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The role of temozolomide as adjuvant therapy in glioblastoma management: a systematic review and meta-analysis.

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Abstract

Introduction The persistent challenge of temozolomide (TMZ) resistance and the eventual recurrence of tumors underscore the need for ongoing research and the development of novel therapeutic strategies. We aim to consolidate existing evidence related to the safety and efficacy of TMZ as adjuvant therapy to radiotherapy (RT).

Methods Various electronic platforms were used to conduct a systematic literature review, including PubMed, Europe PMC, SCOPUS, and clinicaltrials.gov. The approach aimed to identify all pertinent studies published up to July 25, 2024. The search incorporated terms such as "glioblastoma," "temozolomide," "monotherapy," and "adjuvant" alongside relevant Medical Subject Headings (MeSH). The key metrics were overall and progression-free survival, while secondary measures concentrated on treatment-related adverse effects, notably hematological issues like anemia, leukopenia, thrombocytopenia, and neutropenia.

Results The overall effect estimates from the forest plots show significant differences favoring TMZ + RT over RT alone. The HR for overall survival is 0.64 (95% CI: 0.58, 0.71), showing a considerable improvement with TMZ + RT. Progression-free survival shows a HR of 0.51 (95% CI: 0.45, 0.58), also demonstrating a significant benefit for TMZ + RT.

Conclusions Combining TMZ with RT generally leads to better overall and progression-free survival outcomes compared to RT alone. However, the two treatment groups have similar toxicity.

Keywords Glioblastoma, Overall survival, Progression free survival, Temozolomide.

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Introduction

Temozolomide (TMZ), an oral alkylating agent, has emerged as a pivotal component in the management of glioblastoma, particularly when used as an adjuvant to radiotherapy (RT) [1]. TMZ has been shown to significantly improve patient outcomes, notably increasing the median overall survival compared to RT alone [2]. This combination therapy has thus become the cornerstone of standard care for glioblastoma patients, offering a balance between efficacy and tolerability.

Understanding the molecular mechanisms and potential biomarkers underlying TMZ resistance is critical for improving therapeutic strategies and guiding personalized treatment approaches. For instance, the effectiveness of TMZ in treating glioblastoma is strongly affected by O6-methylguanine-DNAmethyltransferase (MGMT) promoter methylation [3]. MGMT promoter methylation is in association with an improved response to TMZ, making it a valuable predictive biomarker for treatment planning [3]. Unmethylated MGMT (umMGMT), associated with resistance to TMZ due to high MGMT protein levels that repair TMZ-induced DNA damage, necessitates alternative strategies. For these patients, options such as RT alone, hypofractionated RT, or enrollment in clinical trials exploring novel therapies are considered. However, despite its efficacy, TMZ therapy is not without challenges. Issues such as tumor recurrence, TMZ resistance, and variability in patient response based on factors like age, performance status, and extent of tumor resection continue to complicate treatment outcomes [4, 5].

Moreover, while TMZ has ushered in a new era in glioblastoma treatment by improving overall survival and 2-year survival rates, its use has not been associated with a significant increase in adverse events [6]. The persistent challenge of TMZ resistance and the eventual recurrence of tumors underscore the need for ongoing research and the development of novel therapeutic strategies.

Given the critical role of TMZ in glioblastoma management and the ongoing challenges associated with its use, a comprehensive analysis of its safety and efficacy as an adjuvant therapy to RT is warranted. This comprehensive review and meta-analysis examine the safety and efficacy of TMZ as an adjuvant treatment to RT.

Methods

This meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and was conducted without external funding [7]. It relied solely on publicly accessible data, thus obviating the need for ethical review since there was no direct patient involvement.

We conducted a thorough and organized literature search across multiple databases: PubMed, Europe PMC, SCOPUS, and clinicaltrials.gov. The search was designed to include all relevant studies published up to July 25, 2024, using terms such as "glioblastoma," "temozolomide," "monotherapy," and "adjuvant."

The review included studies involving adult glioblastoma patients treated with TMZ as an adjunct to RT, compared to RT alone or other adjuvant treatments. The main outcomes were survival and progression-free survival, while the secondary outcomes focused on treatment-related toxicities such as anemia, leukopenia, thrombocytopenia, and neutropenia.

Randomized controlled studies published in English peer-reviewed journals were eligible. We excluded studies focusing on non-glioblastoma brain tumors, pediatric cases, TMZ monotherapy without RT, studies lacking clinical outcomes, non-comparative studies, case reports, expert opinions, and preclinical research. Publications in languages other than English and those not fully accessible, such as abstracts and conference proceedings, were also excluded.

The study selection process involved searching multiple databases and importing results into reference management software (Zotero), followed by the removal of duplicates. Three reviewers (JH, UP, and SK) independently evaluated titles and abstracts for inclusion and exclusion. Some disagreements were settled by a senior reviewer (MA). For evaluation, full-text publications of possibly suitable research were taken.

Data extraction was performed using a standardized form, tested on a small sample for accuracy. Extracted data included study characteristics, patient demographics, intervention details, comparison group specifics, and outcome measures. During the data extraction process, studies with incomplete or missing key variables were identified and addressed using predefined criteria. When critical information, such as MGMT methylation status, patient outcomes, or details of therapeutic interventions, was unavailable, the authors proactively sought clarification by contacting the original study authors. This process involved sending structured email inquiries and providing a specified timeframe for responses to ensure thorough data retrieval.

Cochrane Risk of Bias 2 assessed bias in the included trials [8]. This tool investigates randomization, outcome measurement, intervention variations, missing outcome data and result selection. Each area was rated "low risk," "some concerns," or "high risk" of bias. Two reviewers independently conducted the assessments.

The statistical analyses were conducted in RStudio utilizing the meta and metafor packages. Risk ratios (RR) for adverse events and hematological toxicities were calculated using a random-effects model and the Mantel-Haenszel method. Hazard ratios (HR) for survival outcomes were calculated using the Der Simonian and Laird approach in a random-effects framework, regardless of

heterogeneity. A p-value of < 0.05 was set as the threshold for statistical significance. The Chi-squared test and I2 statistic measured heterogeneity, whereas funnel plots and Egger's test analyzed publication bias. The statistical significance cutoff value to be considered statistically significant should be under 0.05.

Results

The study identification process commenced with a search across multiple databases and registries. Initially, records were collected from PubMed (117), Europe PMC (1255), SCOPUS (366), and Clinicaltrials.gov (2806), aggregating a total of 4544 entries. After removing duplicates (381), 4163 records remained for review. Of these, 4148 were excluded during the screening, leaving 15 reports for retrieval, all of which were successfully obtained. These 15 reports were then evaluated for eligibility. Eight reports were excluded: four had no overall or progression-free survival data, and three were not randomized controlled trials, and one was a study protocol. Thus, seven papers qualified for the final examination [9, 10, 11, 12, 13, 14, 15]. The detailed PRISMA flowchart shown in Fig. 1.

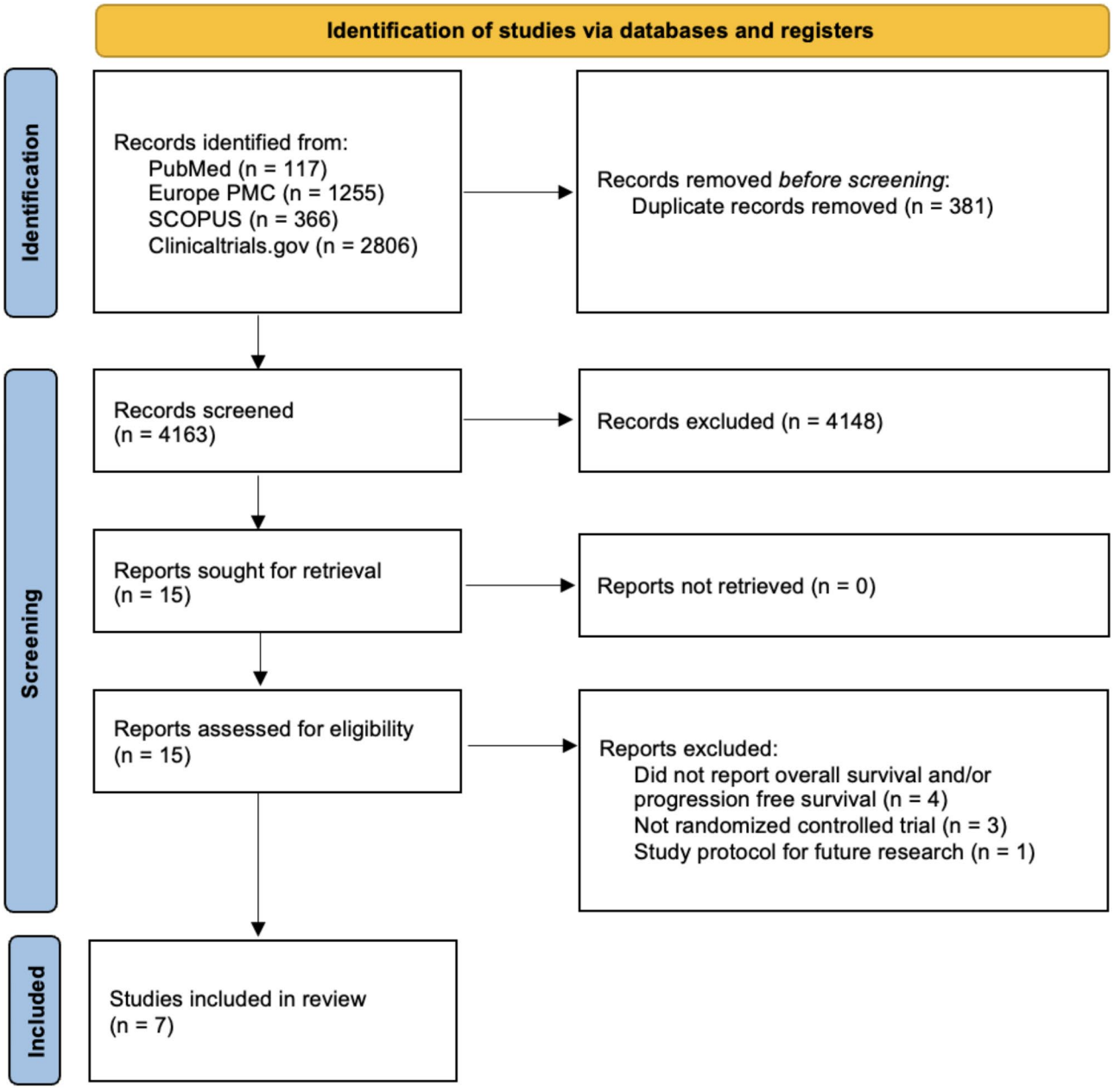

Fig. 1 PRISMA flow showing the processing of study selection

Table 1 Demographic characteristics of the studies addressing the safety and efficacy of temozolomide as an adjuvant to radiotherapy in patients with glioblastoma ($n = 1,978$) were examined

Study ID	Country of study	Cohort size, *n*	Age, years	Male, *n*	Complete resection	Temozolomide details	Median survival
Szczepanek 2013	Poland	28 vs. 30	55 (18–65) vs. 56 (20–68)	18 vs. 16	18 vs. 18	200 mg/m^2 for 5 postoperative days, then 75 mg/m^2 daily, 7 days a week, starting 23 days after surgery.	16 months vs. 12.5 months
Perry 2016	Canada, Europe, Australia, and New Zealand	281 vs. 281	73 (65–90) vs. 73 (65–90)		-	75 mg/m^2 per day for 21 days. Following RT, administered at 150 to 200 mg/m^2 per day for 5 days within a 28-day cycle, up to 12 cycles	9.3 months (8.3–10.3) vs. 7.6 months (7.0–8.4)
Athanassiou 2005	Greece	57 vs. 53	≤ 50 years: 11 vs. 9 > 50 years: 42 vs. 48	36 vs. 34	10 vs. 8	75 mg/m^2 daily orally during RT, followed by six cycles (150 mg/m^2 on days 1–5 and 15–19 every 28 days).	13.41 months (9.53–17.13) vs. 7.7 months (5.32–9.2)
Cohen 2005	Europe, Canada, and Australia	287 vs. 286	55 (18–77) vs. 56 (23–70)	184 vs.177	116 vs. 113	150 or 200 mg/m^2 daily for 5 days every 4 weeks (6 cycles)	14.6 months (13.2–16.8) vs. 12.1 months (11.2–13)
Stupp 2009	Canada, Belgium, Germany, Spain, France, Italy, the Netherlands, Poland, Israel, Sweden, Slovenia, and the United Kingdom	287 vs. 286	55 (18–70) vs. 56 (23–70)	184 vs.177	116 vs. 113	150 or 200 mg/m^2 daily for 5 days every 4 weeks (6 cycles)	14.6 months (13.2–16.8) vs. 12.1 months (11.2–13)
Karacetin 2011	Turkey	20 vs. 20	52.5 (25–72) vs. 51.5 (19–73)	9 vs. 10	14 vs. 8	75 mg/m^2 given daily, one hour before RT and on non-RT days, followed by 6 cycles of 200 mg/m^2 for 5 days every 28 days, starting 4 weeks after RT completion	19 months vs. 11.5 months
Kocher 2008	Germany	29 vs. 33	59 (34–67) vs. 58 (37–69)	15 vs. 26	29 vs. 33	Single daily oral dose of 75 mg/m^2, given 1–2 h before each RT.	14.6 months (12.0–17.2) vs. 17.1 months (13.5–20.8)

mg = milligram; RT = radiotherapy; vs. = versus

The data were presented comparing TMZ as an adjuvant treatment to the control group that received RT alone

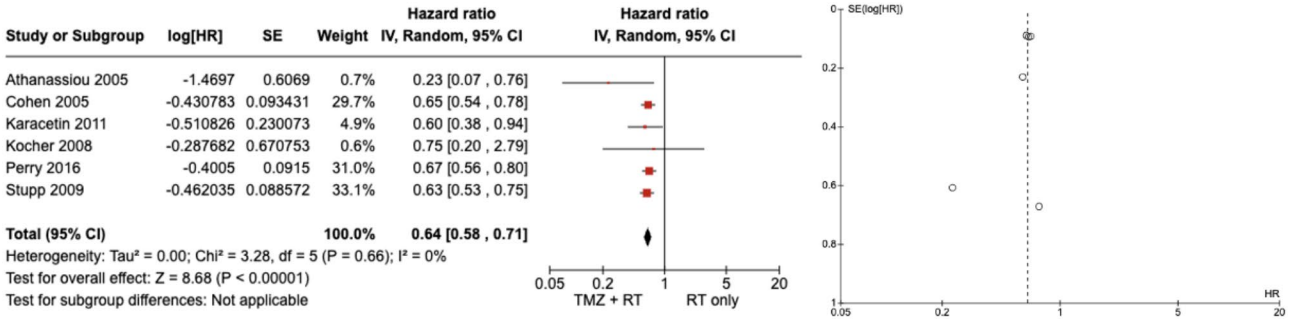

Fig. 2 Meta-analysis comparing the overall survival between the group of TMZ adjuvant to RT vs. RT only

The seven studies collectively involved 1,978 participants, equally divided between 989 in the TMZ + RT group and 989 in the RT-only group. Participants' ages varied, with a total of 886 males, 446 in the TMZ + RT group and 440 in the RT-only group. Among them, 596 had undergone complete resection of glioblastoma—303 in the TMZ + RT group and 293 in the RT-only group. Treatment protocols across studies included initial doses followed by maintenance cycles, with specific dosages and schedules varying. Generally, the RT-only group had lower overall and progression-free survival than the TMZ + RT group. Significant differences were observed at various intervals—24-month, 18-month, 12-month, and 6-month—where the TMZ + RT group consistently demonstrated better outcomes. Although exact administration schedules and dosages varied, the overall trend indicated that TMZ + RT treatment generally leads to improved survival outcomes relative to RT alone. Detailed demographic data are provided in Table 1.

The forest plot-derived effect estimates reveal notable advantages for TMZ + RT over RT alone. For overall survival (Fig. 2), the HR is 0.64 (95% CI: 0.58, 0.71), reflecting

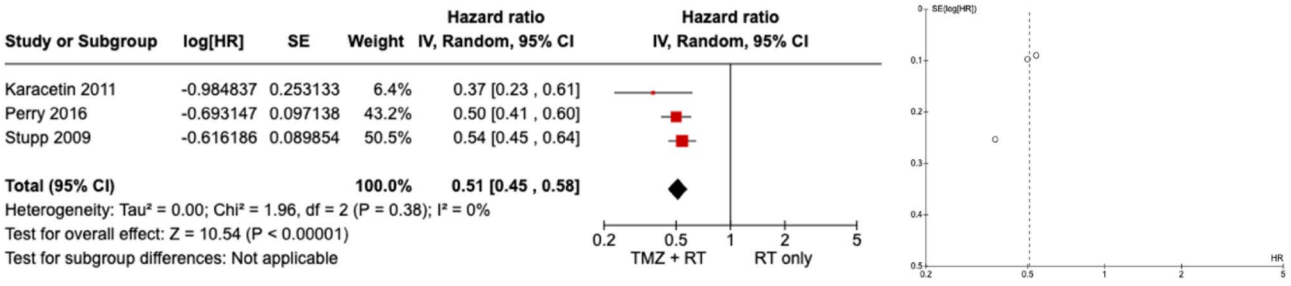

Fig. 3 Meta-analysis comparing the progression free survival between the group of TMZ adjuvant to RT vs. RT only

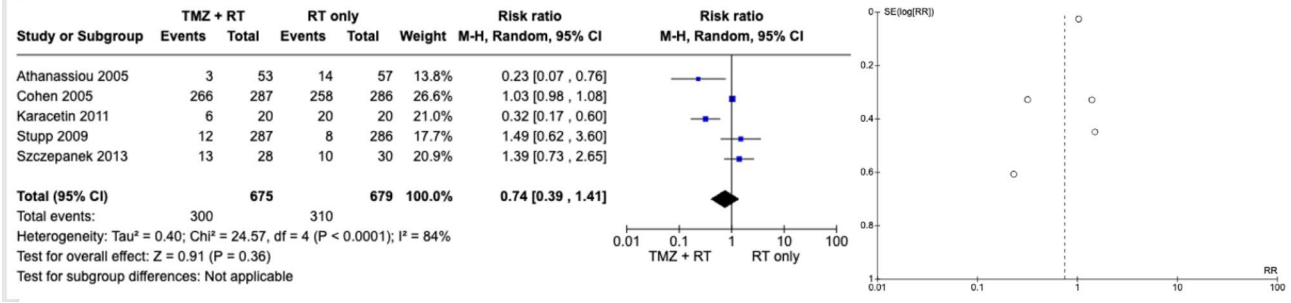

Fig. 4 Meta-analysis comparing the overall toxicities between the group of TMZ adjuvant to RT vs. RT only

a significant enhancement with TMZ + RT. For progression-free survival (Fig. 3), the HR is 0.51 (95% CI: 0.45, 0.58), further indicating a marked benefit with TMZ + RT. Conversely, for toxicities (Fig. 4), the risk ratio (RR) is 0.74 (95% CI: 0.39, 1.41), showing no substantial difference between treatments. Funnel plots for overall and progression-free survival are relatively balanced, implying a low risk of publication bias, whereas the plot for toxicities suggests potential publication bias or heterogeneity. Additionally, comparisons of hematological outcomes (Fig. 5) reveal no significant differences between TMZ + RT and RT alone, with RR for all hematological toxicities at 3.42 (95% CI: 0.95, 6.65) and wide confidence intervals. Funnel plots for these outcomes show asymmetry, suggesting possible publication bias or heterogeneity.

Figure 6 shows a Cochrane Risk of Bias 2 bias assessment showing low bias across domains, confirming robust methodological quality.

Discussions

The addition of TMZ to RT has significantly improved outcomes for glioblastoma patients. When TMZ is used concurrently with and as an adjuvant to RT, there is a notable increase in overall survival compared to using RT alone or just adjuvant TMZ. Research has shown that this combination therapy improves survival rates and progression-free survival [16]. The efficacy of adjuvant TMZ appears to be dose-dependent, with evidence suggesting that at least four cycles are necessary for optimal benefit [17, 18].

The benefit of TMZ in treatment is thought to come from its dual role in sensitizing tumors to radiation and its inherent cytotoxicity. While TMZ can lead to more frequent hematological side effects, it does not notably alter the overall incidence of adverse events. The groundbreaking trial that set TMZ as the standard treatment for newly diagnosed glioblastoma indicated an uprise in median survival from 12.1 to 14.6 months, combined with a notable rise in the 2-year survival rate, which went from 10.4 to 26.5% [17]. These findings underscore the essential role of TMZ in glioblastoma management, solidifying its importance in contemporary treatment methods.

Previous meta-analyses have demonstrated the superiority of combining TMZ with RT for treating glioblastoma compared to RT alone. These studies found that TMZ combined with RT significantly improves overall survival and 2-year survival rates [6, 19]. Additionally, the efficacy of TMZ extends to combinations with other chemotherapeutic agents, showing even greater benefits than TMZ with RT alone. However, better outcomes increase hematological problems, although the overall incidence of adverse events is not significantly higher compared to RT alone. Despite these findings, the mentioned meta-analyses in this field have demonstrated a lack of transparency in their methodologies and inadvertently excluded several eligible studies from their systematic reviews [13, 14, 15]. The selection criteria and search strategies were often insufficiently detailed, making it difficult to replicate their findings or assess the robustness of their conclusions. The omission of relevant studies led

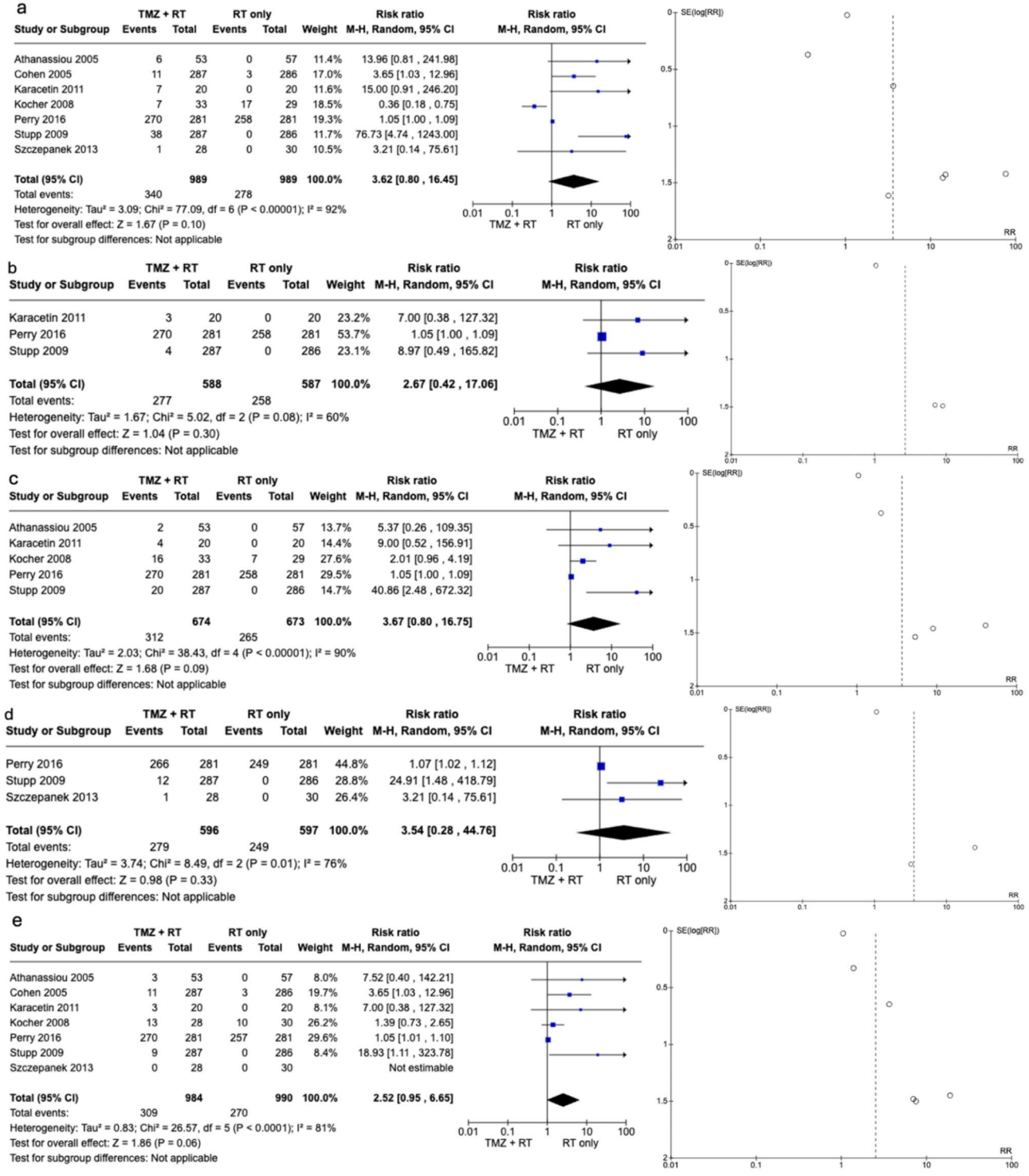

Fig. 5 Meta-analysis comparing **(a)** all hematological toxicities, **(b)** anemia, **(c)** leukopenia, **(d)** neutropenia, and **(e)** thrombocytopenia between the group of TMZ adjuvant to RT vs. RT only

to incomplete and potentially biased results, underscoring the necessity for a revised meta-analysis [20, 21].

Potential limitations of this study include the variability in dosages and administration schedules among the included studies. Secondly, the findings of this systematic review are subject to a high risk of bias due to significant heterogeneity across the included studies. This high level of heterogeneity and the associated risk of bias could influence the interpretation of toxicity outcomes. Nonetheless, the overall conclusions regarding the comparative

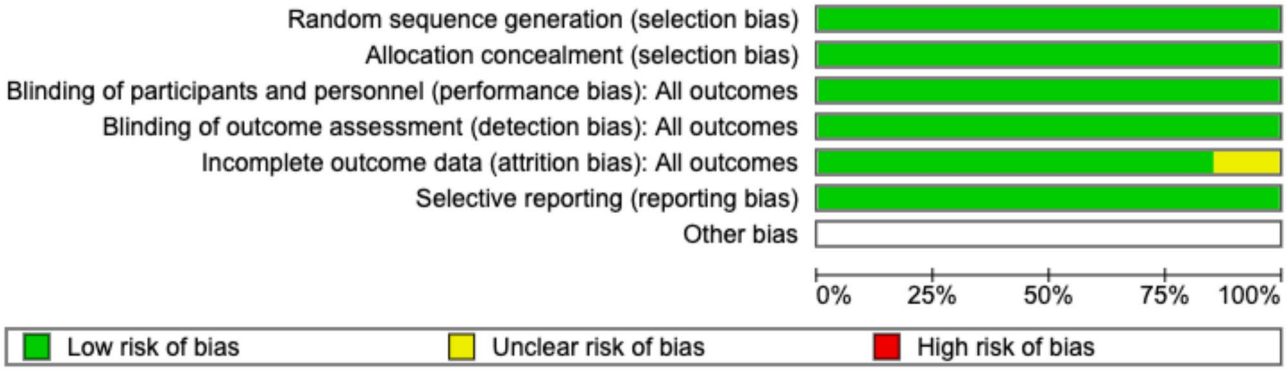

Fig. 6 Cochrane RoB version 2 for potential bias assessment

safety of TMZ combined with RT versus RT alone remain clinically meaningful and relevant. The findings of this systematic review are subject to a high risk of bias due to significant heterogeneity across the included studies, which may introduce potential sources of error. This high level of heterogeneity and the associated risk of bias could influence the interpretation of toxicity outcomes. Nonetheless, the overall conclusions regarding the comparative safety of TMZ combined with RT versus RT alone remain clinically meaningful and relevant. Moreover, the limited number of studies could restrict the generalizability of the results, as it prevented us from performing meta-regression to evaluate the influence of confounding factors [22]. Finally, the focus on published data might exclude unpublished studies with varying outcomes, which could further affect the overall findings.

Conclusions

The systematic review highlights that adding TMZ to RT generally leads to improved overall and progression-free survival rates compared to RT alone. However, the analysis of toxicity outcomes presents a nuanced picture. While toxicity levels appear comparable between TMZ + RT and RT-only groups in terms of overall reported toxicities, the asymmetry in the funnel plots for specific adverse effects indicates potential heterogeneity or publication bias. This suggests that the observed parity in toxicity outcomes should be interpreted cautiously. Variability in dosing and treatment schedules across studies further adds to the complexity of the analysis. Despite these limitations, the overall evidence supports the benefit of combining TMZ with RT for improved survival outcomes, albeit with a need for careful monitoring of adverse effects in clinical practice. Future studies addressing the heterogeneity and potential biases in toxicity reporting are warranted to refine the understanding of TMZ's safety profile.

Abbreviations

HR	Hazard ratio
MeSH	Medical Subject Headings
TMZ	Temozolomide
RT	Radiotherapy
MGMT	Methylguanine-DNA methyltransferase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk Ratio

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Author contributions

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not Applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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