Efficacy and Safety of Immunotherapy and Standard of Care in High-Grade Gliomas: A Systematic Review and Meta-analysis

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Review

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Abstract

BACKGROUND: Immunotherapy combined with standard of care (SOC) is often used for high-grade glioma (HGG). There are few comparisons of immunotherapy with SOC treatment or without SOC treatment (IMT) versus SOC. It is important to understand what interventions exist and their relative effectivenesses. METHODS: The Cochrane Library, Embase, Medline, and the Web of Science Core Collection were systematically searched by two librarians. Retrieved hits were screened for inclusion. Subgroup analysis was used to examine the main factors associated with overall survival (OS) and progression-free survival (PFS), which were used as primary endpoints to assess the efficacy and safety of IMT. This study was registered with PROSPERO, number CRD42019112356. RESULTS: The search yielded 2,315 results, of which 11 met the eligibility criteria. We identified 6 publications through exploration. Compared to SOC alone, IMT including viral therapy (VT) and dendritic cell vaccination improved the OS (HR = 0.55, 95% CI 0.42-0.72; p < 0.0001) and PFS (HR = 0.67, 95% CI 0.53-0.84; p = 0.0005). CONCLUSIONS: We found that IMT in the era of TMZ has an improved effectiveness over SOC. Our findings support the use of immunotherapy for brain tumors to improve HGG outcomes.

Background

Malignant tumors account for 32.8% of primary brain and central nervous (CNS) system tumors. High-grade gliomas (or malignant gliomas) account for approximately 80.5% of the 24,560 new cases of malignant primary brain and CNS tumors in the United States each year[1]. High-grade gliomas (HGGs), are mainly anaplastic astrocytomas (AA; WHO grade III) and glioblastoma multiforme (GBM; WHO grade IV) [2, 3]. Glioblastomas account for approximately 50 to 60% of malignant gliomas[1]. HGGs' prognosis is another issue. . The median overall survival (OS) times associated with the SOC (TMZ combined with radiotherapy) were 14.6 months for newly diagnosed GBM (WHO grade IV)[4], 7.4 months for recurrent grade IV gliomas, and 11.4 months for recurrent grade III gliomas[5].

Despite remarkable advances in neurosurgery, radiotherapy and chemotherapy, HGG patients still face a poor prognosis. Standard of care for HGG usually entails surgery followed by maximal surgical resection, followed by radiotherapy plus concomitant and adjuvant temozolomide (TMZ) chemotherapy, sometimes including carmustine and the PCV (procarbazine+CCNU+vincristine) scheme as alternative chemotherapy strategies or bevacizumab as a targeted therapy. Among patients whose tumors contained a methylated MGMT promoter, a survival benefit was observed in patients treated with TMZ and radiotherapy[6]. In addition, microsatellite instability (MSI) arises in GBM during TMZ therapy and mediates TMZ resistance[7]. Resistance to chemotherapy in HGG appears to be another concerning issue. The possible susceptibility of HGGs to IMT has not been explored.

The concept of cancer immunotherapy could be tracked back to William Coley, who first used bacteria to cure cancer in 1891[8]. His success meant that the immune system could recognize and control tumor growth. In recent years, immunotherapies have gained much research attention, and more evidence shows that high-grade gliomas can obtain benefits from the use of immunotherapies[9]. Six meta-analyses published between 2014 and 2018 indicated that improved OS and PFS were obtained via administration of immunotherapy in HGG patients [10–15]. To the best of our knowledge, ours is the first meta-analysis to include such detailed subgroup analyses. In addition, we also used more stringent criteria than other meta-analyses to decrease the possible differences caused by the clinical background.

The interventions of the current systematic review included immunotherapies categorized as follows:

1. Dendritic cell (DC) vaccination
2. Viral vector-based vaccines (AdvHSV-tk and PVSRIPO)
3. Immunopotentiators: TGF-b_2 inhibitor and Cpg-ODN

To verify and quantify the efficacy and safety of the combination of immunotherapy and SOC, the current meta-analysis utilized survival data from published papers. We also hope to inform clinicians of which kind of immunotherapy is more effective than SOC for HGG patients.

Methods

Search strategy and selection criteria

For this systematic meta-analysis, we searched for randomized controlled trials (RCTs) that met the following criteria: papers published from the creation of the database to December 1,2018; papers comparing immunotherapy with SOC treatment or without SOC treatment (IMT) and standard of care (SOC) in adults (age ≥18); and papers including patients with a diagnosis of HGG according to standardized diagnostic criteria.

Two authors (S.N. Zhang and X.D. Hu) searched online using single terms and phrases through the four databases, Cochrane Library, Embase, PubMed, and Web of Science, for relevant articles published up to December 1, 2018. Search terms included "glioma", " astrocytoma", "glioblastoma", "immunity", "immunotherapy", "viruses", "humans" and "randomized". An English language restriction was included. Clinical trials registered on the website http://ClinicalTrials. gov were also explored.

The following inclusion criteria were adopted: studies including a therapy intervention restricted to IMT; studies including adults with HGG; and studies including two arms with IMT and SOC. SOC entails surgery, radiotherapy, or chemotherapy. All included studies were in English.

The following exclusion criteria were adopted: studies lacking relevant outcome data; trials with a nonstandard of care control arm; phase I trials; phase II single-arm trials; and animal or cell trials. Abstracts and presentations from all major conference proceedings were excluded.

Data extraction and quality assessment

Two investigators (X.Y. Peng and X.M. Liu) extracted relevant information from the included articles. The HR has been described as a more suitable measure for analyzing time-to-event outcomes than the odds ratio (OR) or relative risk (RR), and thus, the HR data were extracted [16, 17]. When reports of HR and 95% CI were not available, the estimated value was derived indirectly from Kaplan–Meier curves according to the methodology described by Jayne F Tierney[16]. Dot plots of the graphical data were extracted via Engauge Digitizer 4.1 software (http://digitizer.sourceforge.net/).

Statistical analysis

Our statistical analyses were performed by R (version 3.6.1 for Windows; https://www.r-project.org/). The specific protocol for operation has been previously published [18].

The primary end points were overall survival (OS) and progression-free survival (PFS), and publication bias and secondary end points were analyzed via subgroup analysis, the Galbraith radial plot method and cumulative meta-analysis.

The hazard ratios and 95% confidence intervals (CIs) were calculated for OS and PFS. A random-effects model was used in the presence of significant heterogeneity, while a fixed-effects model was used when there was no significant heterogeneity. Heterogeneity across trials was assessed with the I^2 test, and $I^2 > 50\%$ and $p < 0.1$ suggested that there was significant heterogeneity.

Subgroup analysis was conducted. Heterogeneity across the entire study was examined via the Galbraith radial plot method. Sensitivity analysis was performed to explore the impact of each individual study by removing 1 study at a time. Publication bias was examined by funnel plots.

Results

Trial selection

Overall, 2,315 citations were identified by the researchers, and 66 potentially eligible articles were retrieved in full text. We excluded 55 reports but included 4 additional studies from other sources, resulting in 11 publications describing the efficacy of IMT between 2004 and 2018. However, we found significant negative results associated with immunopotentiators. Therefore, we concluded that immunopotentiators could not benefit HGGs and excluded 2 studies (Figure 1A). Nonetheless, the use of TMZ also had a large impact on the results. We excluded 3 studies whose SOC regimen did not contain TMZ (Figure 1B). Thus, 6 studies were used for the meta-analysis (Supplementary Figure 1).

Main characteristics of the studies

First, we studied those papers using AdvHSV-tk + GCV/DC vaccines/the TGF-β_2 inhibitor trabedersen/Cpg-ODN/recombinant nonpathogenic polio–rhinovirus chimera (PVSRIPO). We classified these studies into groups according to their use of viral therapy (AdvHSV-tk + GCV/PVSRIPO), DC therapy, or immunopotentiators (trabedersen/Cpg-ODN). A total of 524 participants were provided with IMT, and 747 participants were provided with SOC (a total of 1,271 participants).

A total of 914 participants from viral therapy studies (393 patients in the experimental arm and 521 patients in the control arm) were included. Three of the studies containing TMZ in the SOC regimen also reported PFS. The details can be found in Table 1. There were three studies on DC therapy. All studies used TMZ in the SOC regimen. Ninety participants underwent DC therapy (43 patients in the experimental arm and 47 patients in the control arm) (Table 2). An immunopotentiator (IP) was used in two studies that applied TMZ in the SOC regimen (88 patients in the experimental arm and 179 patients in the control arm) (Table 3).

After preliminary qualitative synthesis, we found that HGGs did not benefit from immunopotentiators (trabedersen/Cpg-ODN). Moreover, the use of TMZ in the standard of care regimen also had a large impact on evaluating efficacy. TMZ has been included in the SOC since 2005[19]. We thought it was more practical to evaluate SOC regimens that contained TMZ.

Thus, in the final meta-analysis, we included 481 participants who were confirmed to have HGG by clinical, radiological or MRI evidence. A total of 174 participants were provided with IMT (including VT and DC vaccine), while 307 participants were provided with SOC (TMZ and/or radiotherapy).

Primary endpoints

OS

First, we employed a random-effect model to assess the efficacy of IMT versus SOC according to the HR of OS. A total of 1,271 participants in 11 studies were included in this meta-analysis. The results showed that IMT decreased the risk of death by 26% compared with the SOC (HR = 0.74, 95% CI 0.56-0.99; $p = 0.0458$). However, substantial heterogeneity was found ($tau^2=0.1315$; $I^2= 65.5\%$). Patients were divided into subgroups according to immunotherapy type (Figure 2A, B). We found that the source of heterogeneity was the use of TMZ and IPs.

We employed a fixed-effect model to assess the efficacy of immunotherapies other than IPs versus TMZ-containing SOC by determining the HR of OS. A total of 481 participants in 6 studies were included in this meta-analysis. The results showed that IMT decreased the risk of death by 45% compared with the SOC (HR = 0.55, 95% CI 0.42-0.72; $p < 0.0001$). Substantial heterogeneity was not found ($tau^2=0.0544$; $I^2= 29.7\%$).

Publication bias was explored with an inverted funnel plot, which showed slight asymmetry around the 95% CI cutoff, and Egger's test showed no significant bias (p = 0.089) (Figure 2C).

Sensitivity analysis was performed to assess which study influenced our results. We did not find any study that had a potential impact on the results, and the results did not change by removing any one study (Figure 2D).

PFS

With respect to PFS, we used a fixed-effect model to assess the efficacy of IMT versus the SOC according to the HR. We pooled six trials, for a total of 316 participants (113 patients were treated with IMT, and 203 patients were treated with SOC). The results showed that IMT decreased the risk of recurrence by 41% compared with the SOC (HR = 0.67, 95% CI 0.53-0.84; p = 0.0005). Significant heterogeneity was not found (tau^2 = 0.0784, p = 0.018; I^2=38.7%) (Figure 3B).

Publication bias was explored with an inverted funnel plot, which showed slight asymmetry around the 95% CI cutoff, but Egger's test showed no significant bias (p = 0.1857) (Figure 3A).

Sensitivity analysis was performed to assess which study influenced our current results. We did not find any study that had a potential impact on the results, and the results did not change by removing any one study (Figure 3C).

Secondary endpoints

Subgroup analysis

In addition to exploring the source of heterogeneity, we also tried to identify the factors influencing the efficacy of IMT versus SOC. (Table 4)

As mentioned above, dividing the studies into subgroups according to immunotherapy type manifested a statistical difference between viral therapy, DC vaccines and immunopotentiators (IPs) in the meta-analysis (p < 0.05). This result indicated that IPs did not benefit HGGs. Dividing the studies into subgroups according to SOC type showed that the use of TMZ may have some synergy.

We excluded studies whose SOC regimen did not contain TMZ and IP trials and pooled 6 trials into the meta-analysis. The results showed that randomized controlled trials had a smaller effect size than historical controlled trials. (p = 0.015; Figure 4B). Moreover, the results also suggested that the area from which the patients were recruited may be a main factor for the efficacy of IMT in HGG patients in China, and these patients may benefit more from IMT than patients in other areas of the world. (p = 0.05; Figure 4B).

In addition, subgroup analyses according to clinical stage and clinical trial's type showed that these factors were unlikely to be the main factors influencing the efficacy of IMT (Figure 4C, 4D).

Galbraith radial plot

We drew a Galbraith radial plot and found that no study fell outside the 95% confidence interval cutoff. This hinted at homogeneity within the studies regarding viral therapy and DC therapy. (Supplementary Figure 2A)

Cumulative meta-analysis

We ordered these studies on the basis of the year of publication. The statistical results of the cumulative meta-analysis showed that the confidence interval decreased and the results became more convincing as the publication year increased.

Discussion

Immunotherapy is playing an increasingly important role in the treatment of tumors, maximizing the retention of noncancerous cells and the killing of cancer cells. After many attempts, immunotherapy has gradually earned a place as one of first/second-line treatments. However, several kinds of immunotherapy exist. Which kinds of immunotherapy behave better in the treatment of high-grade glioma is a question among many clinicians and researchers.

We performed a systematic review of the efficacy and safety of IMT and SOC in adult HGG patients. The present results show that IMT yields better results than SOC.

The gold standard endpoint in clinical practice is OS. We utilized this endpoint to compare the efficacies of IMT and SOC. In our study, the order of efficacy of various immunotherapies was as follows: DC therapy > viral therapy > immunopotentiators. Additionally, immunopotentiators may have a potential negative effect on the OS of HGG patients. Why does DC therapy behave the best and IPs behave the poorest? It seems that improving the natural immunity of the human body may be detrimental to treating HGGs. Immunotherapies such as DC therapy and VT include exogenous supplementations of vaccines with killing ability.

Why are there no checkpoint inhibitors in our study? Some studies on MSI and TMB can explain our reasoning. TMB and MSI could be biomarkers to identify HGG patients who may benefit from PD-1/PD-L1 inhibitors. HGGs in adults have lower MSI than pediatric HGGs (p < 0.05) [22]. However, another study found no statistically significant association between TMB, influx of cytotoxic $CD8^+$ T cells, and immune checkpoint expression in HGGs[23]. Thus, there is still no final conclusion regarding the efficacy of PD-1/PD-L1 inhibitors, and no trials met our inclusion criteria.

In regard to the poor results obtained when attempting to prolong OS with immunopotentiators, one of the articles claimed that their negative result was unexpected, and it may be explained by the selection bias of the enrolled patients with recurrent GBM or the different mode of administration of CpG-28 used

in Renata Ursu et al's study [24].

There were some shortcomings in our study. First, because the number of incorporated studies was insufficient, we should be wary about the evaluation of the efficacy and safety. Second, the subgroups based on immunotherapy type were divided into open-label and double-blind groups. However, there was only one trial in the double-blind group. This is mainly due to the insufficient number of studies, and we hope for more double-blind trials in the future. Third, the overall survival of patients in the control arm was only 2.0 -3.3 months in Ji et al's study[29], which was shorter than that in any other trials. Considering the national conditions in China, the delayed treatment time may be a result of the negative connotations associated with seeking medical treatment and the difficulty in seeking medical treatment. Fourth, we found that the patients from China benefited the most. We hypothesize that racial differences and regional lifestyle differences may be important causes, despite the lack of comprehensive studies that have explored the causes.

In addition, researchers have made efforts to accelerate precision medicine. Yao 2018 et al (DC therapy) found the IDH^{WT} $TERT^{MT}$ had better efficacy in GBM patients treated with IMT versus the control treatment [25]. However, Annick et al (viral therapy) confirmed that the IDH R132 mutation in GBM patients treated with IMT had provided no survival advantage[26]. The efficacy of immunotherapy in the context of MGMT mutations was only reported in one article by Ursu et al (who used immunopotentiators), and the study showed no statistically significant difference between groups[24].

Moreover, this meta-analysis also suggests that immunotherapy is less effective in the late stages, such that use it early stages could have better results[27]. In the future, we hope that more trials of immunotherapy will emerge; at that time, we will update our reviews about it.

Abbreviations

SOC: standard of care, such as surgery, chemotherapy, and radiotherapy; IMT: immunotherapy combined SOC treatment OS: overall survival; PFS: progression-free survival; ORR: objective response rate; AE: adverse events; GBM: glioblastoma; TMZ: temozolomide; CNS: central nervous system; HMCTs: historical-matched control trials; NOS: Newcastle Ottawa quality assessment; AA: anaplastic astrocytoma; HGG: high-grade glioma; DCV: dendritic cell vaccine; PVSRIPO: recombinant nonpathogenic polio–rhinovirus chimera; MGMT: O-6-methylguanine-DNA methyltransferase MSI: microsatellite instability; TCGA: The Cancer Genome Atlas; NCI-CTC: National Cancer Institute – Common Toxicity Criteria.

Declarations

Ethics approval and consent to participate

This study is a systematic review and meta-analysis that provides secondary research evidence. The ethics is not applicable. Also, the consent is unable to be obtained because the patients are not traceable. However, all the information is sufficiently anonymized. Details have been removed from the case descriptions to ensure anonymity. The editors and reviewers have reviewed the available details and are satisfied that the information supports the authors' conclusions. Acknowledgements

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Availability of data and materials

Data supporting the conclusions of this study are provided within the manuscript. Raw data is available from PROSPERO, number CRD42019112356.

Authors' contributions

Shengnan Zhang conceptualized formal analysis and screened literature. Libo Xu, Guanyu Chen and Qian Wang took part in revision and writing instructions. Jiangmin Liu was responsible for statistical analysis. Xindan Hu screened literature. Naiyan Wen and Xiaomin Liu extracted data from literature.

Xinyu Peng and Lei Fan assessed risk of bias. Baofeng Guo and Ling Zhang provided with instructions on methodology.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publish

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Table

0	First author(year) [ref.]	Method	NCT number	Phase	Patients（E/C）	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Characteristics	Follow up Time
TMZ is NOT in SOC	Rainov 2000[21]	Randomized	N/A	III	124/124	Open-label	60.2	58.3	AdvHSV-tk+GCV +SOC	SOC	≥70	Europe	Newly diagnosed GBM	21.6
	Immonen 2004[28]	Randomized	N/A	II	17/19	Open-label	51.9	56.5	AdvHSV-tk+GCV+SOC	SOC	≥70	Europe	PR/REC HGG	56
TMZ is in SOC	Westphal 2013[20]	Randomized	2004-000464-28[a]	III	119/117	Open-label	58	57	AdvHSV-tk+GCV	SOC	≥70	Europe	Newly diagnosed GBM	14
	Ji 2015[29]	Randomized		II	22/22	Open-label	49	54	AdvHSV-tk+GCV	SOC	N/A	China	Recurrent HGG	60
	Wheeler 2016[30]	Historical	NCT00589875	II	43/128	Open-label	57	60	AdvHSV-tk+GCV +SOC	SOC	≥70	USA	Newly diagnosed HGG	60
	Desjardins 2018[31]	Historical	NCT01491893	IV	61/104	Open-label	55	55	PVSRIPO	SOC	≥70	USA	Recurrent GBM	27.6

Table 1. Main Characteristics of studies that use viral therapy (VT) for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; a: EudraCT number; PVSRIPO, recombinant nonpathogenic polio–rhinovirus chimera; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent; ref.,reference number.

	First author(year)	Method	NCT number	Phase	Patients(E/C)	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Characteristics	F u T
TMZ is in SOC	Cho 2012[32]	Randomized	N/A	II	18/16	Open-label	58	58.5	DCV+SOC	SOC	>70	China	Newly diagnosed GBM	5
	Vik-mo 2013[32]	Historical	NCT00846456	N/A	6/7	Open-label	57	55.9	DCV+SOC	SOC	N/A	Europe	Newly diagnosedGBM	3
	Yao 2018[25]	Randomized	NCT01567202	II	22/21	Double Blind	48	50	DCV+SOC	Placebo+SOC	≥60	China	PR/REC GBM	1

Table 2. Main Characteristics of studies that use DC therapy for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent;ref.,reference number.

	First author(year)	Method	NCT number	Phase	Patients(No.)E/C[a]	Blind	Median Age(E)	Median Age(C)	Intervention	Control	KPS score	Region	Patients Characte
TMZ is in SOC	Ursu 2017[24]	Randomized	NCT00190424	II	39/42	Double Blind	62.0	59.0	CpG-ODN+SOC	SOC	≥60	Europe	Recurren GBM
	Bogdahn 2011[3]	Randomized	N/A	IIb	27/12	Open-label	39.0	40.0	TGF-β2 inhibitor(Trabedersen)	SOC	≥70	Europe	Recurren AA=39
					62/33		56.5	45.5					Recurren GBM=95

Table 3. Main Characteristics of studies that use immunopotentiator therapy for the treatment of HGGs. Follow-up Time, months; EMOS, experimental group median overall survival time, months; CMOS, control group median overall survival time, months; EMPFS, experimental group median progression-free survival time, months; CMPFS, control group median progression-free survival time; HGG, high-grade glioma; GBM, glioblastoma; PR/REC: Primary or recurrent;ref.,reference number.

Variable	No. of Studies	No. of Participants		OS, HR(95%CI)	I^2 value(%)	*p* value[b]
		IMT[a]	Ctrl			
Therapy type						
DC vaccine	3	43	47	0.38 [0.21;0.68]	0	0.004**
Immunoactivator	2	88	179	1.23 [0.83;1.82]	0	
Viral therapy	6	393	521	0.76 [0.54;1.07]	70	
SOC type						
TMZ	8	262	486	0.63 [0.43; 0.94]	56.8	0.037*
Not TMZ	3	262	261	1.05 [0.80; 1.39]	58.1	
Therapy type						
DC vaccine	3	43	47	0.38 [0.21;0.68]	0	0.228
Viral therapy	3	393	521	0.61 [0.45;0.82]	70	
Intervention type						
With SOC	4	91	181	0.48 [0.33; 0.72]	0	0.896
Alone	2	83	126	0.52 [0.22; 1.23]	75	
Study Design						
Historical control	3	115	245	0.68 [0.49; 0.94]	0	0.015*
Randomized	3	59	62	0.33 [0.20; 0.54]	0	
Recruiting area						
China	3	59	62	0.33 [0.20; 0.54]	0	0.050*
USA	2	109	238	0.69 [0.50; 0.96]	0	
Norway	1	6	7	0.59 [0.15; 2.29]	/	
Stage						
HGG	2	70	156	0.46 [0.25; 0.85]	45	0.742
GBM	4	104	151	0.60 [0.43; 0.85]	36	
Label type						
Open-label	5	153	285	0.58 [0.43; 0.77]	85.3	0.551
Double Blind	1	21	22	0.40 [0.18; 0.88]	11.7	

Table 4. Subgroup Analysis of IMT and Death Incidence for Each Variable. [a] IMT: Immunotherapy; [b] *p* value for subgroup differences (random effects model was applied in first two variables; fixed effects model was applied in other variables);*$p<0.05$;**$p<0.01$.

Supplementary File Legend

Supplementary Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of search strategy

Supplementary Figure 2. Secondary endpoints. A, Galbrith radial plot showed heterogeneity between studies. B, Cumulative meta-analysis.

Figures

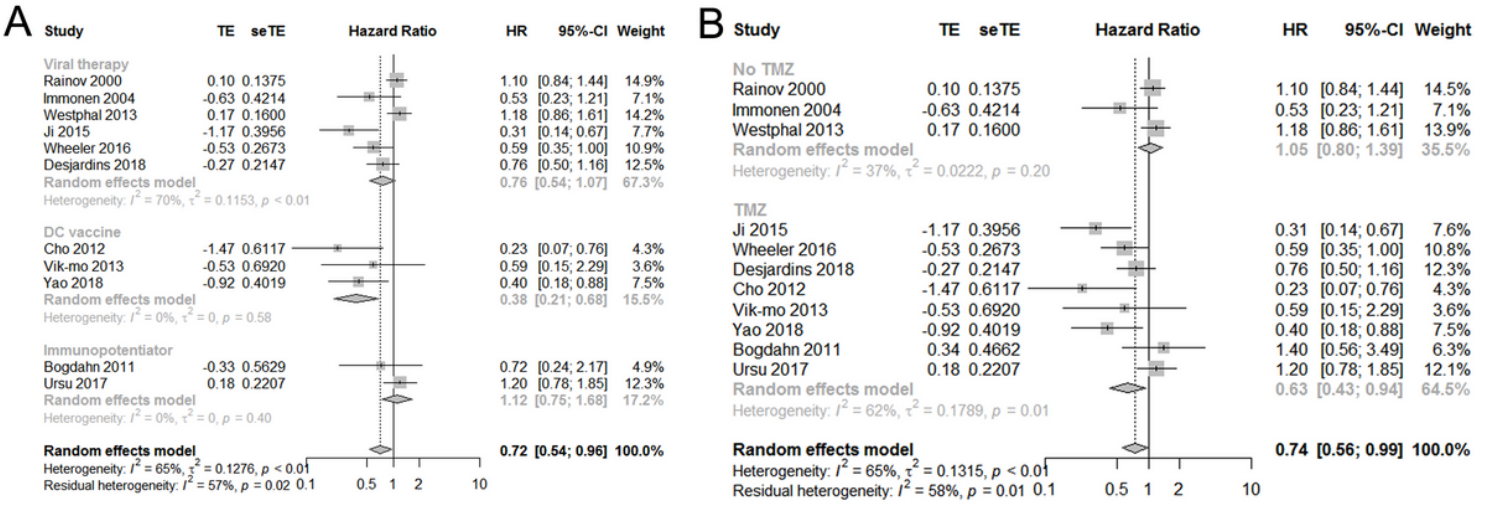

Figure 1

Preliminary qualitative synthesis. A, Subgroup analysis in accordance with IMT type. B, Subgroup analysis in accordance with TMZ applying. C, Forest plot for ORR. D, Forest plot for AE. Studies are listed on the left and HR with 95% CI are on the right. Box sizes are inversely proportional to the standard error of the study; therefore, larger boxes indicate greater weight of the trial in the meta-analysis estimation. E, Galbraith radial plot. Plot the inverse of the normalized estimate with respect to its standard error. If the point is close to the slope of the scatter, it means homogeneity.

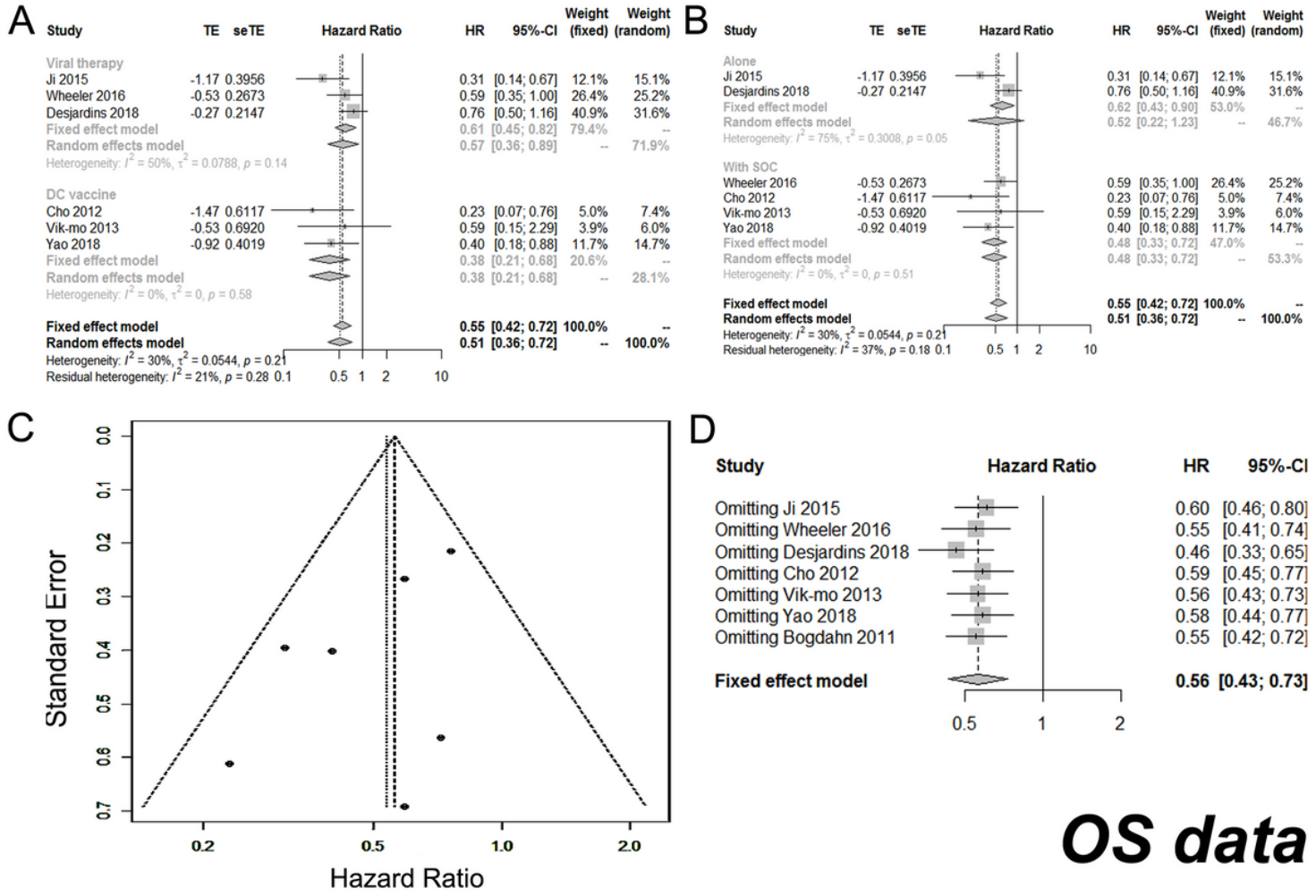

Figure 2

Meta-analysis in accordance with OS. A, Subgroup analysis in accordance with IMT type. B, Subgroup analysis according to application of SOC in experiment arm. C, Inverted funnel plot presenting publication bias of OS. D, Sensitivity analysis diagram. After deleting one study at a time and leaving the others the same, to observe which ones have a significant potential impact on the results.

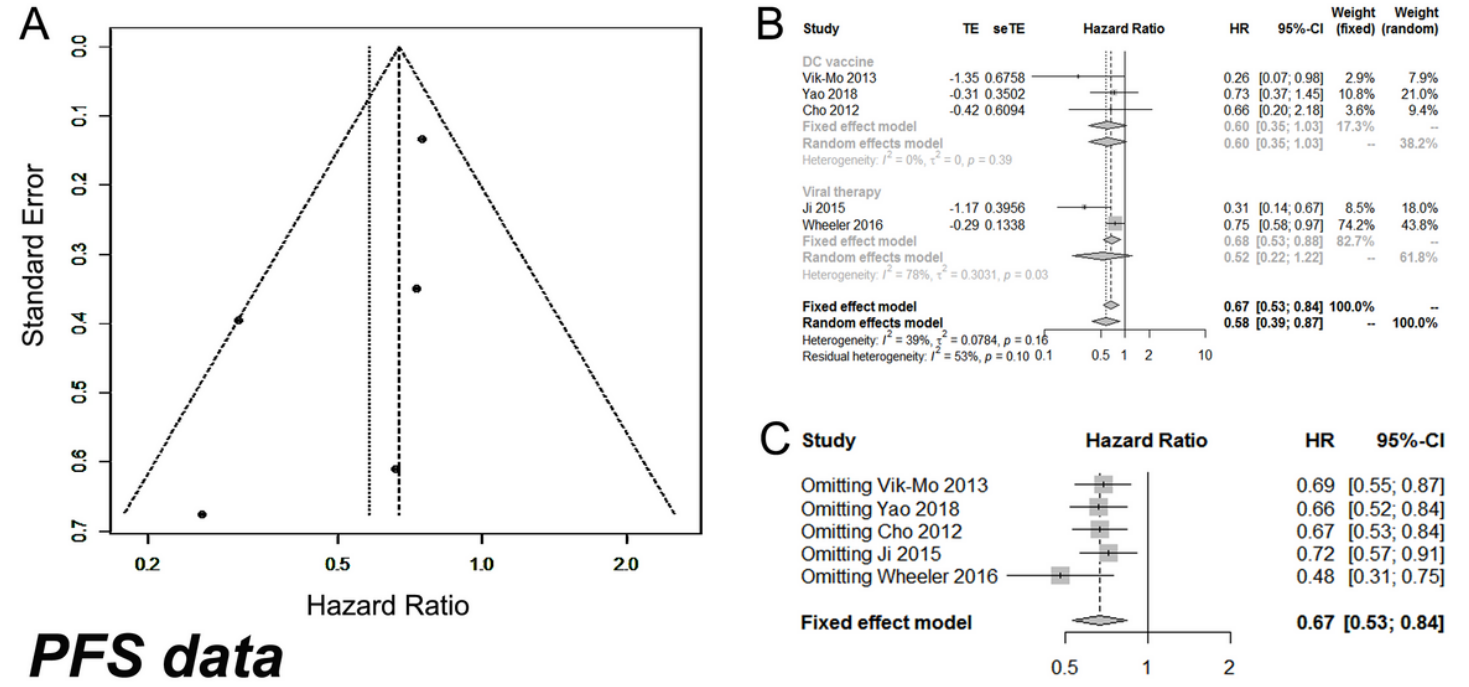

Figure 3

Meta-analysis in accordance with PFS. A, Inverted funnel plot presenting publication bias of OS. B, Subgroup analysis in accordance with IMT type. C, Sensitivity analysis diagram. After deleting one study at a time and leaving the others the same, to observe which ones have a significant potential impact on the results.

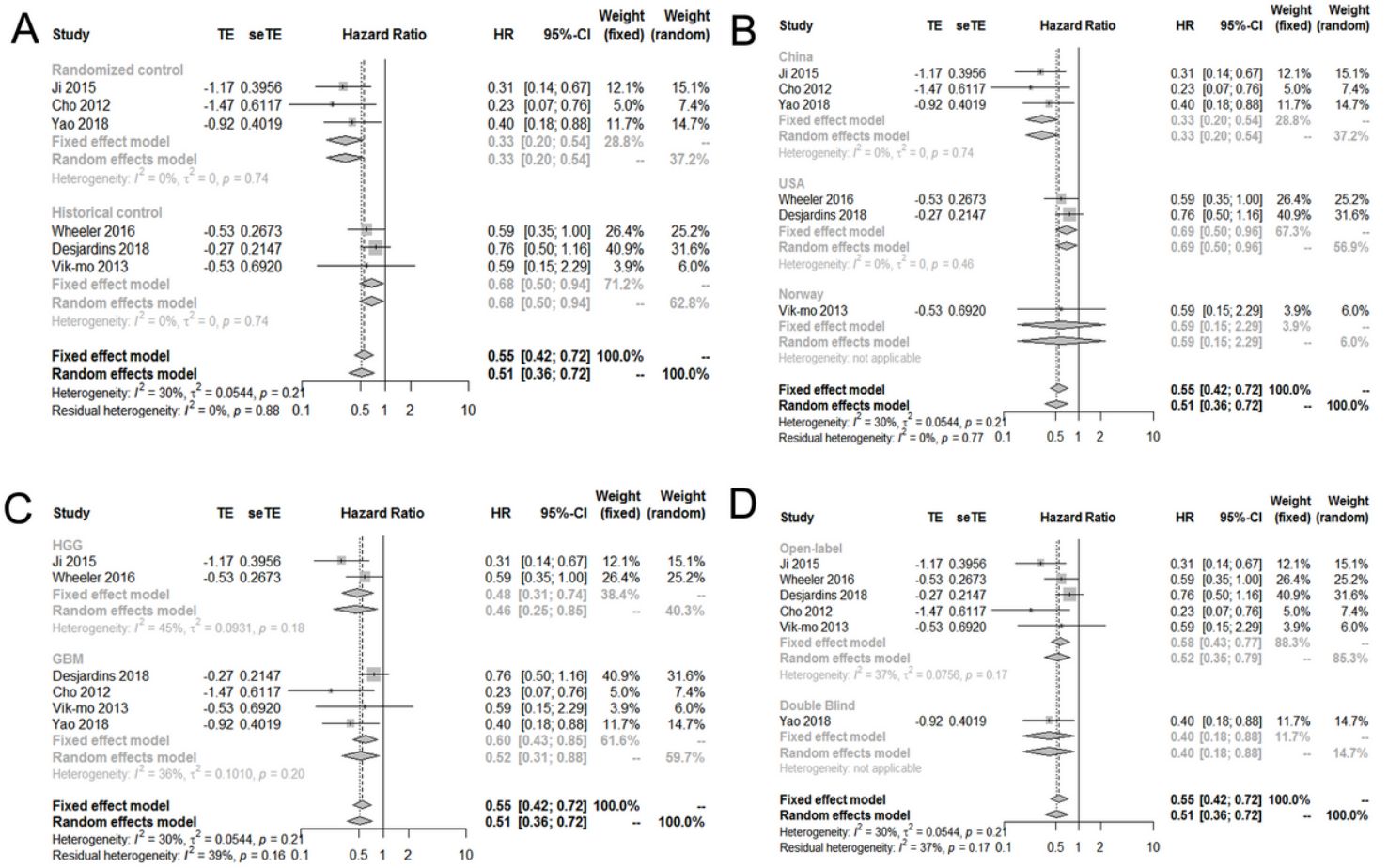

Figure 4

Subgroup-analysis in accordance with OS. A, Subgroup analysis in accordance with RCT or not. B, Subgroup analysis according to recruiting area. C, Subgroup analysis in accordance with clinical stage. D, Subgroup analysis in accordance with label type.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfigure3.pdf
- supplementaryfigure1.tif
- supplementaryfigure4.area.tif
- supplementaryfigure2.tif
- SupplementaryTables.docx