The prognostic role of Ki-67/MIB-1 in meningioma: a systematic review with meta-analysis

Ning Liu, MD, Si-Ying Song, MD, Jia-Bao Jiang, MD, Ting-Jian Wang, MD, PhD, Chang-Xiang Yan, MD, PhD

Abstract

Background: Ki-67 is a typical immunohistochemical marker for cell proliferation. Higher expression of Ki-67 is correlated with poor clinical outcomes in several cancers. However, the prognostic value of Ki-67 on the prognosis of meningiomas is still controversial. The purpose of this meta-analysis was to evaluate the prognostic value of Ki-67 in meningiomas.

Methods and materials: We searched Medline and EMBASE from inception to December 31, 2018, to identify relevant articles. Using a fixed or random effects model, pooled hazard ratios (HRs) for overall survival (OS) and disease/progression/recurrence-free survival (D/P/RFS) were estimated.

Results: A total of 43 studies, comprising 5012 patients, were included in this analysis. Higher Ki-67 expression levels were significantly associated with worse OS (HR = 1.566; 95% CI: 1.217–2.013) and D/P/RFS (HR = 2.644; 95% CI: 2.284–3.087) in meningiomas. Subgroup analysis revealed that all the included factors (ethnicity, tumor grade, HR sources, definition of cutoffs, cutoff values) for heterogeneity investigation can affect the pooled results. Among them, the definitions of cutoffs and cutoff values factor are the two main contributors toward heterogeneity. Multivariable meta-regression analysis also showed that methodologies used for cutoff value definition contributed to the high inner-study heterogeneity.

Conclusions: Higher Ki-67 expression levels negatively influenced survival in meningiomas. A higher cutoff value (≥4%) is more appropriate for prognosis prediction. It is highly recommended that Ki-67 expression profile could be assessed in meningiomas treatment for predicting survival. And patients with elevated expression of Ki-67 need to have close follow-ups.

Abbreviations: CI = confidence interval, CNS = central nervous system, D/P/RFS = Disease /Progression /Recurrence-free survival, HR = Hazard ratios, IHC = immunohistochemistry, OS = Overall survival, PCNA = proliferating cell nuclear antigen, WHO = World Health Organization.

Keywords: Ki-67, meningioma, meta-analysis, prognostic role

1. Introduction

Meningiomas are usually considered clinically benign tumors, which account for 36.4% of all central nervous system (CNS) neoplasms.[1,2] According to the 2016 World Health Organization (WHO) classification scheme, meningiomas are stratified into 3 groups: grade I (benign), grade II (atypical), and grade III (anaplastic).[3,4] The initial choice of treatment for meningioma is gross total microsurgical resection mostly with improved postsurgery outcomes.[5] However, tumor recurrence and progression after surgical treatment are frequent, and these patients are prone to associate with poor overall survival (OS).[2,6] Thus, identification of risk factors in predicting tumor recurrence and progression is needed. The histological grade and the extent of resection are reported as the two most important, widely accepted predictive factors of meningioma recurrence and progression.[7] Nevertheless, the recurrence rates for grade I patients were reported as high as 7% to 20%,[3,7] and those for patients who received complete resection were 10% to 30%.[6] Therefore, it is vital to find other prognostic parameters to improve evaluation of recurrence and progression in patients with meningioma.

Increased cell proliferation activity was considered the most important mechanism of oncogenesis.[8] Ki-67/MIB-1 is a typical immunohistochemical marker for cell proliferation. It is increasingly popular due to its minimal tissue requirements and suitability to routinely fixed tissues.[9] The negative effect of Ki-67 on clinical outcomes has been extensively identified in most solid tumors, such as gastrointestinal stromal tumors, renal cell carcinoma, thyroid cancer, prostate cancer, bladder cancer, and oral squamous cell carcinoma.[10–13] Moreover, Ki-67/MIB-1 is found to be more predictive of survival than expression of p53[16] and proliferating cell nuclear antigen (PCNA) in brain...
tumors.\textsuperscript{[17,18]} And numerous studies have shown that Ki-67/MIB-1 is an independent predictor in meningiomas prognosis.\textsuperscript{[19–21]} However, the prognostic role of Ki-67 in meningiomas remains unclear. Some studies\textsuperscript{[16,22,23]} indicated negative association between Ki-67 expression level and meningiomas prognosis while others\textsuperscript{[19,24]} reported insignificant results. The inconsistency was probably ascribed to the great diversity of cutoff values of Ki-67/MIB-1 index for analysis, definition of cutoff values, and sample’s composition of tumor grade among studies. Therefore, we conduct this meta-analysis study to evaluate the prognostic value of Ki-67/MIB-1 in meningiomas.

2. Methods

2.1. Search strategy

This meta-analysis was registered in PROSPERO (registration CRD42018093940). There is no need for ethical approval of this meta-analysis because all the included studies have clearly stated ethical approval in their manuscripts. We performed a thorough search for available literatures in electronic databases of Medline and EMBASE until December 31, 2018. Medical Subject Headings and Emtree headings were searched and combined with the following keywords: “meningioma OR meningeal neoplasms” and “prognosis OR survival OR mortality OR outcome OR treatment OR recurrence OR predictor.” We also manually scanned the references of included articles in order to check more potential studies. The full search strategies are presented in Supplementary Table S1, http://links.lww.com/MD/D839 (see Table S1, Supplemental Content, which illustrates full search strategies).

The eligible studies were selected based on the following criteria:

1. studies were published in English as a full essay;
2. all patients were diagnosed with histologically confirmed meningioma;
3. the Ki-67 expression was detected by immunohistochemistry (IHC);
4. correlation between Ki-67/MIB-1 expression and prognosis of patients with meningioma was investigated;
5. hazardous risks (HRs) with 95% confidence interval (CI) for survival analysis were provided or could be calculated from the provided data;
6. Ki-67/MIB-1 expression level was analyzed as a dichotomous variable with cutoff values provided or data to calculate;
7. for cohorts included in more than one publication, the most complete and recent study was selected for analysis.

Two reviewers (TJW and SYS independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies that met all selection criteria were retrieved.

2.2. Data extraction and quality assessment

The data were extracted from the identified studies by two investigators independently. The following variables were captured from all included studies: first author, publication year, ethnicity, number of cases, grade, grade criteria, patient age, definition of cutoffs, cutoff values, outcome measures, and risk estimates; any disagreement was resolved by discussion between the two reviewers or consultation with a third reviewer. HR with its 95% CI of each included study was extracted or estimated from Kaplan–Meier survival curves by the open digitizing program (Engauge Digitizer).\textsuperscript{[25,26]} If results of both univariate and multivariate analysis were reported, the latter was used first as it offered a more accurate risk estimate. We used a set of modified predefined criteria to evaluate the quality of all included studies.\textsuperscript{[27,28]}

2.3. Statistical analysis

Data were analyzed by using Stata SE14.0 (Stata Corp LP, College Station, TX). Weights for each study in the analysis were calculated using the method reported by Mizuki.\textsuperscript{[29]} The HR with its 95% CI and redefined weight was used to define the prognostic value of Ki-67 expression in meningiomas. Inter-study heterogeneity was evaluated using the Chi-Squared test and expressed as I² index. A fixed effects model was used when the value of $P_{\text{heterogeneity}}$ was >.05 and I² < 50%; otherwise, a random effects model was applied. To investigate the potential origin of the heterogeneity, subgroup analysis and meta-regression were performed for OS or disease/progression/recurrence-free survival (D/P/RFS) analysis according to the ethnicity, tumor grade, HR sources, and definitions of cutoffs and cutoffs. In addition, sensitivity analysis was carried out to investigate the influence of each included study on the pooled HR. Begg funnel plot and Egger’s linear regression test were conducted for evaluating publication bias. Additionally, Duval and Tweedie’s “Trim and Fill” method was applied to estimate a corrected effect size after adjustment for publication bias.\textsuperscript{[30]} Two-tailed value of $P<.05$ was considered statistically significant.

3. Results

3.1. Search results

The detailed study selection process is presented as a flowchart in Figure 1. Potentially relevant citations were initially retrieved through initial search of relevant databases. After duplicates were removed and title/abstract screened, 138 articles remained for full-text assessment. Ninety-five articles were further excluded for lack of HRs with estimates of 95% CIs or data to calculate.

3.2. Study characteristics

Summary of major characteristics of included studies is shown in Table 1. A total of 43 studies published from 1996 to 2017 with 5012 patients were included in the final meta-analysis.\textsuperscript{[16,19–24,31–60]} Among these studies, 17 studies were conducted in Eastern countries and 26 studies in Western countries; the sample size ranged from 23 to 422; 4 studies comprised only low-grade (grade I) meningioma patients, 18 studies only high-grade (grade II/III) patients, and 21 studies both low- and high-grade patients; 14 articles reported OS and 38 articles reported D/P/RFS; HR and 95% CIs data were extracted directly from 25 studies, or were calculated from Kaplan–Meier survival curves in 18 studies. According to the quality assessment, 7 studies had quality scores of 7 or less, and the rest 36 studies had a score of more than 7 (see Table S2, http://links.lww.com/MD/D840, Supplemental Content, which illustrates the quality assessment of included studies).
3.3. Overall survival

There were 14 studies with 1173 patients taken for analysis for OS. No significant association between the Ki-67/MIB-1 expression and OS was found (HR = 1.009; 95% CI: 0.999–1.019; P = .073; I² = 77.2%; I² heterogeneity < .001) (see Figure S1, http://links.lww.com/MD/D837, Supplemental Content, which illustrates the association between the Ki-67/MIB-1 expression and OS). However, it is noticed that the pooled HR was mainly ascribed to 2 studies with extremely large weight.[56,62] In order to reduce the contribution of these 2 studies, recalculated weights were applied to get the adjusted HR and 95% CI. Consequently, a negative prognostic value of Ki-67 was tested, whereas a marked heterogeneity was observed among these studies (HR = 1.565; 95% CI: 1.217–2.013; P = .000; I² = 100.0%; I² heterogeneity < .001, Fig. 2).

To explore the source of heterogeneity, subgroup analysis on OS was conducted by ethnicity, tumor grade, HR sources (HR calculated from univariate analysis or multivariate analysis), and definitions of cutoffs and cutoff values (Table 2). The results showed that

1. a negative effect of Ki-67 on OS was shown in both Eastern (HR = 1.783; 95% CI: 1.060–2.998; P = .029; I² = 84.8%) and Western (HR = 1.502; 95% CI: 1.126–2.003; P = .006; I² = 100.0%) subgroups;
2. for HR sources subgroup analysis, only HR estimated from UV method was adversely correlated with OS (HR = 1.749; 95% CI: 1.233–2.481; P = .002; I² = 100.0%);
3. in the definition of cutoffs subgroup analysis, higher Ki-67 expression was associated with poor OS in “arbitrary” (HR = 2.604; 95% CI: 1.336–5.074; P = .005; I² = 56.8%) and “others” (HR = 1.800; 95% CI: 1.211–2.673; P = .004; I² = 88.7%) subgroups;
4. when it came to cutoff values subgroups, higher Ki-67 reactivity was significantly associated with deteriorated OS only in the “> 4%” subgroup (HR = 1.655; 95% CI: 1.261–2.173; P = .000; I² = 100.0%);
5. regarding tumor grade subgroup analysis, the negative prognostic value of higher Ki-67 expression level was demonstrated only in the “Low + High” subgroup (HR = 1.297; 95% CI: 1.058–1.589; P = .012; I² = 100.0%) and “High” subgroup (HR = 2.078; 95% CI: 1.310–3.296; P = .000; I² = 84.8%).

3.4. Disease/progression/recurrence-free survival

Thirty-eight studies comprising 4717 patients were included for D/P/RFS analysis. The Ki-67 expression had a significant association with poor D/P/RFS (HR = 1.090; 95% CI: 1.057–1.124; P < .001; I² = 85.0%; I² heterogeneity < .001) (see Fig. S2, http://links.lww.com/MD/D838, Supplemental Content, which illustrates the association between Ki-67 expression and D/P/RFS). However, it is noticed that the pooled HR was mainly determined by four studies with extremely large weight.[35,56,62,63] Hence, redefined weights according to Mizuki method of the included studies were applied to get the adjusted HR and 95% CI.[29] Intriguingly, the significant association was also identified with a marked between-study heterogeneity (HR = 2.644; 95% CI: 2.264–3.087; P < .001; I² = 100.0%, I² heterogeneity < .001, Fig. 3).

To investigate the potential origin of the between-study heterogeneity, subgroup analysis was performed according to the following factors: ethnicity, tumor grade, HR sources, and definitions of cutoffs and cutoff values (Table 3). The results displayed that...
Table 1

| Reference                  | Sample size | Grade | Age criteria | Definition of cutoffs | Cutoff value | Outcome measures | HR (obtained) |
|---------------------------|-------------|-------|--------------|-----------------------|--------------|------------------|---------------|
| Matsuno et al, 1996       | Japan       | I-III| WHO          | 50.9                  | Arbitrary    | 3%               | RFS           |
| Hsu et al, 1998           | USA         | III  | WHO          | 54 (15–78)            | Arbitrary    | 3%               | PFS           |
| Perry et al, 1998         | USA         | III  | NR           | 15–93                 | Others       | 4.2%             | RFS           |
| Korshunov et al, 2002     | Russia      | III  | WHO          | 48                    | Others       | 4.4%             | RFS           |
| Nakabayashi et al, 2003   | Japan       | III  | WHO          | 52.9                  | Arbitrary    | 5%               | RFS           |
| Roser et al, 2004         | Germany     | I    | WHO          | 64 (15–94)            | Data distribution (Median) | 4% | RFS           |
| Torp et al, 2005          | Norway      | III  | WHO          | 58 (31–82)            | Arbitrary    | 10%              | RFS           |
| Barresi et al, 2006       | Italy       | II   | WHO          | 63.5 (21–64)          | Others       | 4%               | OS            |
| Kim et al, 2006           | Germany     | I-I   | WHO          | 59 (4–88)             | ROC curve analysis | 12% | RFS           |
| Brunu et al, 2007         | Spain       | III  | WHO          | 58.5 (16–63)          | ROC curve analysis | 9.9% | OS; RFS MV |
| Yang et al, 2008          | Korea       | III  | WHO          | 49.6 (17–77)          | Data distribution (median) | 5% | OS; RFS MV |
| Nakasu et al, 2009        | Japan       | I    | WHO          | 53.6 (13.5–85.4)      | Others       | 4%               | OS; RFS UV/MV |
| Vranic et al, 2010        | Slovenia    | I-III| WHO          | 51.5 (6–81)           | Arbitrary    | 3%               | PFS           |
| Ohba et al, 2011          | Japan       | I-III| WHO          | 56.8                   | Arbitrary    | 10%              | PFS           |
| Guillaumeau et al, 2012   | France      | III  | WHO          | 56 (90–95)            | Arbitrary    | 5%               | PFS           |
| Jensen et al, 2012        | USA         | I-I   | WHO          | 56 (3–84)             | Others       | 5%               | RFS           |
| Jiang et al, 2012         | China       | III  | WHO          | 51                     | Arbitrary    | 5%               | RFS           |
| Kim et al, 2012           | Korea       | III  | WHO          | 49 (12–82)            | Data distribution (median) | 8% | RFS           |
| Oya et al, 2012           | Japan       | I    | WHO          | 55.2 (12–60)          | Arbitrary    | 3%               | RFS           |
| Wang et al, 2012          | China       | II   | WHO          | 12.1 (2–18)           | Arbitrary    | 3%               | OS            |
| Sanz et al, 2013          | Spain       | III  | WHO          | 58 (24–62)            | Arbitrary    | 4%               | RFS           |
| Ke et al, 2013            | Korea       | I-I   | WHO          | 50.3 (8–79)           | Others       | 4%               | OS            |
| Kim et al, 2014           | Korea       | II   | WHO          | 56.6 (26.4–67.2)      | ROC curve analysis | 6% | RFS           |
| Paia et al, 2014          | Turkey      | I-I   | WHO          | 59.5 (25–84)          | Others       | 5%               | RFS           |
| Yamaguchi et al, 2014     | Japan       | III  | WHO          | 60                     | Data distribution (median) | 15% | RFS UV |
| Choi et al, 2015          | Korea       | II   | WHO          | 53 (13–78)            | ROC curve analysis | 13% | PFS           |
| Kling et al, 2015         | USA         | I    | WHO          | 57.6                   | Arbitrary    | 10%              | RFS           |
| Yoon et al, 2015          | Japan       | II   | WHO          | 58 (9–90)             | Arbitrary    | 10%              | OS            |
| Zhu et al, 2015           | China       | I    | WHO          | 50.4 (20–79)          | Data distribution (median) | 6.5% | PFS UV |
| Baumgarten et al, 2016    | Germany     | I-I   | WHO          | 58 (17–64)            | Data distribution (median) | 5% | PFS           |
| Champsaur et al, 2016     | UK          | II   | WHO          | 57 (44–88)            | Data distribution (median) | 15% | RFS           |
| Guadagno et al, 2016      | Italy       | I-I   | WHO          | 58 (21–81)            | Arbitrary    | 5%               | OS; RFS UV |
| Ling et al, 2016          | France      | III  | WHO          | 62.7 (33–90)          | Data distribution (median) | 9.9% | OS; PFS UV/MV |
| Marcisciano et al, 2016   | USA         | I-I   | WHO          | 53.5 (13–88)          | Arbitrary    | 3%               | PFS           |
| Nanda et al, 2016         | USA         | II   | WHO          | 60 (21–88)            | Data distribution (median) | 15% | RFS           |
| Winther et al, 2016       | Norway      | I-I   | WHO          | 60 (25–88)            | ROC curve analysis | 3% | RFS           |
| Cai et al, 2017           | China       | III  | WHO          | 53 (28–74)            | Data distribution (median) | 5.9% | PFS           |
| Champsaur et al, 2017     | UK          | II   | WHO          | 56.9                   | Data distribution (median) | 15% | RFS           |
| Guachotte et al, 2017     | France      | I-I   | WHO          | 61 (29–85)            | Data distribution (median) | 16.7% | OS; PFS UV |
| Karsy et al, 2017         | Canada      | I    | WHO          | 55.4                   | ROC curve analysis | 3% | OS; PFS MV |
| Kim et al, 2017           | USA         | I-I   | WHO          | 56.4                   | Arbitrary    | 3%               | OS; RFS UV |
| Liu et al, 2017           | China       | II   | WHO          | 55.8 (21–81)          | Arbitrary    | 15%              | OS; DFS MV   |
| Shen et al, 2017          | China       | II   | WHO          | 50.2 (20–80)          | Data distribution (median) | 20% | OS UV |

DFS = disease-free survival, MV = multivariate, NR = not reported, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, UV = univariate.

1. a negative effect of Ki-67 on D/P/RFS was shown in both Eastern (HR = 3.355; 95% CI: 2.232–4.846; P = .000; I² = 68.7%) and Western subgroups (HR = 2.413; 95% CI: 2.052–2.837; P < .000; I² = 100.0%).
2. for HR sources subgroup analysis, HRs estimated from both UV (HR = 2.585; 95% CI: 1.929–3.464; P < .000; I² = 100.0%) and MV (HR = 2.567; 95% CI: 2.167–3.042; P < .000; I² = 100.0%) methods were adversely correlated with D/P/RFS.
3. in the definition of cutoffs subgroup analysis, higher Ki-67 expression was associated with poor D/P/RFS in all subgroups.
4. when it came to cutoff values subgroup, higher Ki-67 reactivity was significantly associated with deteriorated D/P/RFS in both the “≤ 4%” (HR = 2.603; 95% CI: 1.974–3.433; P < .000; I² = 97.1%) and “>4%” (HR = 2.667; 95% CI: 2.215–3.211; P < .000; I² = 100.0%) subgroups.
5. regarding tumor grade subgroup analysis, the negative prognostic value of higher Ki-67 expression level was demonstrated in all subgroups.

3.5. Meta-regression analysis

We also conducted a meta-regression analysis to investigate the impact of various study characteristics on the study estimates of HR. For the OS subset, ethnicity, HR sources, tumor grade, and definitions of cutoffs and cutoff values were entered as explanatory factors. As shown in Table S3, http://links.lww.com/MD/D841, only the geographical origin and definition of cutoffs...
presented statistically significant association with poor OS in the univariate regression analysis (see Table S3, http://links.lww.com/MD/D841, Supplemental Content, which illustrates the meta-regression analysis in OS subset). Further multivariate regression analysis was conducted by geographical origin and definitions of cutoffs. In multivariate model, the significant association was only presented in definition of cutoffs variable. Nevertheless, for the D/P/RFS subset, all included variables failed

![Figure 2](image-url). The hazard ratio (HR) of Ki-67 expression associated with OS in meningioma patients calculated by redefined weight.

| Stratified analyses | No. of patients | No. of studies | Pooled HR (95% CI) | P value | $P_D$ value | Heterogeneity |
|---------------------|-----------------|----------------|--------------------|---------|-------------|---------------|
|                     |                 |                |                    |         |             | $I^2$ | $P_H$ value |
| Ethnicity           |                 |                |                    |         |             |               |
| Eastern             | 281             | 5              | 1.783 (1.060–2.998) | .029    |             | 84.8% | .000        |
| Western             | 892             | 9              | 1.502 (1.126–2.003) | .006    |             | 100.0% | .000        |
| Grade               |                 |                |                    |         |             |               |
| Low                 | 207             | 1              | 0.940 (0.719–1.223) | .651    |             | -     | -           |
| Low + High          | 357             | 4              | 1.297 (1.058–1.589) | .012    |             | 100.0% | .000        |
| High                | 609             | 9              | 2.078 (1.310–3.296) | .002    |             | 84.8% | .000        |
| HR sources          |                 |                |                    |         |             |               |
| UV                  | 722             | 9              | 1.749 (1.233–2.481) | .002    |             | 100.0% | .000        |
| MV                  | 451             | 5              | 1.309 (0.932–1.841) | .121    |             | 63.9% | .026        |
| Definition of cutoffs|                |                |                    |         |             |               |
| Data distribution (median/mean) | 330 | 4 | 1.040 (0.725–1.492) | .830 | .000 | 99.9% | .000 |
| ROC curve analysis  | 235             | 2              | 1.086 (0.828–1.425) | .551    | 78% | .033 |
| Arbitary            | 367             | 5              | 2.604 (1.336–5.074) | .005    | 56.8% | .055 |
| Others              | 241             | 3              | 1.800 (1.211–2.673) | .004    | 88.7% | .000 |
| Cutoff values       |                 |                |                    |         |             |               |
| $\leq 4\%$          | 547             | 6              | 1.402 (0.832–2.360) | .204    |             | 100%  | .000        |
| $> 4\%$             | 626             | 8              | 1.655 (1.261–2.173) | .000    |             | 100%  | .000        |

MV = multivariate, UV = univariate.
to reach statistical significance in univariate analysis (see Table S4, http://links.lww.com/MD/D842, Supplemental Content, which illustrates the meta-regression analysis in D/P/RFS subset).

3.6. Sensitivity analysis

Sensitivity analysis was performed to examine the stability of the current meta-analysis. The result for the OS subset is presented in Table S5, http://links.lww.com/MD/D843, and indicated that studies reported by Ling et al[56] and Gauchotte et al[62] were not stable and significantly influenced the pooled HR (see Table S5, http://links.lww.com/MD/D843, Supplemental Content, which illustrates the sensitivity analysis in OS subset). After excluding these two studies, the meta-analysis of the remaining studies was stable. The pooled HRs (random effect model) for OS changed from 1.565 (95% CI: 1.217–2.013; P = .000) to 1.737 (95% CI: 1.272–2.371; P = .000), and the I² changed from 100.0% to 82.10%. For D/P/RFS analysis, 4 studies[35,56,62,63] were found attributed to the instability of the result (see Table S6, http://links.lww.com/MD/D844, Supplemental Content, which illustrates the sensitivity analysis in D/P/RFS subset). Their exclusion made combined HRs under a random effects model alter from 2.644 (95% CI: 2.264–3.087; P = .000) to 2.937 (95% CI: 2.472–3.491; P = .000), and the I² decreased from 100.0% to 88.30%. The combined HR for D/P/RFS was similar after the exclusion of selected studies, with a stability of meta-analysis confirmed.

3.7. Publication bias

Publication bias is also a potential factor that influenced the pooled results. Funnel plots were drawn to evaluate possible publication bias. The shapes of the funnel plots of both OS and D/P/RFS did obviously show asymmetry (Fig. 4A and B). Quantitative assessment by Egger test for the OS and D/P/RFS subset suggested that our analysis was not stable (P = .001 and
$P = .000$, respectively) (Fig. 4C and D). After refilling “missing” studies by Trim and Fill method, the adjusted pooled HR was still significant for OS (HR = 1.005; 95% CI: 1.004–1.007) and D/P/RFS (HR = 1.008; 95% CI: 1.005–1.010) (see Table S7, http://links.lww.com/MD/D845, Supplemental Content, which illustrates the publication bias assessment in OS subset and D/P/RFS subset).

4. Discussion
Negative prognostic factors in meningiomas include young age, male gender, low Karnofsky performance status, high grade, high mitotic rate, subtotal surgical resection, and involvement of the optic nerve. Among these factors, histological grading is the most important determinant of prognosis. Nevertheless, it has

| Stratified analyses          | No. of patients | No. of studies | Pooled HR (95% CI) | $P$ value | $P_D$ value | Heterogeneity |
|-----------------------------|-----------------|----------------|-------------------|-----------|-----------|--------------|
|                             |                 |                |                   |           |           | $I^2$ | $P_H$ value |
| Ethnicity                   |                 |                |                   |           |           |               |
| Eastern                     | 1307            | 15             | 3.355 (2.323–4.846) | .000      |           | .000 | .687 | .000         |
| Western                     | 3410            | 24             | 2.413 (2.052–2.837) | .000      |           | .000 | 100.0% | .000         |
| Grade                       |                 |                |                   |           |           |               |
| Low                         | 650             | 4              | 2.205 (1.390–3.497) | .001      | .000      | 98.8% | .000 | .000         |
| Low + High                  | 2932            | 20             | 2.924 (2.362–3.620) | .000      |           | .000 | 100.0% | .000         |
| High                        | 1135            | 15             | 2.260 (1.841–2.773) | .000      |           | .000 | 77.3% | .000         |
| HR sources                  |                 |                |                   |           |           |               |
| UV                          | 1516            | 12             | 2.585 (1.929–3.464) | .000      |           | .000 | 100.0% | .000         |
| MV                          | 3201            | 27             | 2.567 (2.167–3.042) | .000      |           | .000 | 100.0% | .000         |
| Definition of cutoffs       |                 |                |                   |           |           |               |
| Data distribution (median/mean) | 1534          | 14             | 1.834 (1.470–2.288) | .000      |           | .000 | 100.0% | .000         |
| ROC curve analysis          | 693             | 6              | 2.561 (1.562–4.199) | .000      |           | .000 | 98.5%  | .000         |
| Arbritary                   | 1594            | 15             | 3.876 (2.845–5.281) | .000      |           | .000 | 99.7%  | .000         |
| Others                      | 896             | 4              | 2.564 (1.949–3.371) | .000      |           | .000 | 95.2%  | .000         |
| Cutoff values               |                 |                |                   |           |           |               |
| ≤ 4%                        | 1717            | 12             | 2.603 (1.974–3.433) | .000      | .000      | .000 | 97.1%  | .000         |
| > 4%                        | 3000            | 27             | 2.667 (2.215–3.211) | .000      | .000      | .000 | 100.0% | .000         |

MV = multivariate, UV = univariate.
been proved inadequate in evaluating the survival outcomes.\(^{10,68}\) Thus, development of biomarkers may be a promising strategy to improve the prognostic accuracy.\(^{70}\)

This current study contained of 43 studies and 5012 individuals. To our best knowledge, this was probably the most comprehensive meta-analysis to evaluate the prognostic value of Ki-67 in patients with meningiomas. Our results showed that higher Ki-67 expression was negatively associated with OS as well as D/P/RFS in meningiomas. This negative effect widely existed regardless of different clinical characteristic (ethnicity, tumor grade) and methodological difference between studies (cutoff definition, cutoff value, and HR calculation). Taken together, Ki-67 was a promising biomarker for meningiomas prognosis prediction.

In the present study, we did comprehensive investigation on the between-study heterogeneity through subgroup analysis, meta-regression, and sensitivity analysis. It is suggested that various cutoff values between different studies may be a major contributor to the high heterogeneity in subgroup analysis and meta-regression analysis. We chose 4% as a threshold based on a literature reviewing.\(^{71}\) As a result of subgroup analysis, higher Ki-67 expression (> 4%) was associated with poor OS and D/P/RFS. Moreover, cutoff value (> 4%) also contributed to a majority of heterogeneity in meta-regression. One possible explanation for these findings may be due to an obvious variety of the original cutoff values (2%–20%) among our included studies. An appropriate cutoff value of Ki-67 was important to predict clinical outcomes in patients with meningiomas. Therefore, we suggested that cutoff value more than 4% would be a reasonable choice for further studies.

In addition, we found that methodological difference in the definition of cutoff value was another factor that influenced the pooled HR estimation. According to the included studies in this meta-analysis, we observed 40% studies defined cutoff value by arbitrary method. Both subgroup analysis and meta-regression analysis showed that arbitrarily defined cutoff value was ascribed to high inter-study heterogeneity. Cutoff value may be changeable due to various factors, such as clinical characteristic (ethnicity, tumor grade) and methodological difference (cutoff definition, cutoff value, and HR calculation). Thus, we suggested that a uniform method to define cutoff value was necessary for future study to reduce the method error between studies.

It is a pity that although we have done comprehensive investigation, the source of heterogeneity is still not completely explained. The significant heterogeneity may be due to the following reasons: first, the tumor grading criteria adopted for each study were different; secondly, the concomitant variables for outcome analysis of each study varied a lot; thirdly, cohorts with small scales would bring sample error.

The systematic evidence provided by the present meta-analysis has far-reaching clinical implications. First, a close follow-up is necessary for patients with higher Ki-67 expression level to have close follow-ups. However, the sources of heterogeneity were still not completely explained and obvious publication bias was also observed. Further well-designed studies are therefore needed to enhance the robustness of this conclusion.

5. Conclusion

In conclusion, our meta-analysis indicated the significant negative prognostic value of high Ki-67 expression level in the prognosis of meningiomas, especially for patients with Ki-67 index higher than 4%. It is strongly advised for patients with higher Ki-67 expression level to have close follow-ups. However, the sources of heterogeneity were still not completely explained and obvious publication bias was also observed. Further well-designed studies are therefore needed to enhance the robustness of this conclusion.

Author contributions

Data curation: Tingjian Wang, Siying Song, Jiabao Jiang.

Methodology: Tingjian Wang.

Supervision: Changxiang Yan.

Writing – original draft: Tingjian Wang, Ning Liu.

Writing – review & editing: Ning Liu.

Changxiang Yan orcid: 0000-0001-8764-1596.

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