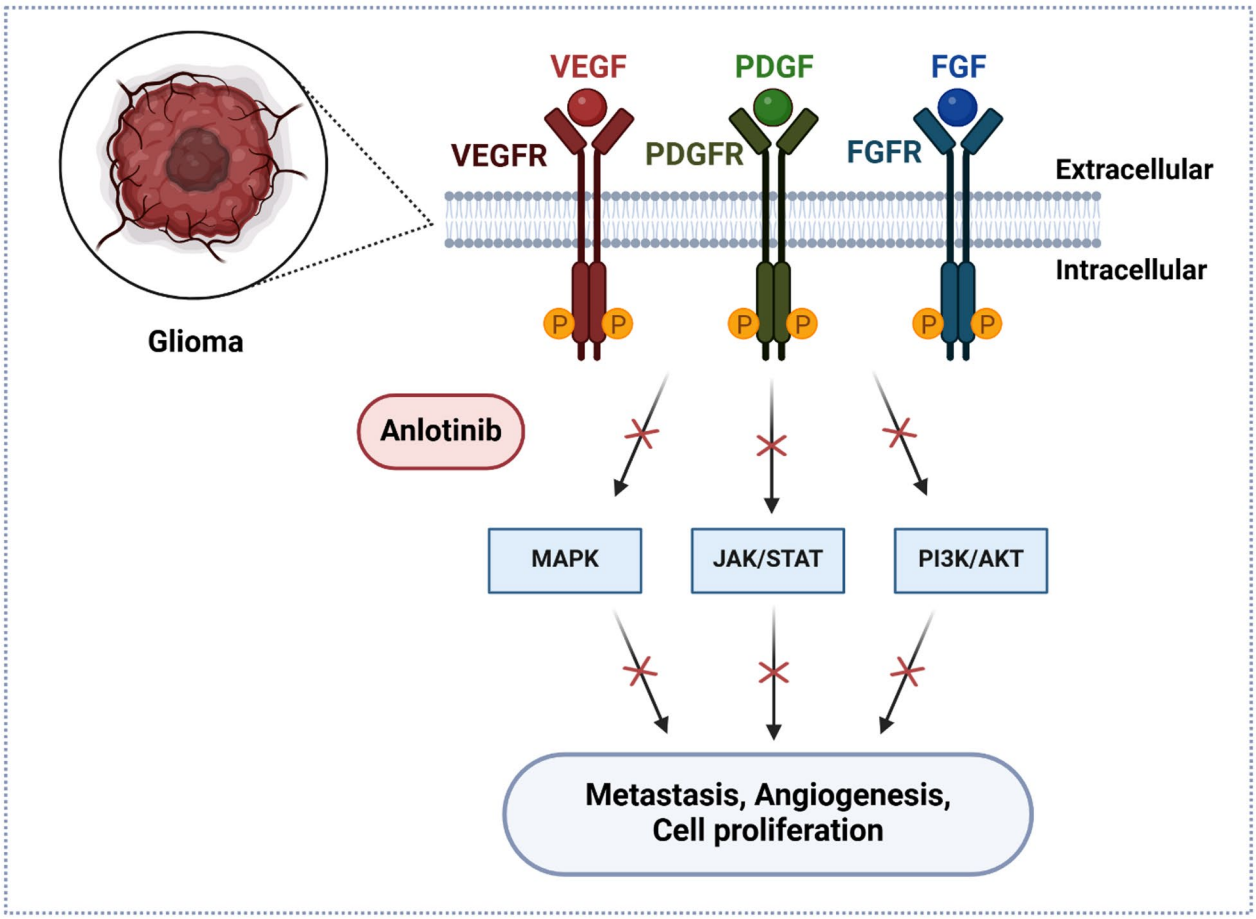


Fig. 1 Mechanism of action of Anlotinib

Method

Study design

This systematic review and meta-analysis adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12] for the primary aim of assessing the efficacy and safety of Anlotinib in glioma.

Search strategy

A comprehensive literature search was conducted across PubMed, Embase, Web of Science, and Scopus, with no language restrictions applied, up to December 9, 2024. Each database used specifically tailored search strategies by combining controlled vocabulary terms, as in PubMed and Embase, and free-text terms. The search query included Anlotinib and catequentinib for covering the Anlotinib-related terms, and glioma, glioblastoma, anaplastic astrocytoma, and gliosarcoma for covering the glioma-related terms. Detailed search strings are provided in Table S1.

Eligibility criteria

The PICO framework was designed as follows: Patients with high-grade glioma, Intervention: Anlotinib, Comparator: standalone administration of chemoradiotherapy (if not available, comparator is considered non), Outcome: elements related to Survival Rates, Response Rates, and Adverse Events in different grades and time frames.

Inclusion criteria

(1) English-language studies or Chinese-language studies under the condition that the full-texts were available; (2) Clinical studies on patients with Glioma; (3) Studies evaluating the outcomes after treating with Anlotinib; (4) Peer-reviewed Original studies, including case series (>5 patients), case-control studies, cross-sectional studies, randomized and non-randomized clinical trials, cohort studies, and conference abstracts with peer-reviewed articles.

Exclusion criteria

(1) non-English studies and Chinese-language studies whose full-texts were not available; (2) in vivo or in vitro studies; (3) studies on patients without glioma; (4) studies on patients who were not treated with Anlotinib; (5) case reports, conference abstracts without peer-reviewed articles, review articles, commentary articles, or book chapters; (6) grey literature reports without peer-reviewing.

Study Selection, data Extraction, and quality assessment

Title and abstract screening for eligibility was performed by two independent reviewers, followed by full-text review for articles that met the inclusion criteria. Notably, the third reviewer's discussion and consultation resolved the discrepancies. Afterwards, data were extracted using a standardized form that included characteristics of the study (e.g., study design, country, and sample size), patient demographics, treatment regimens, and outcomes such as OS, PFS, Local Control (LC), and radiological response rates according to the RANO criteria, and adverse events. Notably, we utilized the Cochrane risk-of-bias (ROB 2) tool for the quality evaluation of all included randomized controlled trials [13, 14], and the "ROBINS-I" for retrospective studies [15].

Statistical analysis

The right effect size was chosen using the Cochrane Handbook for Systematic Reviews of Interventions [12]. The random effect model and restricted maximum likelihood (REML) approach were used for the meta-analysis (Chap. 9: Analyzing data and executing meta-analyses). Together with 95% CIs, pooled estimates of survival outcomes, radiological response rates, and adverse event rates were computed. Significance of the heterogeneity was defined as chi-square P-value < 0.05, and interpretation of I2 metrics was conducted as follows: negligible heterogeneity as 0% to 40%, moderate heterogeneity as 30% to 60%, substantial heterogeneity as 50% to 90%, and considerable heterogeneity as 75% to 100% (Chap. 9.5.2: Identifying and measuring heterogeneity). Notably, Statistical significance was defined as a p-value < 0.05. By utilizing leave-one-out approach, the sensitivity analysis was performed in the analysis domains, where each included study was sequentially removed to assess its influence on the overall effect size, and if a single study significantly altered the pooled effect estimate, its influence was further investigated.

Egger's test was also employed to assess potential publication bias. By using subgroup analyses, outcomes across different treatment regimens were compared (Table S2). Meta-regression was then performed in context of Glioma and also GBM to assess the significant factors of outcomes and sources of heterogeneity (Table S3 and Table S4). The safety profile of study was shown in supplementary file. All statistical analysis was done using the STATA v.17 program and the Risk-of-Bias plots were generated using "robvis" tool [16].

Results

Study selection

Database searches yielded a total of 3,792 records: PubMed (644), Scopus (1,650), Web of Science (139), and Embase (1,359). After we eliminated 1,806 duplicate records, we evaluated 1,986 distinct records based on their title and abstract. We excluded 1,856 records because they did not meet the inclusion criteria. 130 full-text reports were requested for retrieval, and full-texts of 13 reports were not found. Following full-text assessment, 100 reports were excluded for the following reasons: 87 due to irrelevance to the study scope, 11 due to duplication, and 2 due to the wrong patient and population. In the end, this systematic review and meta-analysis included 17 studies, all under retrospective cohort or phase II clinical trial design, with a total of 473 patients, and 204 patients with glioblastoma were included (Fig. 2a).

Quality assessment and risk of bias

Utilizing the "RoB2" and "ROBINS-I", the studies were assessed for possible biases and quality of study conduct. RoB2 was used to assess the quality of randomized clinical trials, and ROBINS-I was applied for observational studies. 9 trials comprising 10 records underwent the RoB2 quality assessment. 4 records yielded an overall "Some concerns" score for risk of bias, and 6 records yielded an overall "Low" score for risk of bias. Given the single-arm design of many studies, no proper assessment could be made for bias arising from the randomization process. The most frequent domain of bias was biases due to the selection of the reported study, with 3 records of "Some concerns". Other domains of biases (deviation from intervention, missing outcome data, and measurement of the outcome) were found in 2 records. 8 studies comprising 8 records underwent the ROBINS-I quality assessment. 1 record yielded an overall "Serious" score for risk of bias; 4 records yielded an overall "Moderate" score for risk of bias, and 3 records yielded an overall "Low" score for risk of bias. The most frequently witnessed domain of bias was due to missing data: 1 record yielded a "Serious" score, 1 record yielded a "Moderate" score, and 2 records with "No information". Bias in the selection of the reported outcome and the selection of participants did not qualify as "Low" risk of bias in 3 records. Biases due to deviation from the intended intervention were qualified as "Moderate" risk of bias in 2 records. The least concerning domains of bias were biases due to confounding and measurement of outcomes, with only 1 record not receiving "Low" risk of bias for each domain.

Study characteristics

A total of 17 studies involving 473 patients were included in this systematic review and meta-analysis. Among these studies, 8 were retrospective cohort studies or case-control studies, while 9 were clinical trials. Notably, 2 studies were multicenter, while others were conducted in one institution. Patients in the included studies, aged from 4 to 75 years. Glioma patients were mainly presented with either Brainstem, Thalamus, or Multifocal lesions (Tables 1 and 2).

Treatment characteristics

The included studies evaluated the effects of Anlotinib alone, or in combination with other modalities, including Radiation strategies like Stereotactic Radiosurgery (SRS), and chemotherapeutic options such as Temozolomide (TMZ) and Bevacizumab (Bev) (Table 3).

Overall survival (OS)

6-Month OS

A total of 4 studies were included in the analysis of 6-month OS. The pooled survival rate was 67% (95% CI: 0.42–0.92). A considerable and significant heterogeneity was observed among studies. ($I^2 = 87.2\%$, $P < 0.01$) (Fig. 3a).

Subgroup analysis revealed statistically significant differences in favor of patients with concurrent radiotherapy compared to those who underwent either alone or in concurrence with TMZ treatment ($P = 0.01$). The comparison between the Anlotinib group, the Anlotinib & Radiotherapy group, and the Anlotinib & TMZ group also resulted in a significant favor for radiotherapy ($P < 0.01$). No statistically significant difference was observed between the group who received prior combined chemo/radiotherapy and the group who also received additional immunotherapy ($p = 0.15$). Notably, the most frequent tumor location subgroup analysis revealed that those with brainstem tumors have a significantly higher 6-month OS compared to patients with multifocal tumors ($p = 0.01$). Additionally, RCT studies demonstrated a significantly higher 6-month OS compared to retrospective studies ($p = 0.01$).

Furthermore, meta-regression analysis identified significant influences on the 6-month OS from female gender ($\beta = 1.3925$, $p = 0.011$), age ($\beta = 0.0153$, $p = 0.027$), grade 4 of tumor ($\beta = 0.8291$, $p = 0.031$), methylation of MGMT ($\beta = 1.4632$, $p = 0.037$), wild type of IDH ($\beta = 0.8011$, $p = 0.040$), and also male gender ($\beta = 0.9519$, $p = 0.085$), while grade 3 of tumor ($\beta = 1.8081$, $p = 0.094$), no-methylation of MGMT ($\beta = 0.9389$, $p = 0.053$), and mutation of

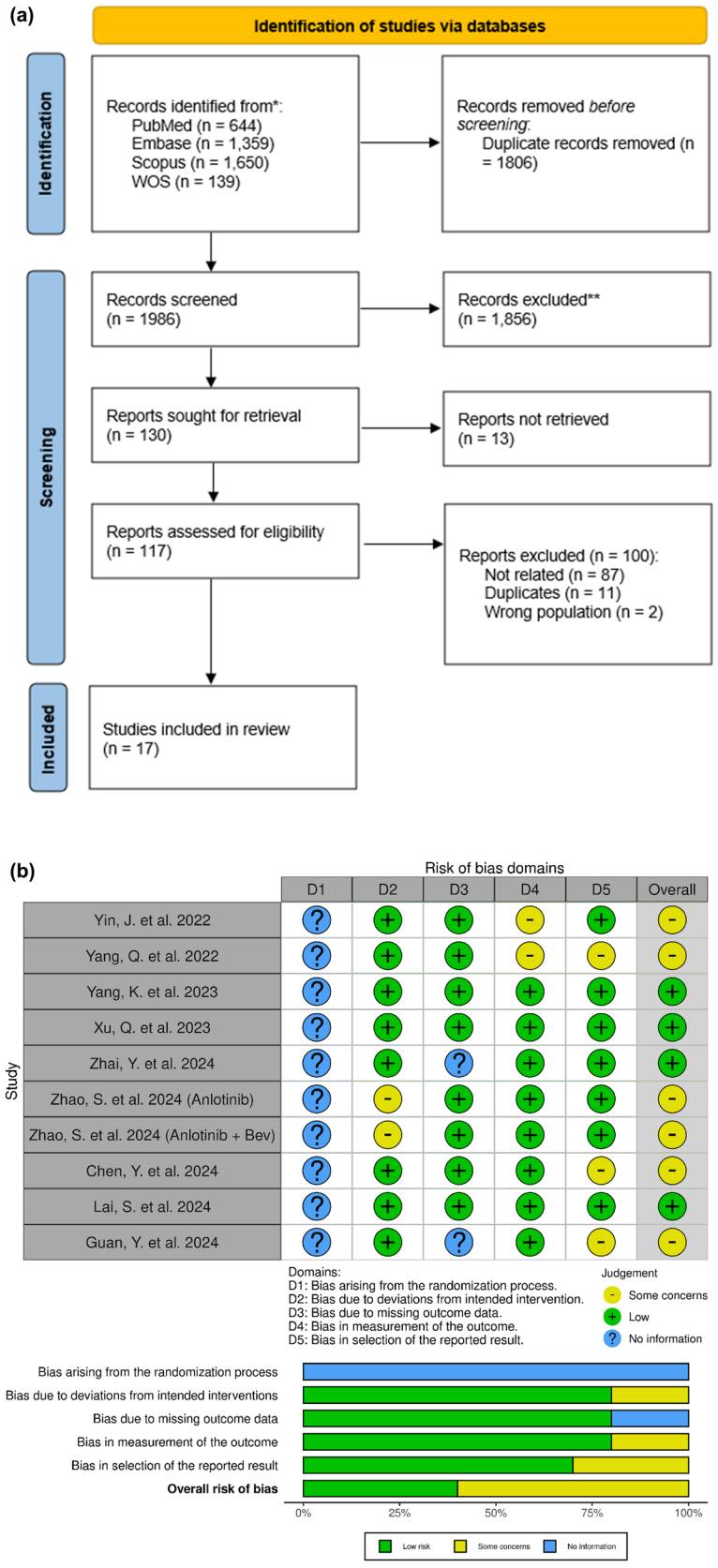


Fig. 2 PRISMA flowchart of study selection process (**a**), Risk of bias assessment results of RoB2 (**b**), and ROBINS-I (**c**)

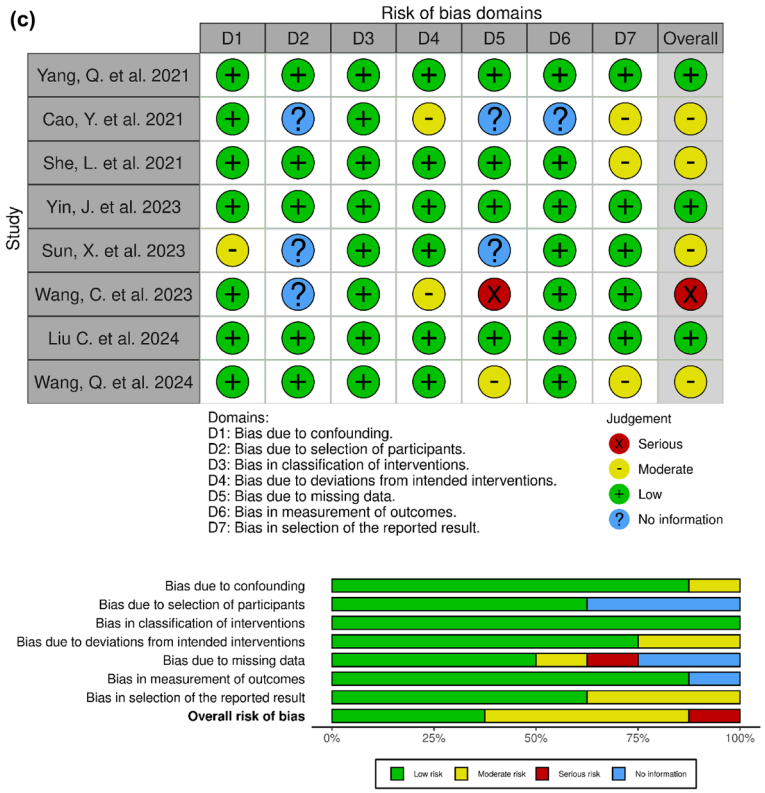


Fig. 2 (continued)

IDH (β = 1.9971, $p = 0.062$) were not found to be significant moderators.

1-Year OS

A total of 8 studies were included in the analysis of 1-Year OS with the pooled survival rate of 50% (95% CI: 0.36–0.64). A statistically significant and considerable heterogeneity was observed among studies (I^2 = 75.24%, $P < 0.01$) (Fig. 3b). Additionally, the results in the GBM patients were 67% (95% CI: **0**.47–0.87), with a statistically significant and considerable heterogeneity observed among the 3 included studies (I^2 = 71.17%, $P < 0.01$).

Subgroup analysis revealed a non-statistically significant difference in the concurrence of either radiotherapy or TMZ ($P = 0.09$). The comparison between the Anlotinib group, the Anlotinib & Radiotherapy group, the Anlotinib & TMZ group, and the Anlotinib & TMZ & Radiotherapy group resulted in a significant difference, with a tendency for higher 1-year OS for the group treated with concurrent TMZ and radiotherapy ($P < 0.01$). No statistically significant difference was observed in 1-year OS of patients with either brainstem or multifocal tumor groups ($p = 0.11$). There was also no statistically significant difference in the comparison between the previous treatment of the chemo/radiotherapy group, the group that received additional immunotherapy, and the surgery group ($p = 0.90$). Additionally, significant differences were observed in the subgroups based on the study's type and source of data in favor of RCTs and multicenter studies ($p < 0.01$ and $p < 0.01$, respectively).

Meta-regression analysis also identified significant influences on the 1-year OS from female gender (β = 1.0944, $p = 0.001$), male gender (β = 0.9096, $p = 0.008$), age (β = 0.0111, $p < 0.001$), grade 4 of tumor (β = 0.5080, $p = 0.030$), methylation of MGMT (β = 1.3068, $p = 0.010$), no-methylation of MGMT (β = 0.8052, $p = 0.001$), and wild type of IDH (β = 0.6311, $p = 0.001$), while grade 3 of tumor (β = 0.0111, $p = 0.093$) and mutation of IDH (β = 1.5195, $p = 0.178$) were not found as significant moderators.

Progression-Free survival (PFS)

6-Month PFS

The pooled 6-month PFS rate was 61% (95% CI: 46–75%), with significant and considerable heterogeneity (I^2 = 87.85%, $P < 0.01$) among the 11 included studies (Fig. 4a). Additionally, the results in the GBM patients were 66% (95% CI: 0.41–0.91) with a statistically significant and considerable heterogeneity was observed among the 5 included studies (I^2 = 93.65%, $P < 0.01$).

Table 1 Demographic characteristics

First Author	Year	Study type	CT code (if a clinical trial)	Source of data	Affiliated Hospital/University	No. of pts with Glioma	Male *n* (%)	Median age (range)	Median Follow-up, months (range)
Yang, Q.	2021	Retrospective	N/A	Single center	Sun Yat-sen University Cancer Center	31	19 (61.3%)	42 (16–75)	6.3 Months (95% CI: 4.6–8.1)
Cao, Y.	2021	Retrospective	N/A	Single center	Radiation Oncology, Jiangsu Province Hospital/The First Affiliated Hospital of Nanjing Medical University, Nanjing, China	30	NR	NR	NR
She, L.	2021	Retrospective	N/A	Single center	Xiangya Hospital	20	10 (50%)	52 (18–71)	13.4 (95% CI: 10.5–16.3)
Yin, J.	2022	Clinical Trial	NR	Single center	Sichuan Cancer Hospital & Institute, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China	14	NR	NR	8.8 (95% CI: 6.3–11.7)
Yang, Q.	2022	phase II Clinical Trial	NCT04547855	Single center	Sun Yat-Sen University Cancer Center	25	NR	49 (23–62)	NR
Yin, J.	2023	Retrospective	N/A	Single center	Sichuan Cancer Hospital Institute	29	14 (48.28%)	50 (15–71)	11.6 (95% CI: 9.4–15.7)
Yang, K.	2023	phase II Clinical Trial	ChiCTR2000040116	Single-center	Cancer Center, Union Hospital	32	19 (59.4%)	50 (27–65)	14.8 (95% CI: 5.5–23.7)
Xu, Q.	2023	phase II Clinical Trial	ChiCTR2000028957	Single Center	The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou	21	9 (42.9%)	55 (27–68)	NR
Sun, X.	2023	Retrospective	N/A	Single Center	The Fifth Affilated hospital of Zhengzhou University, Zhengzhou, Chin	26	11 (42.3%)	NR	NR
Wang, C.	2023	Retrospective	N/A	Single Center	Department of Oncology, Henan Provincial People's Hospital and People's Hospital of Henan University, Zhengzhou, China	23	NR	NR	NR
Zhai, Y.	2024	phase II Clinical Trial	N/A	Single Center	Neurosurgery, The Second Affiliate Hospital of Air Force Medical University/Tangdu Hospital, Xi'an, China	94	57 (60.6%)	NR	NR
Zhao, S. (Anlotinib)	2024	phase II Clinical Trial	NCT04822805	Single Center	Department of Radiation Oncology, Hangzhou Cancer Hospital, No.34, Yanguan Lane, Shangcheng District, Hangzhou, Zhejiang 310, 002, China	18	13 (72%)	52 (35–63)	9.9 (IQR: 5.9–15.1)
Zhao, S. (Anlotinib + Bev)	2024	phase II Clinical Trial	NCT04822805	Single Center	Department of Radiation Oncology, Hangzhou Cancer Hospital, No.34, Yanguan Lane, Shangcheng District, Hangzhou, Zhejiang 310, 002, China	7	5 (71%)	59 (54–67)	9.9 (IQR: 5.9–15.1)
Chen, Y.	2024	phase II Clinical Trial	NCT04668508	Single Center	Sun Yat-sen University Cancer Center	16	NR	32 (18–68)	22.7 (6.0–38.3.0.3)
Lai, S.	2024	phase II Clinical Trial	NCT04119674	Multicenter	Department of Radiation Oncology, The Second Affiliated Hospital of Soochow University, Suzhou 215,000, China	33	17 (52%)	52 (32–69)	25.2 (20.9–29.5)
Liu, C.	2024	Retrospective	N/A	Single Center	Department of Oncology, Xiangya Hospital, Central South University, Changsha, China	15	9 (60%)	17.5 (4–65)	25.9 (17.1–57.0)
Guan, Y.	2024	phase II Clinical Trial	NCT04197492	Single Center	CyberKnife Center, Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, China	22	NR	55 (28–70)	NR
Wang, Q.	2024	Retrospective	N/A	Multicenter	Department of Neurosurgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, People's Republic of China	17	13 (76.5%)	49 (16–75)	NR

Subgroup analysis revealed a significant favor to concurrent administration of either radiotherapy, TMZ, or SRS compared to Anlotinib alone, with SRS showing better results ($P=0.09$). The comparison between the Anlotinib group, Anlotinib & Radiotherapy, Anlotinib & TMZ Group, Anlotinib & TMZ & Radiotherapy Group, and Anlotinib plus SRS group resulted in a significant difference, with a tendency to have a higher 6-month PFS for the group treated with concurrent TMZ and Radiotherapy ($P<0.01$). No statistically significant difference was observed in 6-month PFS of patients with either brainstem or multifocal tumor groups ($p=0.09$). There was no statistically significant difference in the comparison between the prior treatment of the combined chemo/radiotherapy group, the group that received additional immunotherapy, the surgery group, and the group receiving all the mentioned procedures prior to Anlotinib treatment ($p=0.73$). Additionally, significant differences were observed in the subgroups based on the study's type and source of data in favor of RCTs and multicenter studies ($p=0.05$ and $p<0.01$, respectively).

Meta-regression analysis also identified significant influences on the 6-Month PFS from female gender (β=1.3134, $p=0.001$), male gender (β=1.146, $p=0.002$), age (β=0.0128, $p<0.001$), grade 4 of tumor (β=0.7393, $p=0.014$), methylation of MGMT (β=1.5703, $p=0.002$), no-methylation of MGMT (β=0.8617, $p=0.002$), and wild type of IDH (β=0.6669, $p=0.001$), while grade 3 of tumor (β=1.6589, $p=0.052$) and mutation of IDH (β=2.1547, $p=0.061$) were not found as significant moderators.

1-Year PFS

The pooled 1-year PFS rate based on the 5 included studies was 27% (95% CI: 13–41%), with significant, substantial heterogeneity (I^2 = 63.01%, $P=0.03$) (Fig. 4b). Additionally, the results in the GBM patients were 36% (95% CI: 0.12–0.61) with a statistically significant and considerable heterogeneity was observed among studies (I^2 = 73.44%, $P<0.01$).

Subgroup analysis revealed no significant difference between the concurrent administration of either radiotherapy or TMZ compared to Anlotinib alone ($P=0.11$). The comparison between the Anlotinib group, Anlotinib & Radiotherapy, Anlotinib & TMZ Group, and Anlotinib & TMZ & Radiotherapy Group resulted in a significant difference, with a tendency for higher 1-Year PFS for the group treated with concurrent TMZ and Radiotherapy ($P=0.01$). No statistically significant difference was observed in 1-year PFS of patients with either brainstem or multifocal tumor groups ($p=0.10$). There was also no statistically significant difference in the comparison between the prior treatment of the combined chemo/radiotherapy group, the group that received additional immunotherapy, and the surgery group ($p=0.15$). Additionally, significant differences were observed in the subgroups based on the study's type and source of data in favor of RCTs and multicenter studies ($p=0.03$ and $p<0.01$, respectively).

Meta-regression analysis also identified significant influences on the 1-Year from female gender (β=0.5617, $p=0.040$), age (β=0.0059, $p=0.016$), no methylation of MGMT (β=0.3831, $p=0.048$), and wild type of IDH (β=0.3112, $p=0.031$), while male gender (β=0.4377, $p=0.081$), grade 3 of tumor (β=0.4365, $p=0.266$), grade 4 of tumor (β=0.2083, $p=0.266$), methylation of MGMT (β=0.7014, $p=0.083$), and mutation of IDH (β=0.6460, $p=0.431$) were not found as significant moderators.

Disease control rate (DCR)

The pooled DCR was calculated based on the 13 included studies and was equal to 90% (95% CI: 87–94%), with a negligible and insignificant heterogeneity (I^2 = 0.00%, $P=0.07$) (Fig. 5). Additionally, the results in the GBM patients were 88% (95% CI: 0.72–1.00**)** with a statistically significant and considerable heterogeneity was observed among the 3 included studies (I^2 = 81.87%, $P<0.01$).

Subgroup analysis revealed no significant difference between the concurrent administration of either radiotherapy or TMZ compared to Anlotinib alone ($P=0.58$). The comparison between the Anlotinib group, the Anlotinib & TMZ group, and the Anlotinib & TMZ & Radiotherapy group resulted in a not statistically significant difference ($P=0.44$). No statistically significant difference was observed in the DCR of patients with either brainstem, thalamus, or multifocal tumor groups ($p=0.23$). A statistically significant difference was observed in the comparison between the prior treatment of the combined chemo/radiotherapy group, the group that underwent surgery, the group receiving surgery & chemotherapy, and the group that received all the treatments prior to the Anlotinib treatment in favor of the surgery group and the chemo/radiotherapy group to a lesser degree ($p=0.03$). Additionally, significant differences were observed in the subgroups based on the source of data in favor of single-center studies, while none was found based on the study's type ($p=0.01$ and $p=1$, respectively).

Meta-regression analysis also identified significant influences on the DCR from female gender (β=1.8955, $p<0.001$), male gender (β=1.4373, $p<0.001$), age (β=0.0175, $p<0.001$), grade 3 of tumor (β=3.0132, $p=0.016$), and grade 4 of tumor (β=1.0016, $p<0.001$). Methylation of MGMT (β=2.3598, $p<0.001$), no methylation of MGMT (β=1.1832, $p<0.001$), wild type of IDH

Table 2 Tumor characteristics

First Author	ECOG PS:	Median tumor volume	Tumor Histology	Tumor Grade	Tumor Location	Tumor Mutations	MGMT promotor methylation status	IDH status	1p/19q co-deletion	TERT status	Number of Previous Line of therapies	Median number of previous treatments	Previous treatments
Yang, Q.	N/A	NR	High-grade glioma (HGG), including: 1- glioblastoma (GBM), 2- diffuse midline glioma (DMG), 3- anaplastic astrocytoma, 4- anaplastic oligodendroglioma.	Grade 4: 21 (67.7%) Grade 3: 10 (32.3%)	Multi-focal/ dissemination: 22 (71.0%) Focal: 9 (29.0%)	N/A	Methylation 12 (38.7%) Unmethylation 19 (61.3%)	Wild type 22 (71.0%) Mutation 9 (29.0%)	Positive 7 (22.6%) Negative 16 (51.6%) Unknown 8 (25.8%)	N/A	0: 7 (22.6%) 1: 13 (41.9%) ≥2: 11 (35.5%)	2 (IQR 2–3, range 1–6)	Previous anti-angiogenic agents: 13 (41.9%) Previous re-operation: 11 (35.5%) Previous re-radiation: 6 (19.4%)
Cao, Y.	N/A	N/A	Malignant Glioma (MG)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	standard chemoradiotherapy regimen (TMZ and radiotherapy)
She, L.	N/A	N/A	recurrent Glioblastoma (rGBM)	Recurrent: 20	NR	N/A	Methylation: 8 (40%) Unmethylation: 12 (60%)	IDH1 Mutation: +: 2 (10%) –: 18 (90%)	N/A	NR	N/A	N/A	Surgery types Gross total surgery: (90%) Subtotal surgery: (10%) History of targeted therapy before recurrence Yes: 3/20 (15%) No: 17/20 (85%)
Yin, J.	NR	NR	GBM: 10 (71.4%), Anaplastic astrocytoma: 3 (21.4%), Anaplastic oligodendrocyte glioma: 1 (7.1%)	Grage 3 & 4: 14	NR	N/A	NR	NR	NR	NR	NR	NR	N/A
Yang, Q.	NR	NR	GBM	Grade 4	NR	N/A	unmethylated: 17 (70.8%)	wild type 22 (91.6%)	NR	NR	NR	NR	surgery and radiotherapy-TMZ therapy (STUPP regimen)

Table 2 (continued)

First Author	ECOG PS:	Median tumor volume	Tumor Histology	Tumor Grade	Tumor Location	Tumor Mutations	MGMT promotor methylation status	IDH status	1p/19q co-deletion	TERT status	Number of Previous Line of therapies	Median number of previous treatments	Previous treatments
Yin, J.	N/A	Median baseline tumor diameter: 4.5 cm (range, 2.7–8.0.7.0).	GBM: 20 DMG: 1 Anaplastic astrocytoma: 5 Anaplastic oligodendroglioma: 3	Grade III: 7 (24.1%) Grade IV: 22 (81.4%)	Multifocal/ dissemination:14 (48.28%), Focal: 15 (51.72%)	MGMT promoter methylation status, IDH status, 1p19q codeletion, TERT status	Methylation 12 (41.38%) Unmethylation 17 (58.62%)	IDH mutation: 6 (20.69%), IDH wild type: 23 (79.31%)	Codeletion 2 (6.90%) Nocodeletion 11 (37.93%) Unknown 16 (55.17%)	Mutation: 21 (72.41%) Wild type: 8 (27.59%)	NR	NR	radiotherapy with concurrent chemotherapy with TMZ
Yang, K.	N/A	N/A	GBM	Grade IV	NR	N/A	unmethylated status: (100%	wild-type: (100%)	NR	NR	NR	NR	surgical resection and concurrent radiotherapy
Xu, Q.	N/A	N/A	rGBM	Grade IV	NR	N/A	methylated 5 (23.8%)	wild-type: 21 (100%) mutation: 0	NR	Mutation: 12 (57.1%)			radiotherapy and temozolomide chemotherapy
Sun, X.	N/A	N/A	rMG	NR	NR	NR	NR	NR	NR	NR			chemoradiotherapy and surgery
Wang, C.	N/A	N/A	rHGG	NR	NR	TP53 wild-type or TP53 mutant-type	NR	NR	NR	NR	N/A	N/A	NR
Zhai, Y.	NR	NR	rHGG	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 (continued)

First Author	ECOG PS:	Median tumor volume	Tumor Histology	Tumor Grade	Tumor Location	Tumor Mutations	MGMT promotor methylation status	IDH status	1p/19q co-deletion	TERT status	Number of Previous Line of therapies	Median number of previous treatments	Previous treatments
Zhao, S. (Anlotinib)	0–1: 14 (78%) 2: 4 (22%)	N/A	Glioblastoma, IDH wildtype, 14 (78%) Astrocytoma, IDH-mutant, grade 4 2 (11%) Diffuse astrocytoma, NOS 2 (11%)	Grade IV 15 (83%) Grade III: 3 (17%)	Brainstem	NR	NR	IDH wildtype 13 (72%) IDH mutant 1 (5%) NOS 1 (5%)	NR	NR	without any intervention 6 (33%) 1 line treatment 5 (28%) 3 line treatment 1 (5%) re-radiation 1 (5%) re-radiation+1 line treatment 1 (5%) re-radiation+2 line treatment 1 (5%) re-operation+1 line treatment 1 (5%) re-operation+re-radiation+1 line treatment 1 (5%) re-operation+re-radiation+2 line treatment 1 (5%)	NR	
Zhao, S. (Anlotinib+Bev)	0–1: 6 (86%) 2: 1 (14%)	N/A	GBM 7 (100%)	Grade IV 7 (100%)		NR	NR	IDH wildtype 7 (100%)	NR	NR	without any intervention 5 (72%) 1 line treatment 2 (28%)	NR	

Table 2 (continued)

First Author	ECOG PS:	Median tumor volume	Tumor Histology	Tumor Grade	Tumor Location	Tumor Mutations	MGMT promotor methylation status	IDH status	1p/19q co-deletion	TERT status	Number of Previous Line of therapies	Median number of previous treatments	Previous treatments
Chen, Y.	N/A	N/A	Malignant brainstem glioma	NR	Brainstem: 16 (100%)	NR	NR	NR	NR	NR	N/A	N/A	radiotherapy (RT), chemotherapy, immunotherapy, or biotherapy naïve
Lai, S.	N/A	N/A	GBM	Grade IV	NR	TERT (81%) CDK6 (52%), TP53 (48%), CDKN2A/B (43%), EGFR (43%)	Methylated 11 (33%) Unmethylated 20 (61%) Undetermined 2 (6%)	mutation: 2 (6%) wild type: 31 (94%)	NR	81%	N/A	N/A	Extent of surgical resection Gross total resection 10 (30%) Near-total resection 6 (18%) Subtotal resection 17 (52%)
Liu, C.	N/A	Mean±SD: 24.0±17.8 cm3	DMG	NR	Thalamus 8 (53.3%) Corpus callosum 0 (0) Basal ganglia 0 (0) Brain stem 6 (40%) Others 1 (6.7%)	H3K27M mutation	-: 14 (93.3%) +: 1 (6.7%)	-: 15 (100.0) +: 0	NR	NR	N/A	N/A	chemotherapy, radiotherapy, or targeted therapy
Guan, Y.	N/A	N/A	rGBM	Grade IV	NR	NR	NR	NR	NR	NR	NR	NR	surgery, standard radiotherapy, and TMZ chemotherapy

Table 2 (continued)

First Author	ECOG PS:	Median tumor volume	Tumor Histology	Tumor Grade	Tumor Location	Tumor Mutations	MGMT promotor methylation status	IDH status	1p/19q co-deletion	TERT status	Number of Previous Line of therapies	Median number of previous treatments	Previous treatments
Wang, Q.	N/A	N/A	rGBM or DGM with H3K27M mutant	Grade IV: 17 (100%)	Frontal lobe: 3, (17.7%) Temporal lobe: 4 (23.5%) Parietal lobe: 2 (11.7%) Occipital lobe: 2 11.7%) Insular lobe: 3 (17.7%) Thalamus: 3 (17.7%)	NR	methylation 5 (29.4%) unmethylation 12 (70.6%)	IDH mutation (6.5%), IDH wild-type (93.5%)	Yes: 0 No: 17 (100%)	7 (35.5%)	N/A	N/A	surgery 7 (41.1%) TMZ 6 (35.2%) Other treatment 5 (29.4%)

(β = 0.9823, $p < 0.001$), and mutation of IDH (β = 3.4178, $p = 0.008$) are moderators.

Radiological response

Overall response rates (ORR)

The pooled ORR of the 15 studies included in the analysis was equal to 55% (95% CI: 44–67%), with a statistically significant substantial heterogeneity ($I^2 = 85.08\%$, $P < 0.01$) (Fig. 6a). Additionally, the results in the GBM patients were 65% (95% CI: 0.40–0.90) with no statistically significant heterogeneity among the 5 included studies ($I^2 = 0.00\%$, $P = 0.30$).

Subgroup analysis revealed a significant difference between the concurrent administration of either radiotherapy, SRS, Bev, or TMZ compared to Anlotinib alone, with a preference to concurrent SRS ($P < 0.01$). The comparison between the Anlotinib group, the Anlotinib & TMZ group, the Anlotinib & Bev group, and the Anlotinib SRS group resulted in a statistically significant difference in favor of SRS treatment ($P < 0.01$). No statistically significant difference was observed in the ORR of patients with either brainstem or multifocal tumor groups ($p = 0.15$). There was no statistically significant difference observed in the comparison between the prior treatment of the combined chemo/radiotherapy group, the group that underwent surgery, the group receiving surgery & chemotherapy, and the group that received all these treatments before being treated with Anlotinib ($p = 0.13$). Additionally, no significant difference was observed in the subgroups based on the source of data or type of study ($p = 0.08$ and $p = 0.13$, respectively).

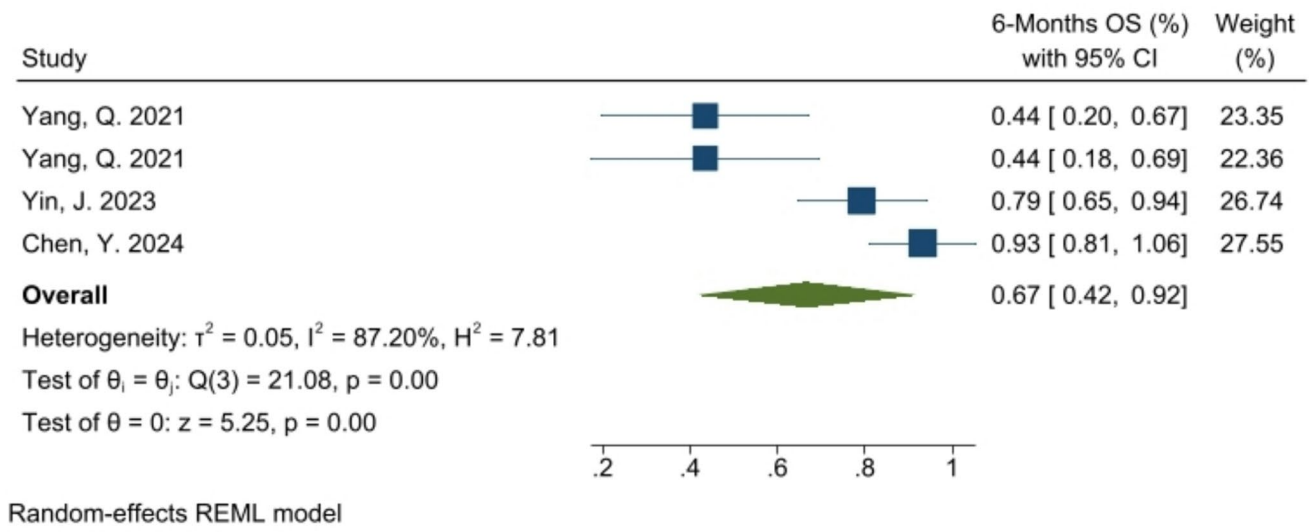
Meta-regression analysis also identified the following moderators: Female gender (β = 1.2018, $p < 0.001$), male gender (β = 0.7848, $p = 0.001$), age (β = 0.0110, $p < 0.001$), grade 3 of tumor (β = 1.6985, $p = 0.021$), grade 4 of tumor (β = 0.5176, $p = 0.005$), methylation of MGMT (β = 1.5078, $p = 0.001$), no-methylation of MGMT (β = 0.8009, $p = 0.001$), wild type of IDH (β = 0.5843, $p < 0.001$), and mutation of IDH (β = 1.8738, $p = 0.029$) have significant influences on the ORR.

Complete response rates (CRR)

The pooled CRR relied on the 6 included studies and was 17% (95% CI: 6–28%), with substantial and significant heterogeneity ($I^2 = 65.58\%$, $P < 0.01$) (Fig. 6b). Additionally, the results in the GBM patients were 21% (95% CI: 0.04–0.38) with a statistically significant and considerable heterogeneity was observed among the 4 included studies ($I^2 = 72.90\%$, $P = 0.02$).

Table 3 Treatment characteristics

First Author	Intervention	Anlotinib Dosage and course	Other treatments	Type of treatment (adjuvant or concurrent)
Yang, Q.	17 patines: Anlotinib 14 pts: Anlotinib + TMZ	10 pts: 12 mg QD 21 pts: 10 mg QD median duration of treatment: 4 cycles (IQR 2.0–6.5; range 1–21).	14 pts: Anlotinib + TMZ	Alone or concurrent with TMZ
Cao, Y.	Anlotinib + TMZ	Anlotinib 12 mg QID + TMZ 200 mg/m2	30 pts: Anlotinib + TMZ	concurrent with TMZ
She, L.	Anlotinib + TMZ	Anlotinib 12 mg OD (for 2 weeks, discontinued for 1 week, repeated every 3 weeks) + TMZ 100 mg/m2 (7 days on, 7 days off)	20 pts: Anlotinib + TMZ	concurrent with TMZ
Yin, J.	Anlotinib	8–12 mg/day, each course taken for 2 consecutive weeks with a break of 1 week	NR	concurrent with TMZ
Yang, Q.	Anlotinib and dose-intense TMZ	12 mg QD from D1-D14 every 3 weeks	TMZ (150 mg/m2) was administered orally from D1-D7 every two weeks	concurrent with TMZ
Yin, J.	Anlotinib 9 (31.03%) Anlotinib + chemotherapy: 20 (68.97%)	NR	Adjuvant chemotherapy: TMZ: 26 (89.66%) Irinotecan: 5 (17.24%) Othera: 1 (3.45%)	Alone or concurrent with TMZ
Yang, K.	Anlotinib	12 mg orally once daily on days 1–14 of a 21-day cycle	Radiotherapy	concurrent with radiotherapy
Xu, Q.	Anlotinib hydrochloride plus temozolomide	NR	NR	concurrent with TMZ
Sun, X.	Anlotinib	12 mg qd	NR	concurrent
Wang, C.	Anlotinib + TMZ	NR	NR	concurrent with TMZ
Zhai, Y.	Anlotinib + TMZ	NR	NR	concurrent with TMZ
Zhao, S. (Anlotinib)	Anlotinib	12 mg (weight ≥ 50 kg) or 10 mg (weight < 50 kg) on days 1–14, with each cycle repeated every 21 days	NR	Alone
Zhao, S. (Anlotinib + Bev)	Anlotinib + Bev	12 mg (weight ≥ 50 kg) or 10 mg (weight < 50 kg) on days 1–14, with each cycle repeated every 21 days	Anlotinib + Bev: In cases where brain MRI examination revealed increased peritumoral edema severity, patients received Bev 10 mg/kg IV for temporary treatment to alleviate edema.	concurrent with Bev
Chen, Y.	Anlotinib + radiotherapy	10 mg orally OD D1-D14 of every 3 weeks,+ concurrently and consolidatedly with radiotherapy	Radiotherapy at 54–60 Gy (1.8–2.0 Gy per fraction, five days per week)	concurrent with radiotherapy
Lai, S.	Anlotinib + STUPP regimen	Anlotinib (8 mg/d;) on D1–14 of each 3-week cycle × 2 cycles during concomitant therapy for a maximum of 8 cycles	1- Radiotherapy: 1.8–2.0 Grays (Gy)/fraction 5 d/w × 6 w for a total dose of 54–60 Gy 2- TMZ (75 mg/m2/d) for a maximum of 49 d	both concurrent with TMZ, and after adjuvant TMZ
Liu, C.	Anlotinib + Radiotherapy + TMZ	12 mg daily in 21-day cycle	1- surgery (either cranial resection or stereotactic biopsy) 2- intensity-modulated radiotherapy (IMRT) with 54–60 Gy in 30 fractions. 3- concurrent chemotherapy TMZ (75 mg/m2/day) [according to STUPP regimen]	concurrent with TMZ
Guan, Y.	Anlotinib + CyberKnife SRS	12 mg, daily, days 1–14/3 weeks)	CyberKnife SRS (25 Gy/5fx)	concurrent with SRS
Wang, Q.	Anlotinib	10 mg: 6 (35.3%) 12 mg: 11 (64.7%) ≥6 cycles: 6 (35.3%) <6 cycles: 11 (64.7%)	TMZ: 6 (35.3%) Radiotherapy: 1 (5.9%) TTF: 2 (11.7%) other target therapies: 2 (11.7%)	N/A



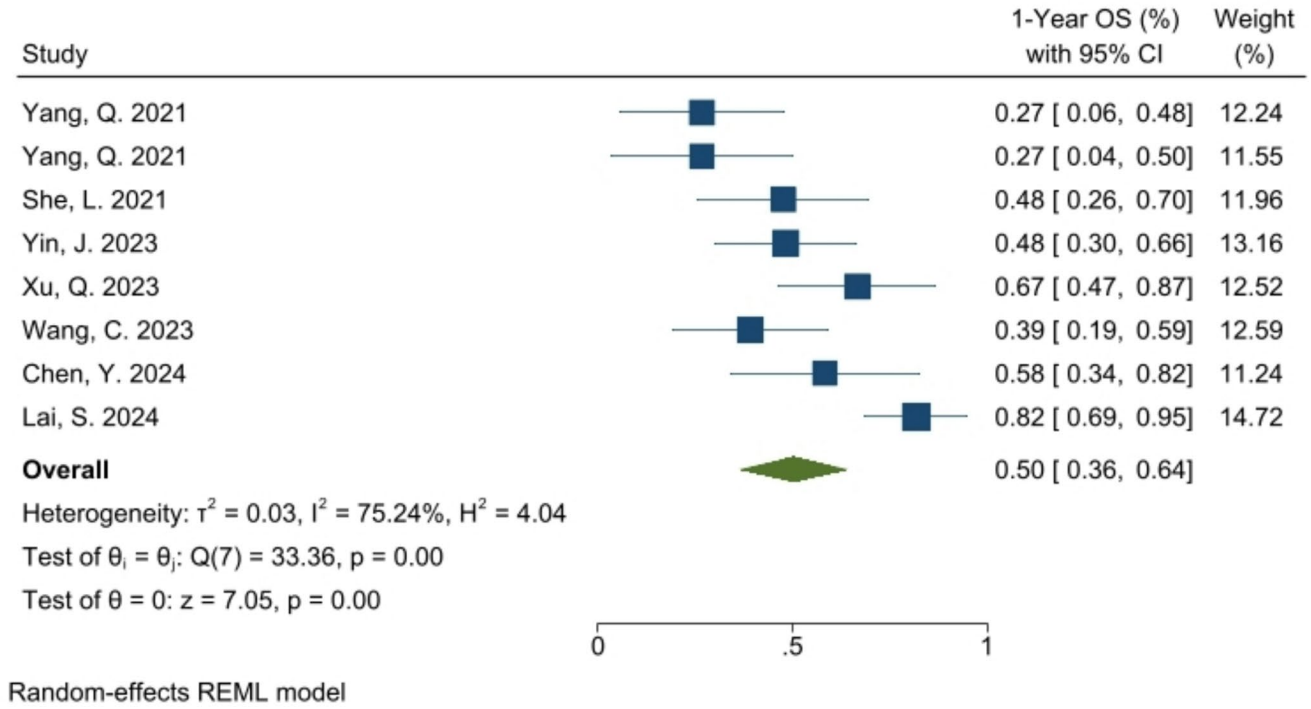
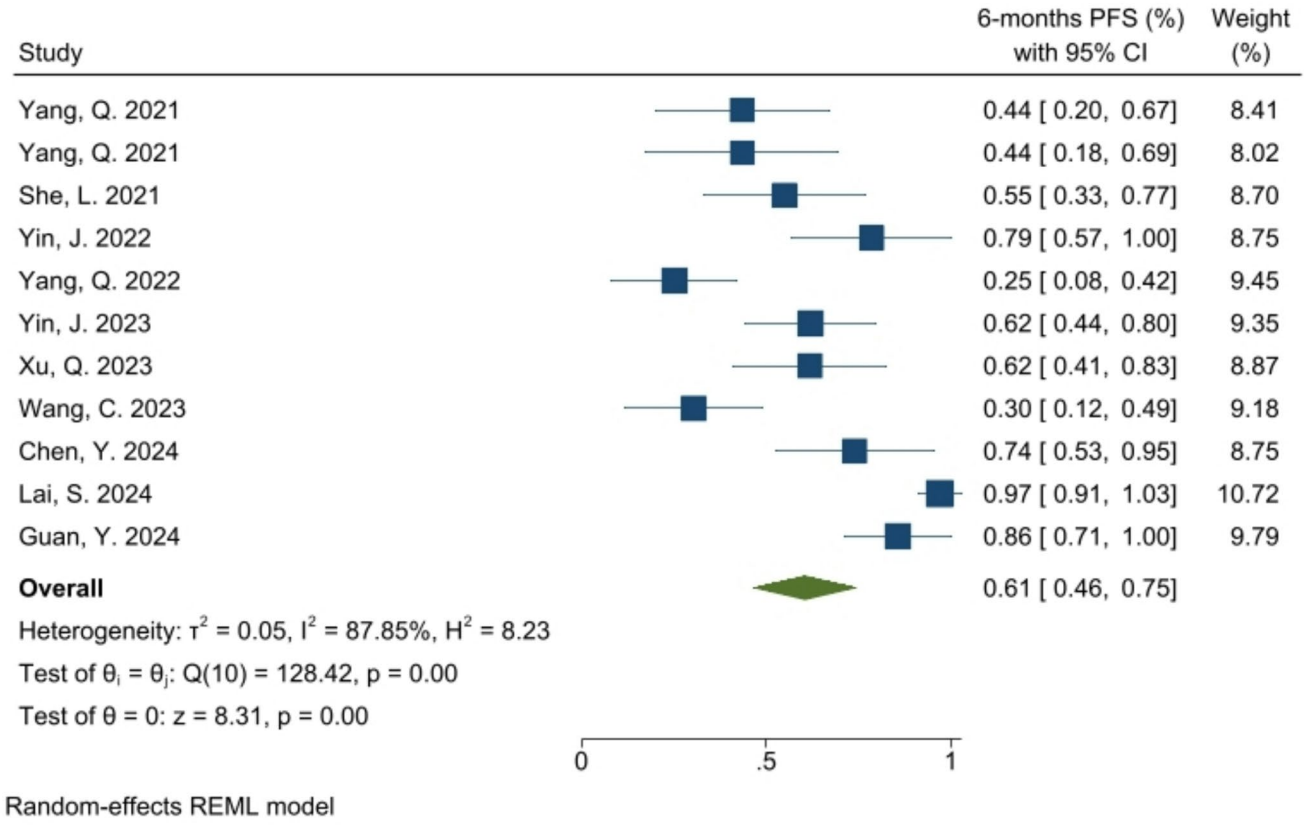


Fig. 3 Pooled overall survival at 6-month (**a**), 1-year (**b**)

Subgroup analysis revealed a not statistically significant difference between the concurrent administration of either radiotherapy, SRS, bevacizumab, or TMZ compared to Anlotinib alone ($P=0.81$). The comparison between the Anlotinib group, the Anlotinib & TMZ group, the Anlotinib & Bev group, the Anlotinib SRS group, and the group receiving Anlotinib & TMZ & radiotherapy at the same time resulted in no statistically significant difference ($P=0.47$). Comparison of ORR in patients with either brainstem or thalamus tumor groups also showed no statistically significant difference ($p=0.35$). Notably, different prior treatments showed no statistically significant difference between the groups receiving chemotherapy/radiotherapy, the group that underwent surgery, and the group that received surgery, radiotherapy, and chemotherapy before Anlotinib ($p=0.13$). Additionally, RCT studies showed a significantly higher CRR compared to retrospective studies ($p=0.01$).

Meta-regression analysis also identified significant influences on the CRR from age ($\beta=0.0036$, $p=0.020$), while female gender ($\beta=0.3683$, $p=0.067$), male



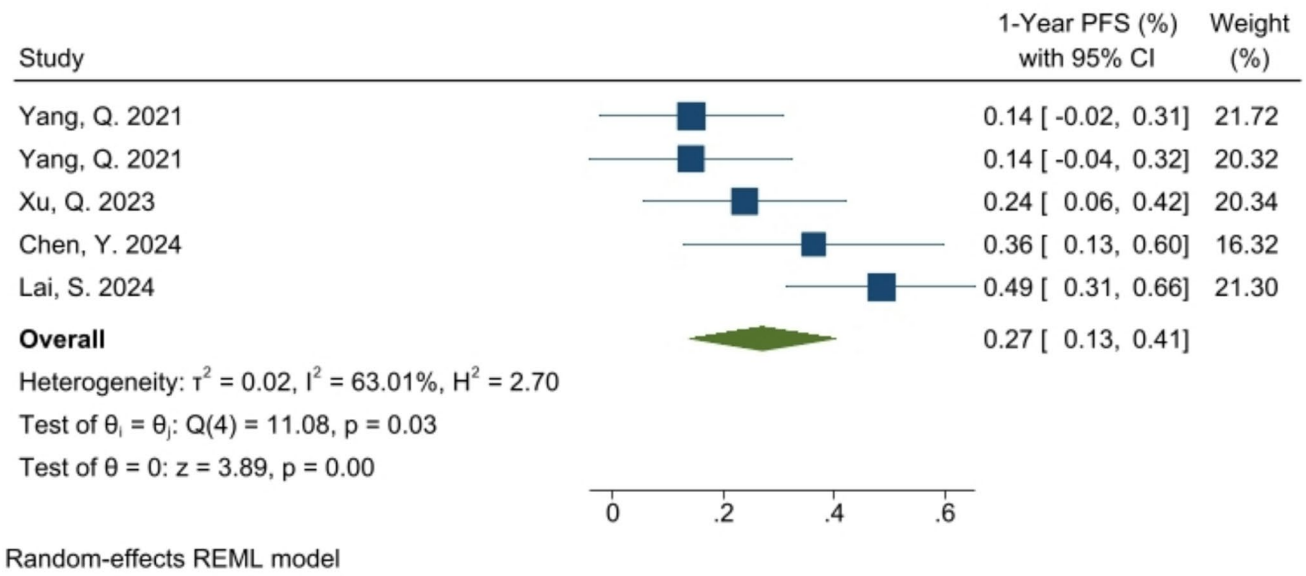


Fig. 4 Pooled Progression-Free survival at 6-month (**a**), 1-year (**b**)

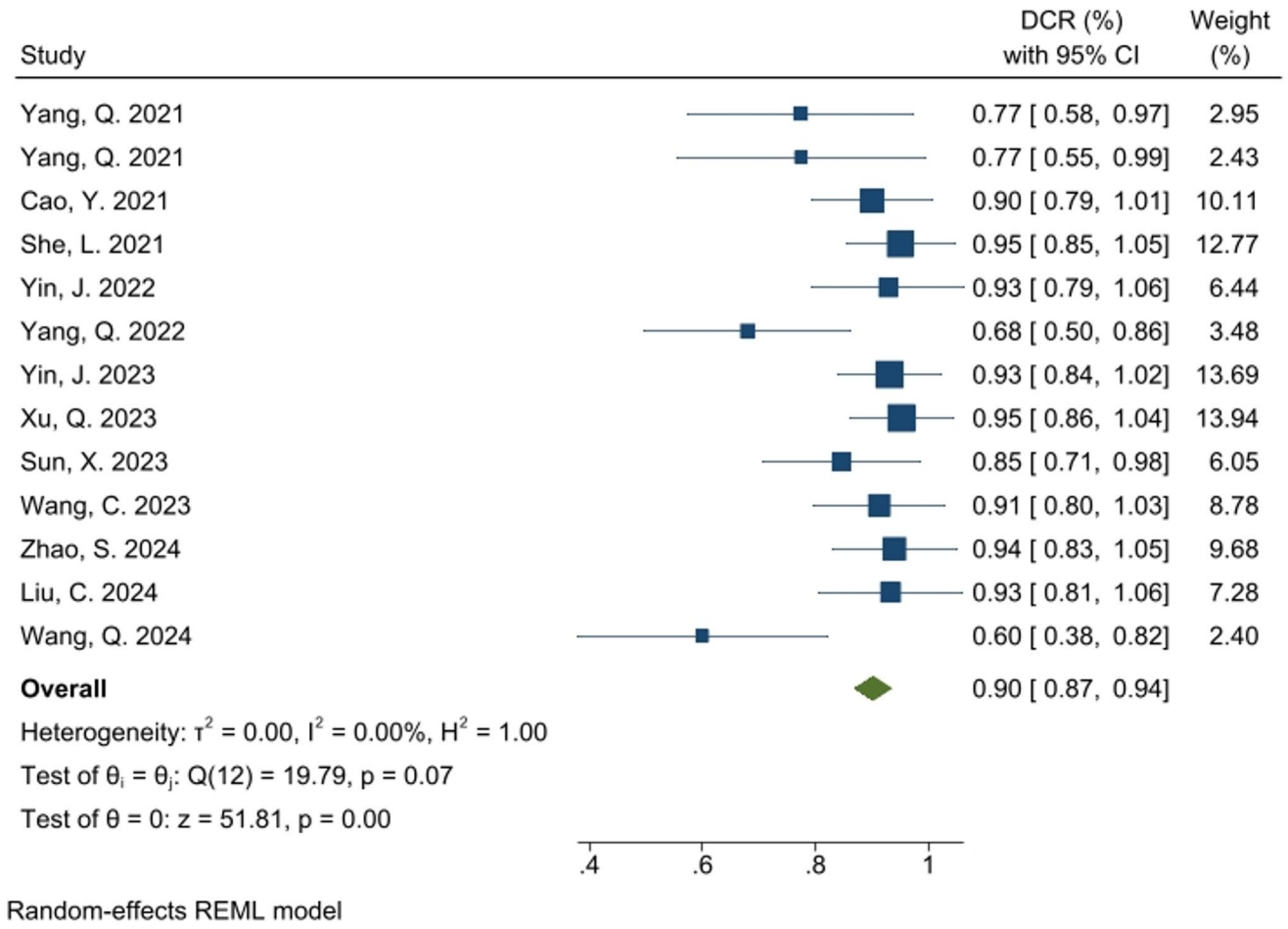


Fig. 5 Disease Control Rate

gender (β = 0.2417, $p = 0.104$), grade 3 of tumor (β = 1.000, $p = 0.342$), grade 4 of tumor (β = 0.1790, $p = 0.276$), methylation of MGMT (β = 0.5207, $p = 0.396$), no-methylation of MGMT (β = 0.2119, $p = 0.290$), wild type of IDH (β = 0.1660, $p = 0.075$), and mutation of IDH (β = 0.5935, $p = 0.445$) were not found as significant moderators.

Partial response rates (PRR)

The pooled PRR was calculated based on the 12 studies that were included and was equal to 37% (95% CI: 25–49%), with a considerable and significant heterogeneity (I^2 = 75.81%, $P < 0.01$) (Fig. 6c). Additionally, the results in the GBM patients were 41% (95% CI: 0.23–0.58) with a statistically significant moderate heterogeneity observed among the 4 included studies (I^2 = 60.64%, $P = 0.05$).

Subgroup analysis revealed a statistically significant difference between the concurrent administration of either radiotherapy, bevacizumab, or TMZ compared to Anlotinib alone in favor of concurrent TMZ administration ($P < 0.01$). The comparison between the Anlotinib group, the Anlotinib & TMZ group, the Anlotinib & Bev group, the Anlotinib & radiotherapy group, and the group receiving Anlotinib & TMZ & radiotherapy at the same time resulted in a statistically significant difference in favor of the Anlotinib & TMZ group ($P = 0.04$). PRR comparison in patients with either brainstem, thalamus, or multi-focal tumor groups also showed a statistically significant difference in favor of the group with multi-focal glioma ($p < 0.01$). Notably, different prior treatments showed a statistically significant difference between the group of chemo/radiotherapy, the group with prior chemo/radio/immunotherapy, the group that underwent surgery, the group with prior surgery and chemotherapy, and the group that received surgery, radiotherapy, a chemotherapy before Anlotinib in favor of the surgery group ($p < 0.01$). Additionally, both type and data source of the studies showed no significant impact on PRR ($p = 0.08$ and $p = 0.99$, respectively).

Meta-regression analysis also identified the following moderators: Female gender (β = 0.9968, $p < 0.001$), male gender (β = 0.5965, $p = 0.003$), age (β = 0.0078, $p < 0.001$), grade 3 of tumor (β = 1.5917, $p = 0.023$), grade 4 of tumor

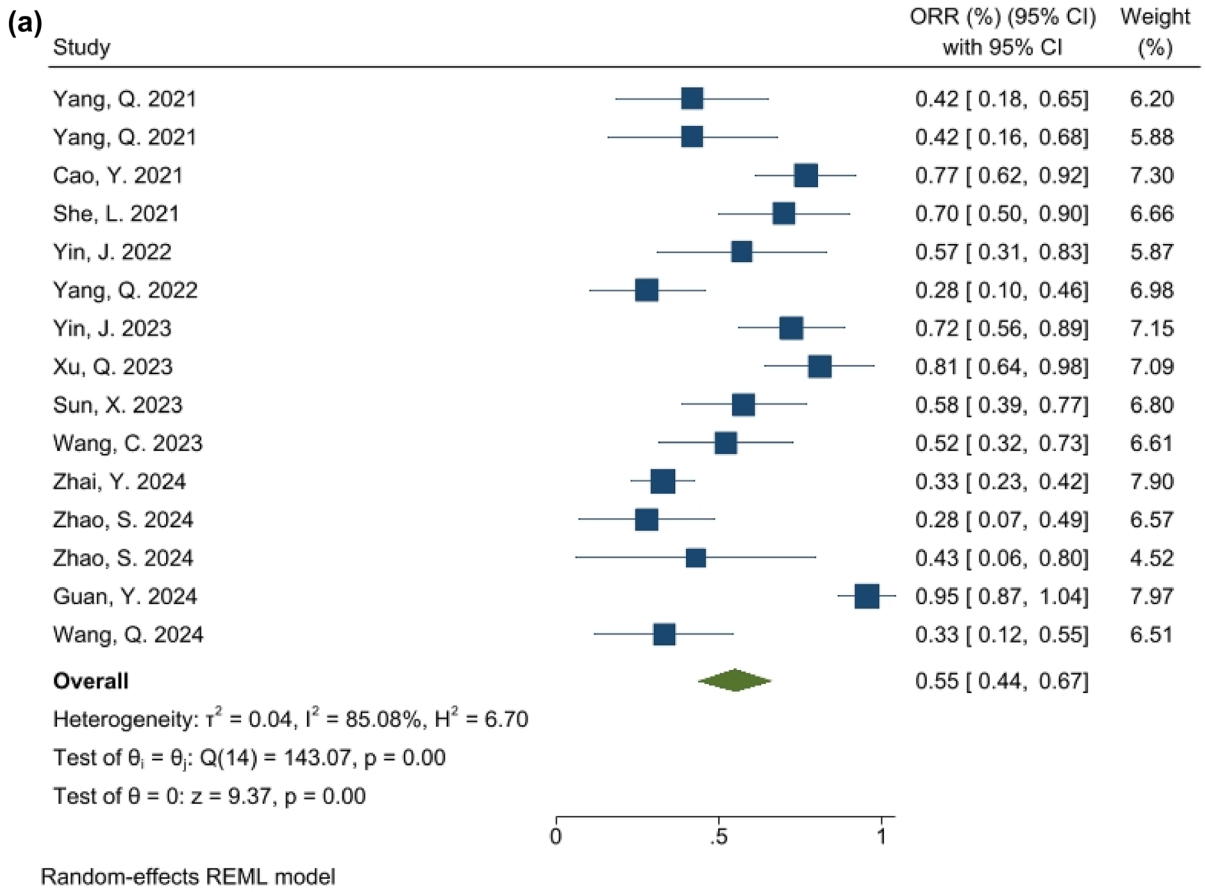
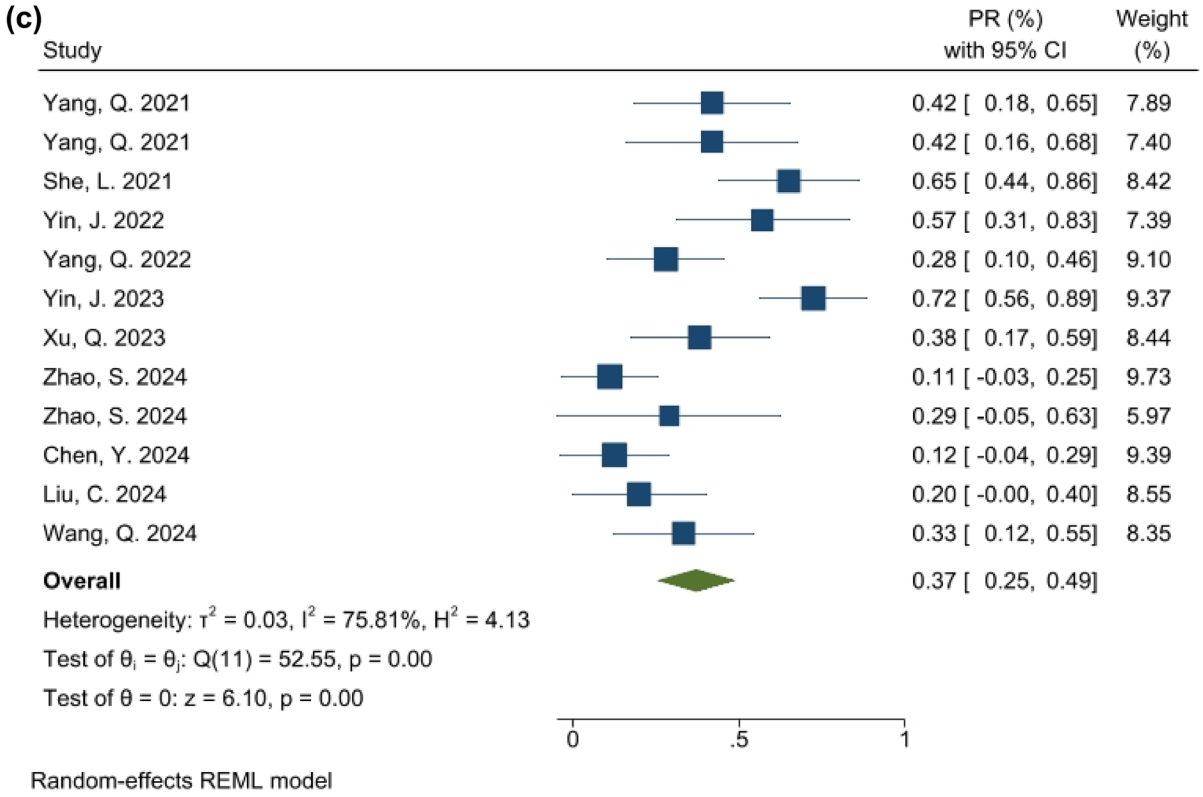


Fig. 6 Overall response rate (**a**), Complete response rate (**b**), partial response rate (**c**), stable disease rate (**d**), progressive disease rate (**e**)

(β = 0.4438, $p = 0.017$), methylation of MGMT (β = 1.3927, $p < 0.001$), no-methylation of MGMT (β = 0.5741, $p = 0.002$), wild type of IDH (β = 0.4288, $p < 0.001$), and mutation of IDH (β = 1.7023, $p = 0.009$) to have significant influences on the PRR.

Stable disease rates (SDR)

Pooled SDR based on the 13 included studies was 39% (95% CI: 25–52%), with a significant and substantial heterogeneity among the studies ($I^2 = 86.02\%$, $P < 0.01$) (Fig. 6d).



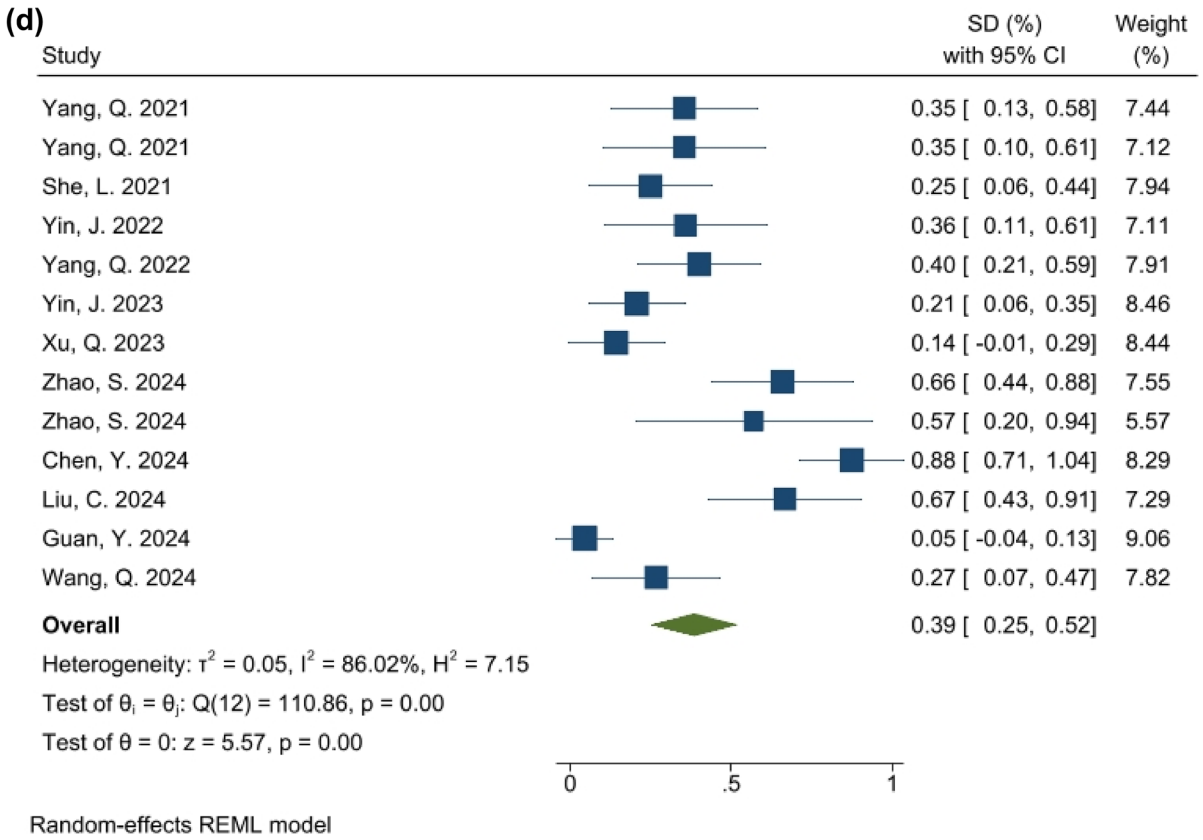


Fig. 6 (continued)

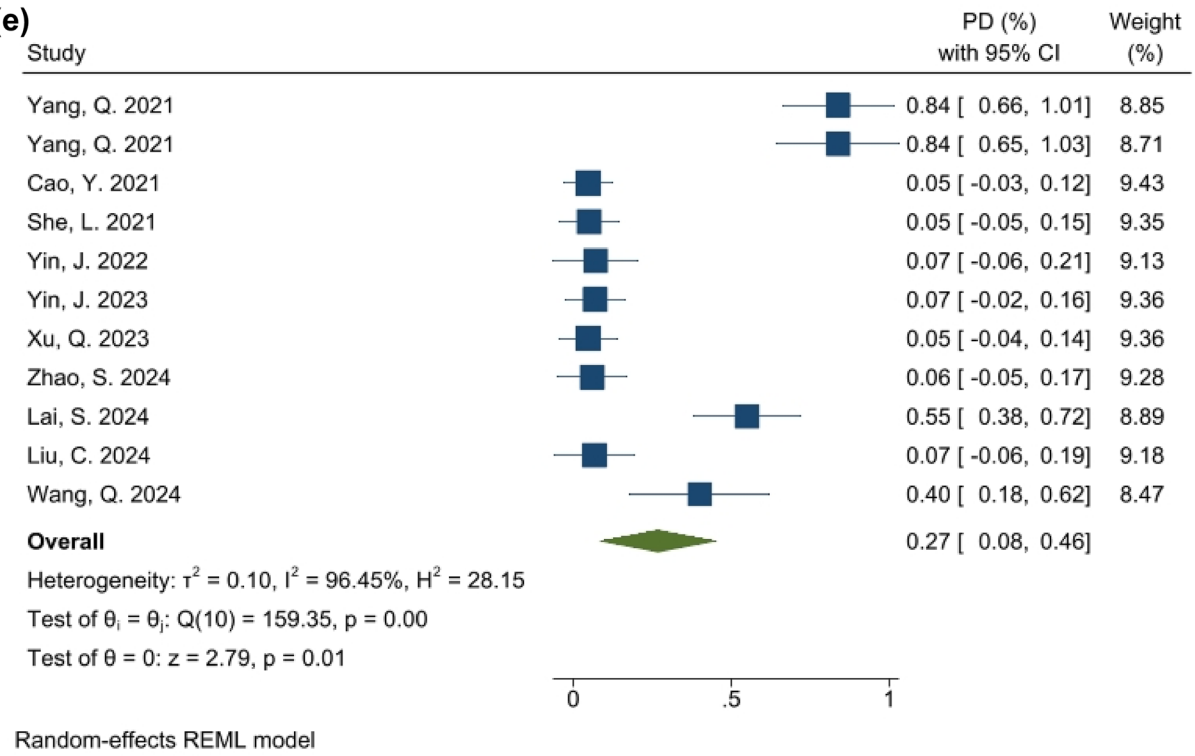


Fig. 6 (continued)

Additionally, the results in the GBM patients were 24% (95% CI: 0.08–0.40**)** with statistically significant heterogeneity among the 5 included studies ($I^2 = 78.49\%$, $P<0.01$).

Subgroup analysis revealed a statistically significant difference between the concurrent administration of either radiotherapy, bevacizumab, or TMZ, and SRS compared to Anlotinib alone, with a tendency to higher SDR in the concurrent administration of radiotherapy ($P<0.01$). The comparison between the Anlotinib group, the Anlotinib & Bev group, the Anlotinib and SRS group, the Anlotinib & radiotherapy group, the Anlotinib & TMZ group, and the group receiving Anlotinib & TMZ & radiotherapy at the same time resulted in a statistically significant advantage in the group that received Anlotinib & TMZ & radiotherapy simultaneously ($P<0.01$). Notably, comparison in patients with either brainstem, thalamus, or multifocal tumor groups also showed a statistically significant difference in favor of the group with brainstem glioma ($p<0.01$). Variety of the prior treatments showed to have a statistically significant impact on SDR. Between the group of chemo/radiotherapy, the group with prior chemo/radio/immunotherapy, the group that underwent surgery, the group with prior surgery and chemotherapy, and the group that received surgery, radiotherapy, and chemotherapy before Anlotinib, the chemo/radio/immunotherapy group had a significantly higher SDR ($p<0.01$). Additionally, both type and data source of the studies showed no significant impact on SDR ($p=0.49$ and $p=0.25$, respectively).

Meta-regression analysis identified the influence of the following moderators: Female gender ($\beta=0.7942$, $p=0.006$), male gender ($\beta=0.6212$, $p<0.001$), age ($\beta=0.0073$, $p=0.003$), grade 4 of tumor ($\beta=0.4624$, $p=0.004$), methylation of MGMT ($\beta=0.8371$, $p=0.012$), no-methylation of MGMT ($\beta=0.4582$, $p<0.001$), wild type of IDH ($\beta=0.4205$, $p<0.001$), and mutation of IDH ($\beta=1.5461$, $p=0.019$) have significant influences on the SDR, while grade 3 of tumor ($\beta=1.3212$, $p=0.77$) showed no significant influence on it.

Progressive disease rate (PDR)

In order to calculate the pooled PDR, 11 studies were included and resulted in 27% (95% CI: 8–64%), with significant and considerable heterogeneity among the studies ($I^2 = 96.45\%$, $P<0.01$) (Fig. 6e). Additionally, the results in the GBM patients were 21% (95% CI: 0.00–0.53**)** with a statistically significant substantial heterogeneity among the 3 included studies ($I^2 = 95.82\%$, $P<0.01$).

Subgroup analysis revealed no statistically significant difference between the concurrent administration of TMZ compared to Anlotinib alone ($P=0.13$). There was also no significant difference in the comparison between the Anlotinib group, the Anlotinib & TMZ group, and the group

receiving Anlotinib & TMZ & radiotherapy at the same time ($P=0.84$). The comparison between patients with either brainstem, thalamus, or multifocal tumor groups also showed no statistically significant difference in PDR ($p=0.06$). Meanwhile, prior treatments showed to have a statistically significant impact on PDR. Between the group of chemo/radiotherapy, the group that underwent surgery, and the group with prior surgery and chemotherapy, the combination of surgery and chemotherapy showed to have a significantly higher SDR ($p=0.01$). Neither type nor data source of the studies showed to have a significant impact on PDR ($p=0.42$ and $p=0.09$, respectively).

Notably, meta-regression analysis identified the influence of the following moderators: Female gender (β=0.6664, $p=0.047$), male gender (β=0.5541, $p=0.018$), age (β=0.0065, $p=0.033$), Grade 3 of Tumor (β=1.8987, $p=0.041$), methylation of MGMT (β=1.1147, $p=0.014$), no-methylation of MGMT (β=0.4707, $p=0.043$), wild type of IDH (β=0.3443, $p=0.040$), and mutation of IDH (β=1.7190, $p=0.040$) have significant influences on the PDR, while Grade 4 of Tumor (β=0.5098, $p=0.101$) showed no significant influence on it.

Adverse events (AE)

Overall adverse event at any grade rate (OAEAGR)

Pooled OAEAGR of the 2 included valid studies was equal to 59% (95% CI: 22–96%), with a significant and considerable heterogeneity among the studies ($I^2 = 87.80\%$, $P<0.01$). It is worth mentioning that the group in which no concurrent radiotherapy was administered showed a significantly higher OAEAGR ($P<0.01$). Additionally, the results in the GBM patients were 20% (95% CI: 0.17–0.32**)** with no statistically significant heterogeneity among the 3 included studies ($I^2 = 30.45\%$, $P=0.22$).

Meta-regression analysis identified no significant influence of the following moderators: female gender (β=1.5710, $p=0.310$), male gender (β=0.9157, $p=0.135$), age (β=0.0116, $p=0.183$), wild type of IDH (β=0.6353, $p=0.297$), and mutation of IDH (β=2.7857, $p=0.307$).

Overall adverse event at grade 3 or higher rate (OAEG3HR)

For the estimation of true OAEG3HR, 2 studies entered the analysis and resulted in 17% (95% CI: 7–27%), with negligible, not statistically significant heterogeneity in results ($I^2 = 48.01\%$, $P=0.11$) (Fig. 7).

Subgroup analysis revealed no statistically significant difference between the concurrent administration of TMZ, Bev, or radiotherapy compared to Anlotinib alone ($P=0.11$). The comparison between patients with either brainstem or multifocal tumor groups also showed no statistically significant difference in OAERG3H ($p=0.07$). The same similarity of subgroups was observed for prior treatments, showing that patients with prior chemo/radiotherapy have no statistically significant difference compared to the group who underwent prior surgery & radiotherapy ($p=0.93$). Although a significant difference was observed for the study's type, with a higher OAEG3HR in RCTs ($p=0.05$).

Notably, meta-regression analysis identified the moderators, male gender (β=0.2982, $p=0.020$), age (β=0.0033, $p=0.023$), and wild type of IDH (β=0.1875, $p=0.022$), to have significant influences on the OAERG3H, while female gender (β=0.3611, $p=0.057$), grade 3 of tumor (β=0.7044, $p=0.531$), grade 4 of tumor (β=0.2559, $p=0.147$), methylation of MGMT (β=0.3314, $p=0.380$), no-methylation of MGMT (β=0.1473, $p=0.079$), and mutation of IDH (β=0.6198, $p=0.317$) showed no significant influence on it.

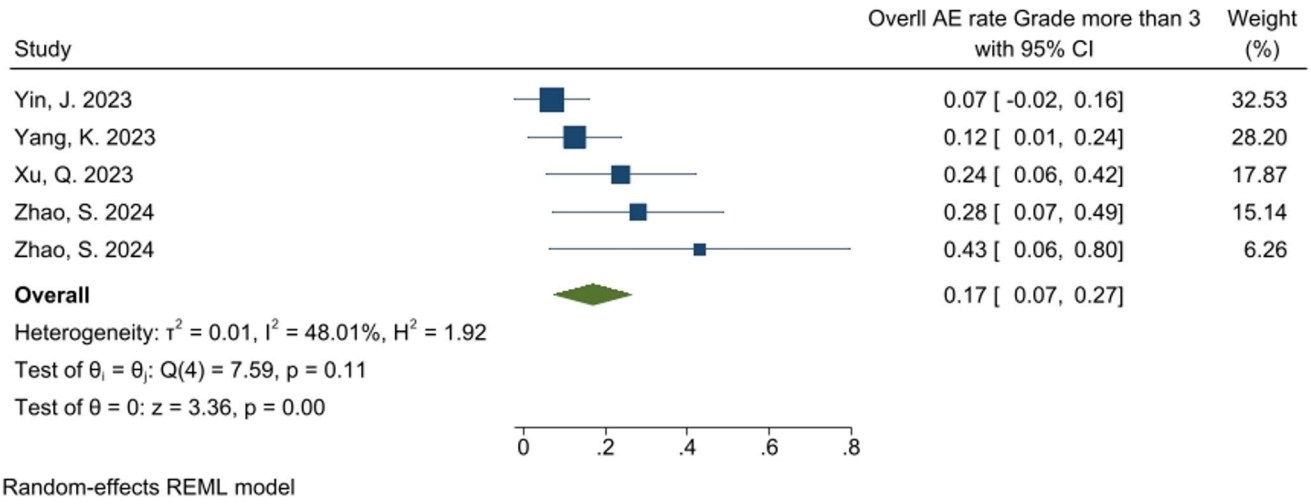


Fig. 7 Overall Adverse Event at Grade 3 or Higher Rate

Overall adverse events

Given the discrepancies between the studies for reporting the AEs, we decided to perform a narrative synthesis to better illuminate the AEs associated with the treatment regimen. The following narration reports the AEs at any grades (I, II, and > II), and grade > II biotoxicities.

Yang et al. investigated the clinical outcomes and safety profiles of Anlotinib in two different protocols: standalone Anlotinib and Anlotinib as an adjuvant to TMZ [17]. The standalone Anlotinib arm had only grade I or II toxicity: 1 patient with hand-foot syndrome, 3 patients with mucositis, 7 patients with hypertension, 2 patients with gastrointestinal reaction, 2 patients with leukopenia, 1 patient with hypothyroidism, 1 patient with proteinuria, 3 patients with hypertriglyceridemia, and 1 patient with bleeding. Similarly, in the other cohort, Anlotinib as an adjuvant to TMZ, patients had only grade I or II AEs: 3 patients with hand-foot syndrome, 4 patients with mucositis, 8 patients with hypertension, 9 patients with gastrointestinal reaction, 8 patients with anemia, 3 patients with thrombocytopenia, 9 patients with leukopenia, 1 patient with hypothyroidism, 3 patients with proteinuria, 7 patients with liver dysfunction, 2 patients with hypertriglyceridemia, 1 patient with bleeding, and 4 patients with abnormality in ECG.

Yang et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the TMZ protocol [18]. This study followed NCI-CTCAE. The Anlotinib as an adjuvant to the TMZ arm had the following biotoxicities: 13 patients with hand-foot syndrome at any grades, 2 patients with grade > II hand-foot syndrome, 9 patients with hypertension at any grades, 7 patients with anemia at any grades, 4 patients with gastrointestinal reaction at any grades, 5 patients with neutropenia at any grades, 9 patients with thrombocytopenia at any grades, 2 patients with grade > II thrombocytopenia, 12 patients with leukopenia at any grades, 8 patients with proteinuria at any grades, 11 patients with hyperbilirubin at any grades, and 1 patient with grade > II hyperbilirubin.

She et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the TMZ protocol [19]. The Anlotinib as an adjuvant to the TMZ arm had the following biotoxicities: 4 patients with hand-foot syndrome at any grades, 1 patient with grade > II hand-foot syndrome, 2 patients with mucositis at any grades, 1 patient with grade > II mucositis, 5 patients with hypertension, 4 patients with grade > II hypertension, 1 patient with rash at any grade, 7 patients with anemia, 1 patient with thrombocytopenia at any grades, 1 patient with liver dysfunction at any grades, 1 patient with hypertriglyceridemia at any grades, and 1 patient grade > II cerebral infarction.

Yin et al. investigated the clinical outcomes and safety profiles of Anlotinib as a standalone protocol [20]. This study followed NCI-CTCAE. No grade > II AEs were observed: 1 patient with hand-foot syndrome, 4 patients with fatigue, 4 patients with hypertension, 2 patients with short-term memory loss, 1 patient with drowsiness, 1 patient with edema, and 1 patient with joint pain and hoarseness.

Yang et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the TMZ protocol [21]. The following grade > II AE was observed in this study: 12 patients with grade > II lymphopenia; lymphopenia was most likely attributed to the TMZ.

Yin et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the TMZ protocol [9]. This study followed NCI-CTCAE. The Anlotinib as an adjuvant to the TMZ arm had the following biotoxicities: 6 patients with hand-foot syndrome at any grades, 5 patients with fatigue at any grades, 6 patients with hypertension, 1 patient with edema, 3 patients with rash, 3 patients with gastrointestinal reaction, 2 patients with anorexia, 2 patients with diarrhea, 3 patients with anemia, 9 patients with thrombocytopenia, 2 patients with grade > II thrombocytopenia, 8 patients with leukemia, 3 patients with headache, 5 patients with memory impairment, 6 patients with liver dysfunction, 6 patients with hypertriglyceridemia, 4 patients with renal function impairment, 3 patients with cerebral hemorrhage, 3 patients with arthrodynia, 3 patients with bleeding gums, 2 patients with palpitation, and 1 patient with sleepiness.

Yang et al. investigated the clinical outcomes and safety profiles of Anlotinib as a standalone protocol [22]. This study followed NCI-CTCAE. The following AEs were witnessed: 12 patients with hand-foot syndrome at any grade, 1 patient with grade > II hand-foot syndrome, 13 patients with hypertension, 1 patient with grade > II hypertension, 5 patients with liver dysfunction, 2 patients with grade > II liver dysfunction, and 9 patients with hematuria.

Xu et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the TMZ protocol [23]. This study followed NCI-CTCAE. The following AEs were witnessed: 1 patient with mucositis, 6 patients with hypertension, 1 patient with grade > II hypertension, 2 patients with rash, 1 patient with anemia, 8 patients with thrombocytopenia, 1 patient with grade > II thrombocytopenia, 14 patients with leukopenia, 2 patients with grade > II leukopenia, 1 patient with headache, 6 patients with hypothyroidism, 5 patients with elevated AST, 1 patient with grade > II elevated AST, 6 patients with elevated ALT, 1 patient with grade > II elevated ALT, 6 patients with hypertriglyceridemia, 1 patient with grade > II hypertriglyceridemia, 1 patient with hypokalemia, 6 patients with

proteinuria, 2 patients with acneiform rash, 1 patients with wound dehiscence, and 1 patient with ischemic stroke.

Sun et al. investigated the clinical outcomes and safety profiles of Anlotinib as a standalone protocol [24]. This study followed NCI-CTCAE. No grade > II AEs were witnessed. The following AEs were witnessed: 10 patients with hand-foot syndrome, 8 patients with hypertension, and 10 patients with weakness.

Zhao et al. investigated the clinical outcomes and safety profiles of Anlotinib in two different protocols: standalone Anlotinib and Anlotinib as an adjuvant to Bevacizumab [10]. The Anlotinib as a standalone had the following biotoxicities: 2 patients with hand-foot syndrome at any grades, 1 patient with mucositis, 3 patients with fatigue, 4 patients with hypertension, 2 patients with grade > II hypertension, 3 patients with neutropenia, 1 patient with grade > II neutropenia, 8 patients with thrombocytopenia, 2 patients with grade > II thrombocytopenia, 4 patients with lymphopenia, 1 patient with hypothyroidism, 4 patients with proteinuria, and 2 patients with oropharyngeal pain. Similarly, in the other cohort, Anlotinib as an adjuvant to Bevacizumab, patients had the following AEs: 1 patient with hand-foot syndrome, 1 patient with mucositis, 3 patients with fatigue, 1 patient with grade > II hypertension, 1 patient with anemia, 2 patients with neutropenia, 1 patient with grade > II neutropenia, 5 patients with thrombocytopenia, 4 patients with lymphopenia, 1 patient with grade > II lymphopenia, 2 patients with proteinuria, 1 patient with elevated AST, 1 patient with elevated ALT, and 2 patients with oropharyngeal pain.

Chen et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the radiotherapy protocol [25]. No grade > II AEs were witnessed up to the last follow-up.

Lai et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the STUPP protocol [26]. This study followed NCI-CTCAE. The following AEs were witnessed: 5 patients with fatigue, 5 patients with hypertension, 4 patients with nausea, 4 patients with vomiting, 10 patients with neutropenia, 4 patients with thrombocytopenia, 11 patients with leukopenia, 1 patient with seizure, 1 patient with proteinuria, 8 patients with elevated AST, 6 patients with elevated ALT, 19 patients with hypertriglyceridemia, 2 patients with grade > II hypertriglyceridemia, 15 patients with Hypercholesterolemia, and 15 patients with Hypoalbuminemia.

Liu et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the STUPP protocol [27]. The AEs witnessed in this study is as follows: 4 patients with hand-foot syndrome at any grades, 1 patient with grade > II hand-foot syndrome, 3 patients with mucositis at any grades, 5 patients with hypertension, 1 patients with grade > II hypertension, 2 patient with rash at any grade, 5 patients with thrombocytopenia at any grades, 2 patients with grade > II thrombocytopenia, 3 patients with leukopenia, 1 patient with hypothyroidism at any grades, 4 patients with proteinuria, 1 patient with grade > II proteinuria, 2 patients with liver dysfunction, and 2 patients with hyperlipidemia.

Guan et al. investigated the clinical outcomes and safety profiles of Anlotinib in the Anlotinib as an adjuvant to the CyberKnife SRS [28]. The AEs witnessed in this study are as follows: 9 patients with hand-foot syndrome at any grade, 5 patients with hypertension, and 6 patients with hypercholesterolemia.

Wang et al. investigated the clinical outcomes and safety profiles of Anlotinib as a standalone protocol [29]. This study followed NCI-CTCAE. The following AEs were witnessed: 9 patients with hand-foot syndrome at any grades, 2 patients with grade > II hand-foot syndrome, 6 patients with mucositis, 3 patients with grade > II mucositis, 8 patients with hypertension, 8 patients with grade > II hypertension, 6 patients with liver dysfunction, 2 patients with grade > II liver dysfunction, 8 patients with myelosuppression, and 2 patients with grade > II myelosuppression.

Death rate (DR)

Pooled Rate of Death in the 4 validated included studies was 71% (95% CI: 61–81%), with insignificant and negligible heterogeneity among them ($I^2 = 0.00\%$, $P = 0.59$) (Fig. 8).

Subgroup analysis revealed no statistically significant difference between the concurrent administration of TMZ compared to Anlotinib alone ($P = 0.17$), and there was also no significant difference in the comparison between the Anlotinib group, the Anlotinib & TMZ group, and the group receiving Anlotinib & TMZ & radiotherapy at the same time ($P = 0.39$). Tumor location also made no statistically significant difference as compared between the groups of brainstem and thalamus ($p = 0.17$).

Even though meta-regression analysis identified female gender ($\beta = 1.6231$, $p = 0.004$), male gender ($\beta = 1.2509$, $p = 0.001$), age ($\beta = 0.0164$, $p = 0.029$), grade 3 of tumor ($\beta = 2.295$, $p = 0.009$), grade 4 of tumor ($\beta = 0.9271$, $p = 0.008$), no methylation of MGMT ($\beta = 1.0014$, $p = 0.001$), and wild type of IDH ($\beta = 0.8799$, $p = 0.001$) to have significant influences on DR, while methylation of MGMT ($\beta = 1.7890$, $p = 0.059$) and mutation of IDH ($\beta = 2.3862$, $p = 0.095$) were associated with no significant influence on it.

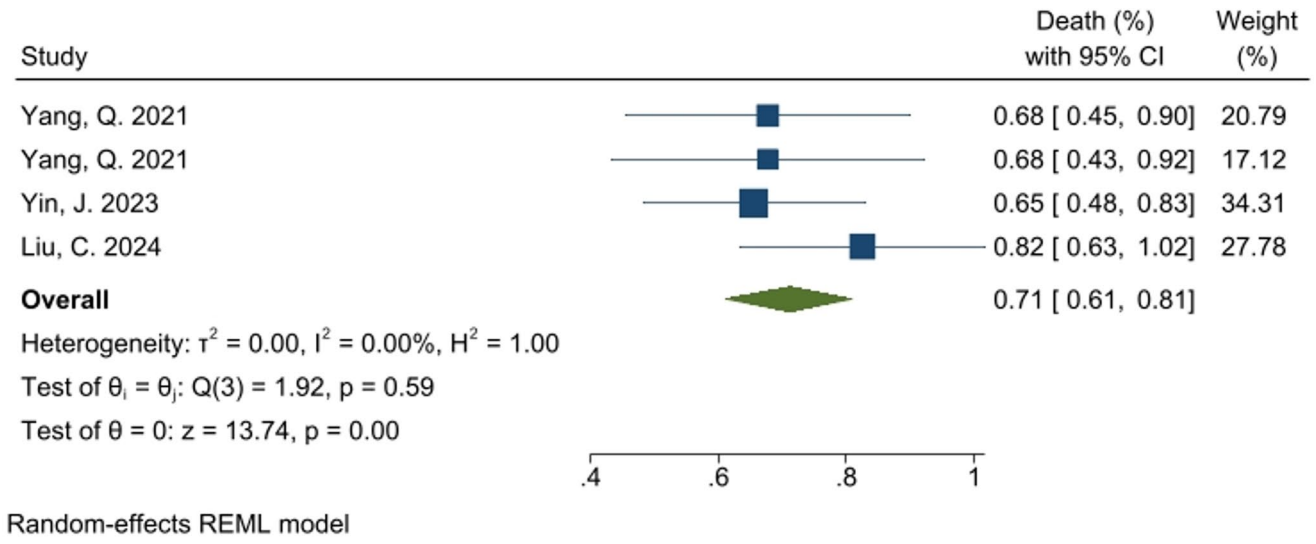


Fig. 8 Death Rate

Sensitivity analysis

To evaluate the robustness of our findings, we conducted a leave-one-out sensitivity analysis across all key outcomes, and the results demonstrated that pooled outcomes of "6-month and 1-year OS-ranging from 0.57–0.74 and 0.45–0.54, respectively- similar to 6-month and 1-year PFS- ranging from 0.56–0.62 and 0.20–0.31, respectively-, remained stable (p values < 0.001) when individual studies were removed. Similar results were obtained in all domains where no substantial variation was observed and no single study excessively influenced the meta-analysis, except for the adverse effects of "Anemia at any grade, Gastrointestinal reactions at any grade, Headache at any grade, and events of Grade 3 or higher in the context of Hypertriglyceridemia, Liver dysfunction, Mucositis and mouth ulcers and Neutropenia" which indicated moderate to severe (P values higher than 0.05) shifts in effect size when removing, suggesting some variability in toxicity reporting and that these adverse events may not be a reliable indicator of the intervention's effect across studies, however these outcomes require further investigation due to inconsistencies across studies. Overall, the sensitivity analysis confirmed the reliability of our findings.

Publication bias

Egger's test suggested significant publication bias for 6-month OS (t = −4.54, p = 0.0452), 1-year OS (t = −2.25, p = 0.0653), 6-month PFS (t = −1.98, p = 0.0792), 1-year PFS (t = 0.42, p = 0.7003), overall response rate (t = −1.43, p = 0.1762), and disease control rate (t = −3.95, p = 0.0023). No significant publication bias was observed for complete response rate (CR) (t = 2.85, p = 0.0462), progressive disease rate (PD) (t = 4.26, p = 0.0021), stable disease rate (SD) (t = 1.64, p = 0.1291), or death rate (t = −0.12, p = 0.9181). Significant publication bias was also noted for adverse events, including hand-foot syndrome of any grade (t = 2.44, p = 0.0331), mucositis or mouth ulcers of any grade (t = 3.09, p = 0.0214), hypertension of any grade (t = 2.55, p = 0.0241), and anemia of any grade (t = 3.22, p = 0.0486). No significant publication bias was detected for hand-foot syndrome grade ≥ 3 (t = 1.07, p = 0.3620), mucositis or mouth ulcers grade ≥ 3 (convergence not achieved), hypertension grade ≥ 3 (t = 1.96, p = 0.1070), neutropenia any grade (t = 0.54, p = 0.6436), neutropenia grade ≥ 3 (convergence not achieved), thrombocytopenia any grade (t = 5.27, p = 0.0012), or thrombocytopenia grade ≥ 3 (t = 1.76, p = 0.147). For overall adverse events, Egger's test indicated significant publication bias for the overall AE rate of any grade (convergence not achieved) and the overall AE rate grade ≥ 3 (t = 2.69, p = 0.0741). Additional adverse events, such as gastrointestinal reactions of any grade (t = 3.62, p = 0.0684), rash of any grade (t = 0.82, p = 0.4964), and fatigue of any grade (t = 1.62, p = 0.2042), demonstrated no significant publication bias based on the results provided. Convergence issues were noted for select adverse events with limited study numbers.

Discussion

Gliomas remain one of the most challenging malignancies in neuro-oncology, characterized by aggressive progression, poor prognosis, and limited therapeutic options [10, 30, 31].

Our systematic review and meta-analysis consolidated the present evidence on the efficacy and safety of Anlotinib in the treatment of gliomas and GBM patients, with the results demonstrating significant improvements in domains such as PFS, OS, ORR, and DCR. From the point of our findings, it could be suggested that the addition of Anlotinib might improve the clinical outcomes of glioma patients [9, 10]. The current protocols and standard of care for glioma patients rely on the maximal surgical resection followed by Adjuvant chemo/radio/immunotherapy regimens and mainly TMZ administration, with the outcomes being often limited by tumor recurrence and resistance [31, 32]. Based on our findings, it could be suggested that the addition of Anlotinib to the frequently applied TMZ might enhance the durability of the clinical management [9, 10], also our findings align with the pharmacological mechanisms of Anlotinib, targeting key pathways of angiogenesis and tumor proliferation [11, 33]. Anlotinib's multi-target mechanism, which inhibits VEGFRs, FGFRs, and PDGFRs pathways, is poised to be an effective agent in disrupting tumor angiogenesis and specifically useful in the management of gliomas, as gliomas have been demonstrated to have an angiogenic nature [11, 33]. In addition to the VEGFRs, FGFRs, and PDGFRs pathways, the mTOR signaling pathway has been demonstrated as a central regulator of tumoral expansion, such as in breast cancer [34], renal cell carcinoma [35], and glioma [36]. In line with the inhibition of the angiogenic factors, Anlotinib has shown promise in disrupting the mTOR signaling axes [37], to ultimately shorten the life span of glioma cells and increase their cellular death rates [38]. Another mechanism through which Anlotinib could exert its anti-tumoral effects is the disruption of cellular metabolism. Due to the pharmacological effects of Anlotinib in glioma cells, amino acid metabolism, energy production, and glycerophospholipid cycles could all be disrupted in a manner that is likely to be closely associated with the mitochondria [39]. Given the role of ROS in damaging the mitochondrial DNA [40], it could be hypothesized that the anti-glioma functions of Anlotinib might involve damage to the structure of the mitochondrial DNA.

While previous studies demonstrate that the anti-angiogenic application of TKIs, such as bevacizumab, in glioma treatment is limited by severe adverse events [41], the manageable safety profile of Anlotinib in the included studies suggests that it could be considered without significant compromise to patient quality of life [9–11, 33]. The safety profile of Anlotinib, enhances the feasibility of its possible integration for routine clinical practice, as common adverse events such as hand-foot syndrome, hypertension, and hematologic toxicities are shown to be generally mild to moderate, with severe (Grade ≥ 3) events being relatively infrequent [23]. Altogether, our findings could suggest that the application of Anlotinib as an adjuvant in the treatment of glioma might improve the clinical outcomes without imposing life-threatening AEs on the patients. However, this study is limited by statistical and methodological issues, and all the results of this study shall be interpreted with maximum caution. Large-scale cohorts and trials with extended follow-up periods are warranted to ensure the clinical outcomes and safety profiles of the addition of Anlotinib.

Negative results

As a well-balanced study should discuss both positive and negative findings, while Anlotinib demonstrated promising efficacy in terms of ORR (55%, 95% CI: 44–67%) and DCR (90%, 95% CI: 87–94%), several subgroup analyses failed to show statistically significant benefits. Notably, in the 1-year OS analysis, the comparison between different treatment regimens revealed non-significant differences between Anlotinib monotherapy and combination therapies ($p=0.09$). Notably, the same results were obtained for 1-year PFS (27%, 95% CI: 13–41%), where no statistically significant advantage was observed in specific treatment subgroups ($p=0.11$). Importantly, the non-significant difference marks the inconclusive findings regarding this clinical outcome of Anlotinib, and it is more likely that the addition of Anlotinib could not outperform the conventional treatment approach.

Publication bias and its implications

Publication bias is an inherent limitation that often favors the dissemination of positive results while underrepresenting negative or inconclusive findings, and similarly our study, utilizing Egger's test detected significant publication bias in several key outcomes, including 6-month OS ($p=0.0452$), 1-year OS ($p=0.0653$), and overall disease control rate (DCR) ($p=0.0023$), and certain adverse events, such as hand-foot syndrome ($p=0.0331$) and hypertension ($p=0.0241$), suggesting that milder toxicities may be underreported in the literature. In this study, the Trim-and-Fill method was not applied, as the number of included studies was already limited, and additional imputed studies could introduce further uncertainty into the meta-analysis. Given the results of Egger's test indicating the inflation of Anlotinib's pooled effect size, it could be concluded that the positive results might have been more preferentially published. Future studies that prioritize prospective trial registration, mandatory reporting of all endpoints, including non-significant results, and comprehensive safety reporting may mitigate these effects, and additionally, the inclusion of conference abstracts and unpublished data in future systematic reviews and meta-analyses may help counterbalance this

bias and provide a more accurate representation of Anlotinib's clinical utility. Meta-analysis studies should incorporate Trim-and-Fill or Bayesian approaches to adjust for potential bias and improve the robustness of findings.

Strengths and limitations of the study

Even though the systematic approach of this meta-analysis, utilizing the comprehensive synthesis of available evidence, rigorous statistical assessments, publication bias evaluations, and the inclusion of both efficacy and safety outcomes of Anlotinib in glioma and GBM management, enhances the credibility of the findings, certain limitations such as high level of heterogeneity (I^2 values, generally being higher than 75%) among the studies-particularly in terms of patient populations characteristics, treatment protocols of different dosages and regimens, and outcome measures- can introduce variability in the pooled estimates, and even though the random-effects model was employed to account for this variability, substantial heterogeneity may still impact the reliability and generalizability of our findings, so to resolve this issues, we conducted meta-regression and subgroup analyses to explore potential sources of heterogeneity. However, the results of meta-regression might be considered "fragile" given the <10 studies in the meta-regression. Especially, "fragility" of compensating statistical analysis for important moderators, MGMT and IDH status, could introduce biases in the survival and tumor control outcomes. Additionally, the relatively small sample size, with 473 patients across the included 17 studies, including 204 GBM patients, where the limited number of participants-particularly in subgroup analyses, may reduce statistical power while increasing the risk of type II errors. As several analyses, such as 6-month and 1-year OS, were based on fewer than 5 studies, the reliability of these estimates may be restricted, and the generalizability of findings could be decreased, especially for specific treatment subgroups. Future large-scale, multicenter RCTs are essential to confirm these results and improve external validity. Furthermore, sensitivity analyses were performed to assess the robustness of our findings, by systematically excluding studies with extreme results or lower methodological quality, we evaluated the stability of the pooled estimates in all domain except for the adverse effects of "Anemia at any grade, Gastrointestinal reactions at any grade, Headache at any grade, and events of Grade 3 or higher in the context of Hypertriglyceridemia, Liver dysfunction, Mucositis and mouth ulcers and Neutropenia" suggesting the variability in toxicity reporting and the and the unreliability of these adverse events due to inconsistencies across studies. Although many of the studies followed the NCI-CTCAE, there were still uncertainties in some of the studies regarding the criteria for assessing the AEs. We tried to better elucidate the AEs using the narrative synthesis, yet the interpretation of AEs demands extreme caution. Another limitation of this study was the inaccessibility to some of the Chinese-language literature. Although being found eligible in the screening, the full texts of these studies could not be retrieved, and reasonable requests to the corresponding authors were left unanswered. We believe that the inclusion of the aforementioned studies could help improve the reliability of our findings. In addition, this study only included records with a clear history of being peer-reviewed; hence, the grey literature records were not considered. Although the grey literature records did not undergo a clear external peer review, the generalizability of our study could be limited by not considering the grey literature. Last but not least, this study is severely limited by the inflation of the Antolinib's pooled effect size due to the preferential publication of positive results. Egger's test indicates the possibility of the presence of publication bias, which damages the generalizability of the results of this study. The possible lack/absence of the negative results, especially the clinical outcomes with a significant p-value of publication bias in Egger's test, could substantially change the findings of out meta-analysis.

Future directions and implications

The findings of this paper could be integrated with the state-of-the-art computational insights and AI applications. Various aspects, such as target identification [42], virtual screening [43], and drug repurposing [44], have been accelerated by AI tools, which could be further extended into Anlotinib's investigation in glioma. Besides, the AI applications could be applied to predict survival, recurrence, and treatment responses [45], which helps deepen our understanding of the clinical benefits of Anlotinib against glioma. The results of this study may open new windows for further research in the context of applications of Anlotinib for the management of Glioma patients, where Biomarker-driven studies that can identify subgroups of patients that are most likely to benefit from Anlotinib, may enhance personalized treatment strategies [23, 46], and studies that investigate the administration of Anlotinib in concurrence with immunotherapy or advanced radiotherapy techniques may yield synergistic effects, improving outcomes [47–49]. A possible suggestion for future studies could be an investigation into the dual administration of anti-CD40 monoclonal antibodies and Anlotinib. For illustration, CD40 is a cell-surface receptor with significant upregulation in glioma [50], and it is importantly involved in the tumor expansion, tumor angiogenesis via VEGF [50]. Considering the anti-angiogenic roles of Anlotinib, the possible synergism between

anti-CD40 targeting and Anlotinib could help increase the clinical outcomes of glioma patients.

Conclusion

Anlotinib's efficacy could be considered thoughtworthy in extending survival outcomes and achieving disease control in high-grade glioma patients, with a manageable safety profile. Subgroup analysis results reveal the considerable outcomes of adding Anlotinib to TMZ and radiotherapy in 6 and 12-month OS and PFS, similar to DCR and concurrent Anlotinib administration with SRS being associated with the highest ORR and CR rates. Given the unavoidable limitations, biases, and statistical "fragilty" in this study, future studies are needed to ensure the clinical outcomes of Anlotinib.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Human Ethics The is a systematic review and meta-analysis study and is deemed to exempt to received ethical approval.

Consent to participate Not applicable.

Consent to publish Not applicable.

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