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Prognostic Value of the Metabolic and Volumetric Parameters of ^{11}C-Methionine Positron-Emission Tomography for Gliomas: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Several studies have demonstrated that ^{11}C-methionine positron-emission tomography provides information on prognosis.

PURPOSE: We performed a systematic review and meta-analysis of the prognostic value of the metabolic and volumetric parameters of ^{11}C-methionine-PET for gliomas.

DATA SOURCES: A systematic search was performed using the following combination of keywords: "methionine," "PET," "glioma," and "prognosis."

STUDY SELECTION: The inclusion criteria were the use of ^{11}C-methionine-PET as an imaging tool, studies limited to gliomas, studies including metabolic parameters (tumor-to-normal ratio) and/or volumetric parameters (metabolic tumor volume), and studies reporting survival data. The electronic search first identified 181 records, and 14 studies were selected.

DATA ANALYSIS: Event-free survival and overall survival were the outcome measures of interest. The effect of the tumor-to-normal ratio and metabolic tumor volume on survival was determined by the effect size of the hazard ratio. Hazard ratios were extracted directly from each study when provided or determined by analyzing the Kaplan-Meier curves.

DATA SYNTHESIS: The combined hazard ratios of the tumor-to-normal ratio for event-free survival was 1.74 with no significance and that of the tumor-to-normal ratio for overall survival was 2.02 with significance. The combined hazard ratio of the metabolic tumor volume for event-free survival was 2.72 with significance and that of the metabolic tumor volume for overall survival was 3.50 with significance.

LIMITATIONS: The studies selected were all retrospective, and there were only 4 studies involving the metabolic tumor volume.

CONCLUSIONS: The present meta-analysis of ^{11}C-methionine-PET suggests that the tumor-to-normal ratio for overall survival and the metabolic tumor volume for event-free survival and overall survival are significant prognostic factors for patients with gliomas.

ABBREVIATIONS: EFS = event-free survival; HR = hazard ratio; MTV = metabolic tumor volume; OS = overall survival; SUVmax = maximum standardized uptake value; SUVmean = mean standardized uptake value; TNR = tumor-to-normal ratio

Primary brain tumors are a heterogeneous tumor group with its own biology, prognosis, and treatment approach. Gliomas constitute the most frequent pathology and account for approximately 50% of primary brain tumors.[1] Glioblastomas are the most common of all malignant central nervous system tumors (46.6%), and their relative survival estimates are rather low: Only 5.5% of patients have been reported to survive 5 years postdiagnosis.[2]

Among various imaging modalities, MR imaging has been found to be the most effective tool for characterizing gliomas.[3] However, the limitations of MR imaging have encouraged the development of other imaging modalities for the clinical management of gliomas. Not only the MR imaging enhancement patterns of local treatment-related changes but also the T2- or fluid-attenuated inversion recovery MR imaging after antiangiogenic treatment has limited value in differentiating disease progression from post-therapy changes.[4] To overcome these drawbacks, advanced imaging techniques such as perfusion MR imaging, MR spectroscopy, and positron-emission tomography have been developed

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and used for the accurate characterization of tumors. Among them, amino acid PET has additive value compared with MR imaging when assessing the response to antiangiogenic treatments because amino acid uptake occurs independent of regional tumor perfusion and blood-brain barrier permeability.[5,6] Several amino acid radiotracers for PET, such as ^{11}C-methionine, [^{18}F]fluoroethyl tyrosine, and 6-[^{18}F]-fluoro-L-dopa, have been used for the metabolic imaging of brain tumors.[7] Various studies have demonstrated the advantages of ^{11}C-methionine-PET in diagnosis, grading, and the differential diagnosis between tumor recurrence and radiation necrosis.[8,9] In addition, ^{11}C-methionine-PET also provides information on patient prognosis because a high uptake in the glioma indicates a high chance of tumor progression and a poor survival rate.[10]

Most previous studies with ^{11}C-methionine-PET have used a semiquantitative tumor-to-normal ratio (TNR, metabolic parameter) to identify the uptake and evaluate the prognosis of brain tumors. The TNR is usually defined as the maximum standard uptake value (SUVmax) of the brain tumor divided by the mean SUV (SUVmean) of the contralateral normal cerebral cortex.[11,12] However, because the TNR reflects only the single voxel with the highest SUV in the tumor, this parameter does not reflect the total tumor uptake.[13] In recent years, volumetric parameters, including the metabolic tumor volume (MTV), have been reported to have prognostic significance for several types of tumors.[14-16] The MTV is defined as the tumor volume within the boundary determined by a certain threshold and theoretically reflects the total tumor amount or tumor burden.[17,18] Currently, there is a lack of comprehensive and detailed reviews on the prognostic value of the MTV and/or TNR of ^{11}C-methionine-PET for gliomas, which could guide physicians in the management of the tumor.

Therefore, we conducted a comprehensive systematic review of the literature on metabolic and volumetric parameters and designed a meta-analysis to assess the prognostic value of the TNR and MTV of ^{11}C-methionine-PET for patients with gliomas.

MATERIALS AND METHODS

Data Search and Selection

We performed a systematic search of MEDLINE and EMBASE and a manual search on July 31, 2017, to identify publications using the following combination of keywords: "methionine," "PET," "glioma," and "prognosis." All searches were limited to human studies. The inclusion criteria were the use of ^{11}C-methionine-PET as an imaging tool, studies limited to gliomas, studies that reported survival data, and studies that included metabolic parameters (TNR) and/or volumetric parameters (MTV). Reviews, abstracts, case reports, and editorials were excluded. Two authors independently conducted the search and screening, and they selected eligible studies for inclusion. Any discrepancies were resolved by consensus.

Data Extraction and Quality Assessment

Two reviewers independently extracted data from the selected publications and recorded the following information: study design, first author, year of publication, country of origin, number of patients, treatment, end point, and evaluated PET parameters. The 2 reviewers scored each publication according to a quality scale used in previous studies.[19] This quality scale was divided into 4 categories: scientific design, generalizability, result analysis, and PET report (On-line Table 1). A value between 0 and 2 was assigned to each item, and each category had a maximum score of 10 points. Scores were expressed as a percentage of the maximum, which was 40 points. All data were extracted, and scores were graded by 2 reviewers who performed comparisons at each step. Any discrepancies were resolved by consensus.

Statistical Analysis

The primary outcome was event-free survival (EFS). Disease-free survival and progression-free survival were defined as EFS, which was measured from the date of the initiation of therapy to the date of recurrence or metastasis.[20] The secondary end point was overall survival (OS), defined as the time from the initiation of therapy until death. The effect of the TNR or MTV on survival was measured by the effect size of the hazard ratio (HR). Survival data were extracted using a methodology proposed by Parmar et al.[21] We extracted the univariate HR estimate and 95% confidence interval directly from each study when provided by the authors. Otherwise, the P values of the log-rank test, 95% CI, number of events, and at-risk numbers were extracted to estimate the HR indirectly. We determined the survival rates from the Kaplan-Meier curves using the Engauge Digitizer (http://markummitchell.github.io/engauge-digitizer/) to reconstruct the HR estimate and its variance, assuming that patients were censored at a constant rate during follow-up. An HR of >1 implied worse survival for patients with a high TNR or MTV, whereas an HR <1 implied better survival for patients with a high TNR or MTV. Heterogeneity between the studies was assessed by a χ^2 test and I^2 statistics as described by Higgins et al.[22] A fixed-effects model was used with Higgins $I^2 \leq 50\%$ and Cochran Q at $P \geq .1$, and a random-effects model was used with Higgins $I^2 > 50\%$ or Cochran Q at $P < .1$. Subgroup analyses were performed according to the tumor grade, tumor stage, calculation methods of the TNR, and references for the MTV. Funnel plots were used to assess publication bias graphically.[23] $P < .05$ was considered statistically significant, and $.05 \leq P \leq .1$ indicated a significant trend. Data from each study were analyzed using Review Manager (RevMan, Version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Characteristics of the Study

The results of the data search and selection are summarized in Fig 1. A total of 14 studies involving 735 patients were included in our meta-analysis. All 14 studies were of a retrospective design.[24-37] The grade of glioma was low in 3 studies,[25,29,31] high in 4 studies,[30,32,35,37] and mixed in 7 studies.[24,26-28,33,34,36] The prognostic value of the TNR was determined in all 14 studies,[24-37] and the prognostic value of the MTV was determined in 4 studies.[32,34,35,37] The tumor parameters used were SUVmax in 13 studies[24-32,34-37] and SUVmean in 1 study.[33] The reference parameters were contralateral cortex SUVmean in 10 studies,[24-27,30-35] SUVmax in 2 studies,[36,37] and undefined in 2 studies.[28,29] The cutoff values of the TNR ranged from 1.51 to 3.42, and those of the MTV ranged from 35 to 60 cm^3 (On-line Table 2). The mean quality score of the selected studies was 58.0%, with a range of 41.9%–71.3% (On-line Table 3).

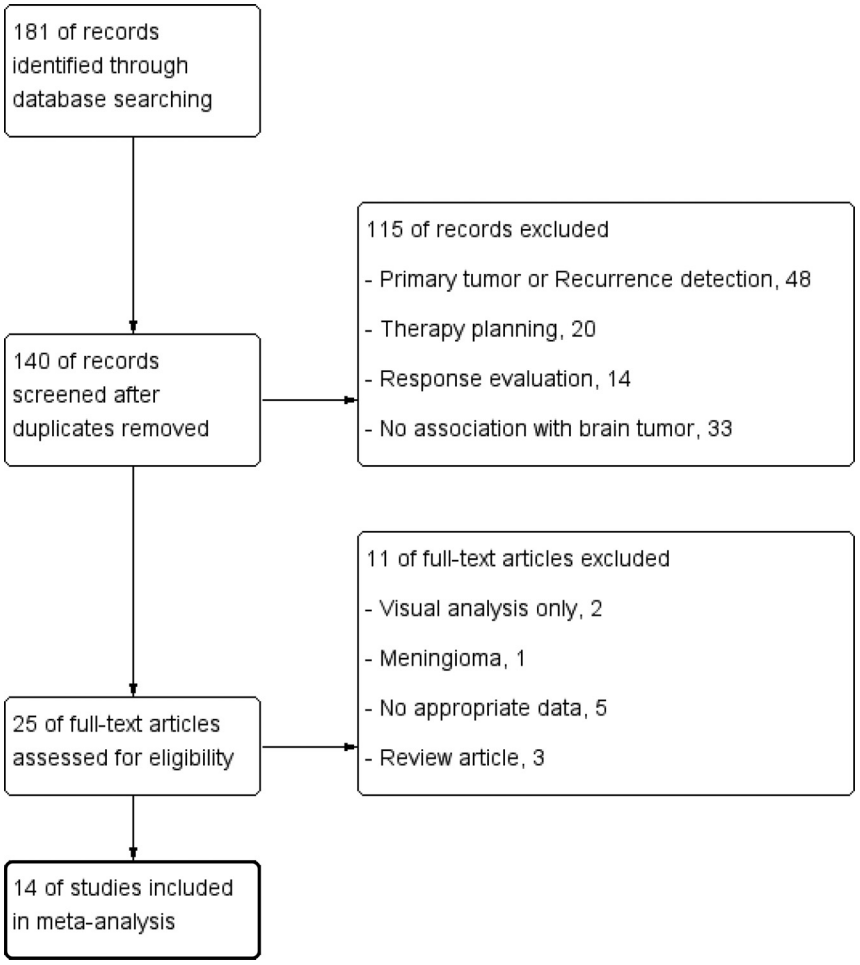

FIG 1. A flow diagram of the study.

Prognostic Value of the TNR and MTV

The effect of the TNR on EFS was analyzed using 5 studies. The combined HR of 1.74 for adverse events was not statistically significant (95% CI, 0.86–3.49; $P = .12$). Heterogeneity was high with statistical significance ($\chi^2 = 16.19$, $P = .003$; $I^2 = 75\%$). The effect of the TNR on OS was analyzed using 11 studies. The combined HR of 2.02 for death was statistically significant (95% CI, 1.55–2.64; $P < .001$). Heterogeneity was moderate with statistical significance ($\chi^2 = 18.86$, $P = .04$; $I^2 = 47\%$) (Fig 2).

The effect of the MTV on EFS was analyzed using 2 studies. The combined HR of 2.72 for adverse events was statistically significant (95% CI, 1.51–4.90; $P < .001$). Heterogeneity was not statistically significant ($\chi 2 = 0.73$, $P = .39$; $I^2 = 0\%$). The effect of the MTV on OS was analyzed using 3 studies. The combined HR of 3.50 for death was statistically significant (95% CI, 1.52–8.06; $P < .003$). Heterogeneity was moderate with statistical significance ($\chi^2 = 6.50$, $P = .04$; $I^2 = 69\%$) (Fig 3).

The results of the meta-analysis are summarized in Table 1, and a visual inspection of the funnel plot suggests no evidence of publication bias, as shown in Fig 4.

Subgroup Analysis

Subgroup analysis was performed in relation to the tumor grade, tumor stage, methods of TNR calculation, and references for the MTV (Table 2). According to the variables, eligible studies were divided into 2 subgroups. Among studies of OS in terms of the TNR, high-grade glioma had a significant HR of 1.76 (95% CI, 1.36–2.28; $P < .001$), and low-grade glioma had an HR of 2.19 with a significant trend (95% CI, 0.98–4.86; $P = .05$). Studies of primary tumors had a significant HR of 1.95 (95% CI, 1.45–2.63; $P < .001$), and those of recurrent tumors had a significant HR of 2.58 (95% CI, 1.31–5.08; $P = .006$). Studies of TNR calculation methods (tumor SUVmax divided by normal contralateral cortex SUVmean) had a significant HR of 1.97 (95% CI, 1.42–2.74; $P < .001$), and those of other calculation methods had a significant HR of 2.15 (95% CI, 1.29–3.60; $P = .003$). Among studies that included the OS in terms of the MTV, high-grade glioma (HR = 5.54; 95% CI, 3.11–9.86; $P < .001$), primary tumor (HR = 3.51; 95% CI, 1.04–11.88; $P = .04$), and references for the MTV (1.3 × SUVmean of the normal contralateral cortex; HR = 3.51; 95% CI, 1.04–11.88; $P = .04$) showed significant results.

DISCUSSION

In the current study, the prognostic value of the TNR and MTV of ^{11}C-methionine-PET for patients with gliomas was evaluated through a meta-analysis of published studies. The TNR for OS and the MTV for EFS and OS were useful in predicting the prognosis of patients. In addition, subgroup analysis demonstrated that tumor grade may affect the prognosis. To our knowledge, this is the first meta-analysis that has investigated the prognostic value of metabolic and volumetric parameters for patients with gliomas.

Most of the previous studies have used the TNR to quantify the intensity of ^{11}C-methionine uptake to determine the prognosis.[24-31,33,36] Our meta-analysis indicated that the TNR for OS (but not the TNR for EFS) of ^{11}C-methionine-PET could be a significant prognostic parameter. A previous study compared ^{11}C-methionine uptake with the pathologic features of tumors and showed that the malignant portions of lesions were coincident with the areas with higher ^{11}C-methionine uptake.[28] In subgroup analysis, the TNR showed significant prognostic value for OS in high-grade tumors; however, only a significant trend was found in low-grade tumors. Regarding the tumor stage for OS, the TNR demonstrated significant prognostic value for both primary and recurrent tumors. Regarding the calculation methods of the TNR for OS, the SUVmax of the tumor divided by the SUVmean of the normal contralateral cortex and other TNR calculation methods revealed significant prognostic values.

The TNR represents the high metabolic activity of the tumor, and the MTV reflects the size of the metabolically active tumor. In theory, volumetric parameters should be more useful than meta-

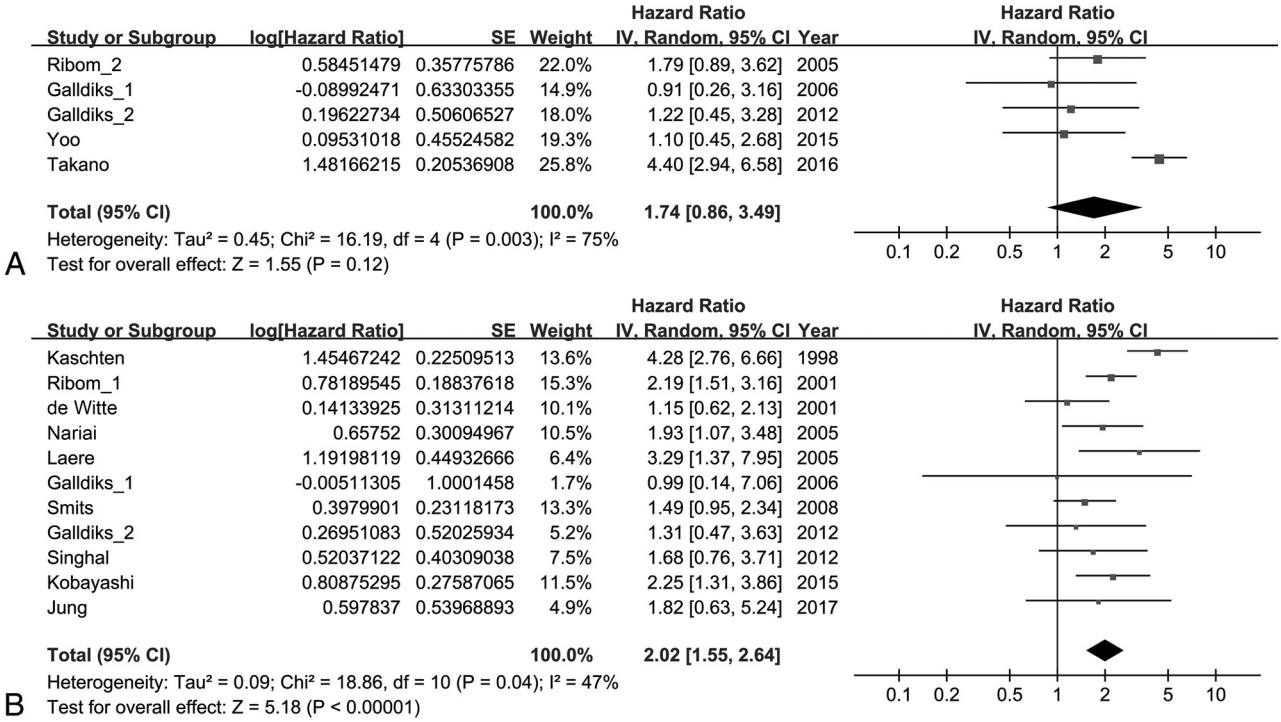

FIG 2. Forest plot results of the EFS (*A*) and OS (*B*) based on the TNR.

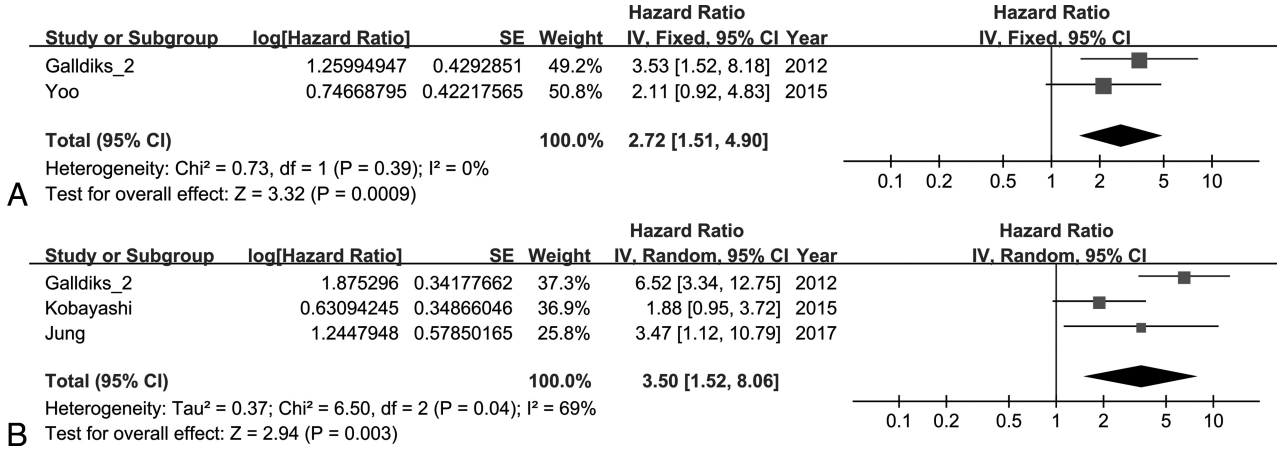

FIG 3. Forest plot results of the EFS (*A*) and OS (*B*) based on the MTV.

Table 1: Summary of the meta-analysis results

Parameters	End Point	No. of Studies	HR	95% CI of HR	*P* Value	I^2 (%)	Model
TNR	EFS	5	1.74	0.86–3.49	.12	75	Random
TNR	OS	11	2.02	1.55–2.64	<.001[a]	47	Random
MTV	EFS	2	2.72	1.51–4.90	<.001[a]	0	Fixed
MTV	OS	3	3.50	1.52–8.06	.003[a]	69	Random

[a] Statistically significant ($P < .05$).

bolic parameters in the prediction of tumor behavior because both metabolic activity and tumor burden are taken into consideration.[17,18] Our meta-analysis indicated that the MTV of ^{11}C-methionine-PET could reflect patient prognosis. The results revealed its significance for both EFS and OS. In comparison with the HR of the TNR, the HR of the MTV for EFS was significant, whereas the HR of the TNR for EFS was not significant. The HR of the MTV for OS was higher than the HR of the TNR for OS; however, it was not statistically significant ($P = .19$; data not shown). Furthermore, previous direct comparison studies reported that the MTV has a better prognostic value than the TNR.[32,34,35,37] The direct comparison results are summarized in On-line Table 4. In subgroup analysis, the MTV had significant prognostic value for OS in high-grade tumors, and its statistical significance was compared with that of the TNR for OS in high-grade tumors ($P < .001$; data not shown). With respect to the tumor stage for OS, the MTV demonstrated significant prognostic value for primary gliomas with higher HRs than those of

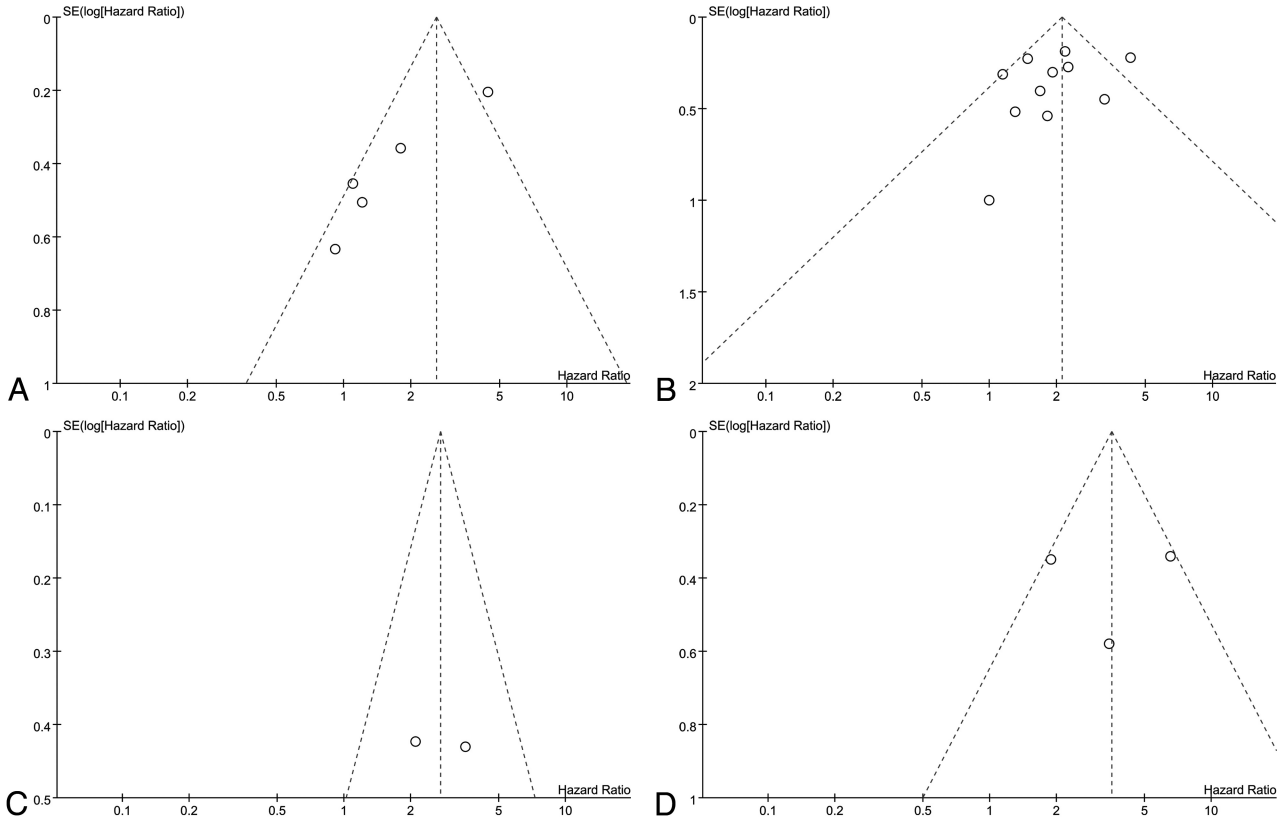

FIG 4. Funnel plot results of the EFS based on the TNR (*A*), OS based on the TNR (*B*), EFS based on the MTV (*C*), and OS based on the MTV (*D*).

Table 2: Results of subgroup analysis

Parameters	End Point	Factor	No. of Studies	HR	95% CI of HR	*P* Value	I^2 (%)	Model
TNR	OS	Tumor grade (high)	7	1.76	1.36–2.28	<.001[a]	22	Fixed
		Tumor grade (low)	6	2.19	0.98–4.86	.05[b]	97	Random
TNR	OS	Tumor stage (primary)	9	1.95	1.45–2.63	<.001[a]	55	Random
		Tumor stage (recurrence)	2	2.58	1.31–5.08	.006[a]	0	Fixed
TNR	OS	Calculation method of TNR (tumor SUVmax/ normal contralateral SUVmean)	8	1.97	1.42–2.74	<.001[a]	60	Random
		Calculation method of TNR (others)	3	2.15	1.29–3.60	.003[a]	0	Fixed
MTV	OS	Tumor grade (high)	2	5.54	3.11–9.86	<.001[a]	0	Fixed
MTV	OS	Tumor stage (primary)	2	3.51	1.04–11.88	.04[a]	85	Random
MTV	OS	Reference for MTV (1.3 × SUVmean of normal contralateral cortex)	2	3.51	1.04–11.88	.04[a]	85	Random

[a] Statistically significant ($P < .05$).
[b] Significant trend ($.05 \leq P \leq .10$).

the TNR. MTV defined by normal contralateral cortex SUVmean × 1.3, was prognostic and showed higher HRs than those of TNR calculation methods.

According to our systematic review and meta-analysis, the TNR could be used for the prognosis of OS, especially in cases of high-grade gliomas. In addition, the MTV could be used for the prognosis of both EFS and OS. Furthermore, the MTV could be superior to the TNR for the prognosis of high-grade gliomas.

There are some limitations to this study. First, the studies selected were all retrospective. There were only 4 studies involving the MTV, and the number of patients in each study was relatively small. In addition, a possible publication bias was not excluded; nevertheless, the funnel plot did not clearly show this. Furthermore, we were unable to determine an optimal cutoff value to categorize the TNR and MTV as high or low due to the lack of individual data. Last, a comparison between the MTV and total lesion glycolysis (TLG = SUVmean multiplied by the MTV, a frequently used parameter in FDG-PET studies) should be performed in the future.[34]

CONCLUSIONS

The TNR and MTV of ^{11}C-methionine-PET are significant prognostic parameters for patients with gliomas. Patients with a high TNR have a higher risk of death, and patients with a high MTV have a higher risk of adverse events or death. The MTV could be used as an incremental predictor of prognosis instead of the TNR.

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