Is the prognostic significance of O6-methylguanine-DNA methyltransferase promoter methylation equally important in glioblastomas of patients from different continents? A systematic review with meta-analysis

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Background: O6-methylguanine-DNA methyltransferase (MGMT) is an independent predictor of therapeutic response and potential prognosis in patients with glioblastoma multiforme (GBM). However, its significance of clinical prognosis in different continents still needs to be explored.

Patients and methods: To explore the effects of MGMT promoter methylation on both progression-free survival (PFS) and overall survival (OS) among GBM patients from different continents, a systematic review of published studies was conducted.

Results: A total of 5103 patients from 53 studies were involved in the systematic review and the total percentage of MGMT promoter methylation was 45.53%. Of these studies, 16 studies performed univariate analyses and 17 performed multivariate analyses of MGMT promoter methylation on PFS. The pooled hazard ratio (HR) estimated for PFS was 0.55 (95% CI 0.50, 0.60) by univariate analysis and 0.43 (95% CI 0.38, 0.48) by multivariate analysis. The effect of MGMT promoter methylation on OS was explored in 30 studies by univariate analysis and in 30 studies by multivariate analysis. The combined HR was 0.48 (95% CI 0.44, 0.52) and 0.42 (95% CI 0.38, 0.45), respectively.

Conclusion: In each subgroup divided by areas, the prognostic significance still remained highly significant. The proportion of methylation in each group was in inverse proportion to the corresponding HR in the univariate and multivariate analyses of PFS. However, from the perspective of OS, compared with data from Europe and the US, higher methylation rates in Asia did not bring better returns.

Key words: O6-methylguanine-DNA methyltransferase, methylation, glioblastoma, prognosis, meta-analysis

Introduction
Glioblastoma multiforme (GBM, WHO grade 4) is the most common primary brain tumor in adults with an annual incidence of 3–4/100,000 and is associated with poor prognosis. Although some clinical trials have demonstrated that the standard treatment improves overall survival (OS) and progression-free survival (PFS), only less than one-third of GBM patients seem to benefit from these therapies, mainly because of GBM resistance to alkylating drugs.
Transcriptionally active O6-methylguanine-DNA methyltransferase (MGMT) gene encodes a ubiquitously expressed suicide DNA repair enzyme that counteracts the normally lethal effects of alkylating agents by removing the alkyl adducts, preventing the formation of cross-links and thereby causing resistance to alkylating drugs.\(^1\) The loss of MGMT protein expression caused by methylation of the MGMT promoter reduces the DNA repair activity of glioma cells, preventing their resistance to alkylating agents.\(^2\) It is believed that patients with GBM who have a methylated MGMT promoter are more sensitive to the killing effects of alkylating drugs, because tumor cells with low MGMT expression were unable to repair such DNA lesions and, thus, were prone to apoptosis, whereas those that do not have a methylated MGMT promoter do not have this benefit.\(^6\,\)\(^8\,\)\(^9\)

Various studies have shown that the MGMT promoter methylation status is an independent prognostic factor to GBM and the assessment of MGMT promoter methylation is currently considered as mandatory for patient selection in clinical trials.\(^7\)\(^-\)\(^10\)\(^,\)\(^6\)\(^8\) However, many differences in high risk factors and postoperative chemoradiation stay in guidelines for the treatment of glioblastoma, among countries, indicating different attitudes to MGMT promoter methylation status. Is the prognostic significance of MGMT promoter methylation independent equally among glioblastomas from different areas? Further explorations are needed in the prognostic value of MGMT promoter methylation in both PFS and OS among patients with GBM.

**Patients and methods**

**Publication selection**

Ethical approval and patient consent are not required as this is a systematic review and meta-analysis of previously published studies. This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.\(^1\)\(^3\)

Two reviewers (Yangyang Jiang and Wei Meng) participated in the citations search, study selection and data extraction, independently. Divergences between reviewers were resolved through consulting with Professor Jie Ma.

Electronic databases, including PubMed, EMBASE, Web of Science, China Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), China Wan Fang database and the Cochrane library, were searched for relevant clinical trials published on the association between MGMT promoter methylation and GBM between January 2000 and June 2017.

The search combined key words: (“O6-methylguanine-DNA methyltransferase methylation” OR MGMT methylation”) AND (“glioblastoma” OR “GBM”) AND (“survival analysis” OR “meta analysis”) AND (“MSP” OR “PSQ”) AND (“survival analysis” OR “meta analysis”) AND (“methylation-specific polymerase chain reaction and pyrosequencing”).

The meta-analysis gathered complete databases from published cohort studies dealing with the prognostic value of MGMT promoter methylation in patients with GBM no matter which therapy was given.

The language in which the papers were written was restricted to English and Chinese. Abstracts were excluded because of insufficient data for meta-analysis. In order to identify the relevant publications, the references cited in the research papers were also scanned. To avoid duplication of data, we carefully noted the author names and the different research centers involved. We evaluated the eligible studies if all the following conditions were met: 1) MGMT promoter methylation status was measured by using identified method such as methylation-specific polymerase chain reaction (MSP) and pyrosequencing (PSQ); (2) inclusion of sufficient data or survival curves to calculate hazard ratio (HR) and 95% CI; and 3) full or special parts of papers investigated the relationship between MGMT promoter methylation and PFS or OS.

**Data extraction**

Two authors (Yangyang Jiang and Wei Meng) independently reviewed and extracted the data needed. Disagreements were resolved through discussion with each other.

We used a predesigned data extraction sheet to obtain the following information: first author, year of publication, region, HR form and sample size and style of postoperative chemoradiation, if given. The formula recommended by Spruance et al was adopted to calculate the corresponding HR of the missing data.\(^1\)\(^4\) Kaplan–Meier curve was read by using Engauge Digitizer version 4.1 (available at: http://sourceforge.net) except if the paper has supplied HR directly.\(^1\)\(^5\) (All the data are shown in Table 1.)

**Statistical analysis**

In some studies, HR and 95% CI were directly obtained from published literature by using univariate or multivariate survival analysis. For studies in which the HR correspond-
Table 1 Main characteristics and results of eligible studies

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Abbreviations: HR, hazard ratio; MGMT, O6-methylguanine-DNA methyltransferase; PFS, progression-free survival; OS, overall survival; N/A, not available or not applicable; M/U, methylation/unmethylation case.

The pooled HR corresponding to the 95% CI was used to assess the prognostic value of MGMT promoter methylation in patients with GBM. The statistical heterogeneity among studies was assessed with the Q-test and I² statistics.16

In patients with GBM. The statistical heterogeneity among studies was assessed with the Q-test and I² statistics.16

ing to the 95% CI was not given directly, published data and figures from original papers were used to calculate the HR according to the methods described by using Engauge Digitizer version 4.1.
A random-effects model was used primarily regardless of heterogeneity. Level of heterogeneity (level of variance) across studies was evaluated using I² statistic. I² of 40, 70 and 100% was used to represent low, moderate and high variance, respectively. If obvious differences for clinical characteristics and methodology were not identified and I² ≤ 40%, a fixed-effects model was adopted. A random-effects model will be used if clinical characteristics and methodology were not identified to be great difference and I² ≤ 40%; in contrast, if the clinical characteristic and/or methodology across studies regardless of I² statistic was considered to be obviously different, qualitative analysis was adopted. The objective impact of MGMT promoter methylation on PFS and OS was considered to be statistically significant if the 95% CI for the HR did not overlap 0. Publication bias was evaluated with funnel plot and Begg’s rank correlation method. The statistical analyses were performed by STATA/MP 13.0 software.

Results
Characteristics of studies
A total of 204 relevant citations were identified at the initial search stage; 151 articles concerned topics not relevant to this study, and finally 53 studies were included in the meta-analysis.

All the included studies were in English. The individual characteristics of the eligible studies are reported in Table 1. The total number of patients was 5103, and the total frequency of MGMT promoter methylation was 45.53%. Of the 53 publications eligible for systematic review, 31 studies reported the HR with corresponding to 95% CI directly, the other 22 studies reported the HR in the style of survival curve availability.

Meta-analysis
Sixteen studies (one in Asia, one in North America, one in Australia and 13 in Europe) reported the effect of MGMT promoter methylation on PFS using univariate analysis. As shown in Figure 1, the HR of the Asian group is 0.47, the HR of the American group is 0.88, the HR of the Australian group is 0.51 and the HR of the European group is 0.49; MGMT promoter methylation was significantly correlated with better PFS according to univariate analysis, with a combined HR of 0.55 (95% CI 0.50, 0.60). The random-effects model (the DerSimonian and Laird method) was used because significant heterogeneity was detected among these studies (p = 0.000, I² = 88.3%).

The effect of MGMT promoter methylation on OS adjusted for other variables was evaluated in 17 studies (five in Asia, 11 in Europe and one in America). As shown in Figure 2, the HR of the Asian group is 0.49, the HR of the European group is 0.44 and the HR of the American group is 0.37; MGMT promoter methylation was significantly correlated with better PFS according to multivariate analysis, with a combined HR of 0.45 (95% CI 0.35, 0.54). The random-effects model (the DerSimonian and Laird method) was used because significant heterogeneity was detected among these studies (p = 0.000, I² = 62.8%).

The effect of MGMT promoter methylation on OS unadjusted for using univariate analysis was evaluated in 32 studies (four in Asia, six in North America, one in Australia and 21 in Europe). As shown in Figure 3, the HR of the American group is 0.49, the HR of the European group is 0.47, HR of the Asian group is 0.73 and the HR of the Australian group is 0.51; MGMT promoter methylation was significantly correlated with better OS according to univariate analysis, with a combined HR of 0.50 (95% CI 0.40, 0.59). The random-effects model (the DerSimonian and Laird method) was used as significant heterogeneity was detected among these studies (p = 0.000, I² = 50.3%).

Thirty-one studies (six in Asia, two in America and 23 in Europe) reported the effect of MGMT promoter methylation on OS using analyses adjusted for other factors. As shown in Figure 4, the HR of the Asian group is 0.56, the HR of the American group is 0.37 and the HR of the European group is 0.44; MGMT promoter methylation was significantly correlated with better OS according to multivariate analysis, with a combined HR of 0.44 (95% CI 0.38, 0.50). The random-effects model (the DerSimonian and Laird method) was used as significant heterogeneity was detected among these studies (p = 0.000, I² = 50.3%).

Publication bias statistics were determined; some publication bias (Begg’s test, p<0.05) was found. Sensitivity analysis was performed to investigate the influence of a single study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable.

Discussion
The association between the MGMT promoter methylation and GBM has been reported in many studies. Evaluations of prognostic factors, such as patients age, gender, nationality, recurrence, tumor location and excision, MGMT testing method and the style of postoperative chemoradiation for tumors are all vital to improve research pursuing new thera-
In general, the population flows more and more frequently among the continents, and most of the prognostic factors are usually determined by circumstances and nationwide medical policies. Therefore, it is more reasonable to set subgroups by areas but not by races. Our meta-analysis was performed to define the prognostic and predictive value of MGMT promoter methylation in glioblastoma patients of different continents. The major strengths of this study include the deliberate distinction of area, the relatively comprehensive sample size, the prospective data collection and the combination of the MSP and PSQ analysis to assess the MGMT promoter methylation status.

MGMT expression protects normal cells from carcinogens; however, it can also protect cancer cells from chemotherapeutic alkylating agents, which include mutations, sister chromatid exchanges, recombination and chromosomal aberrations. It has been shown that glial brain tumors are characterized by a low expression of MGMT, however, the
Significance of MGMT in GBM

Activity of MGMT is commonly increased in relation to surrounding normal tissue. The data of the Adeberg et al study show that delaying postoperative chemoradiation for GBM patients – carried out in order to determine MGMT promoter status – did not have a negative impact on survival time. Indeed, initiating radiation therapy sooner than 24 days after surgery has a negative impact on progression and survival.25

In the older glioblastoma patient, MGMT promoter methylation status is still contentious on clinical decision making. For the elderly with malignant glioma, two recently published Phase III trials have evaluated the place of dose-dense/conventional temozolomide (TMZ) regimes alone as compared with conventional/hypofractionated radiotherapy. OS in methylated patients was better if TMZ treatment was applied, whereas in unmethylated patients radiotherapy alone was more effective. However, in contrast, Gutenberg et al study showed no significant differences in OS for concomitant plus adjuvant administration of TMZ, as the current standard treatment specifies, to sequentially administered TMZ.24
Figure 3 (Continued)
Concerning age, the findings of Gutenberg et al suggest that patients over 65 years of age showed significantly longer PFS and a trend toward longer OS when receiving concomitant plus adjuvant TMZ as compared to the sequential TMZ regimen. Thus, MGMT promoter methylation is an important biomarker for personalized treatment strategies in the elderly subpopulation.

It was found that GBM patients with MGMT promoter methylation had better OS and PFS than those without methylated status by univariate or multivariate analysis regardless of therapeutic intervention and area. It was found that GBM patients with MGMT promoter methylation had better OS and PFS than those without methylated status by univariate or multivariate analysis regardless of therapeutic intervention and area.72,74–78 MGMT gene promoter methylation levels can be used as a sensitive biomarker of using alkylating agents in GBM patients.86,88,89,92 The results suggested that MGMT promoter methylation indicated better clinical prognosis of GBM, and played an independent role with GBM development.80,82–84 Yang et al once have explored the connection between MGMT promoter methylation in glioblastoma and different race, conducting a primary conclusion, GBM patients with MGMT promoter methylation only had longer OS by multivariate analysis in Asian, but with no further exploration of subgroup.31 Also, because of population flow, it is more reasonable and accurate to set subgroup by continent but not by race. Therefore, is the prognostic significance of MGMT promoter methylation independent equally in glioblastomas of different areas?

Figure 3 Data statistics on OS using univariate analysis.

Notes: (A) Forest plot showing the combined relative HR from the random effect model for MGMT promoter methylation on OS using univariate analysis with patients from different areas. The proportion of methylation in European and American groups was in inverse proportion to the corresponding HR except for the Asian group. (B) Begg's test on OS using univariate analysis with different area. (C) Sensitivity analysis on OS using univariate analysis with different area.

Abbreviations: SE, standard error; ES, effect size; HR, hazard ratio; MGMT, O6-methylguanine-DNA methyltransferase; OS, overall survival.
Figure 4 (Continued)
In our univariate analysis of PFS, MGMT promoter methylation ratio of Asian groups is 0.67, the European is 0.41 and the American is 0.24. The HR of Asian groups is 0.47, the European is 0.49 and the American is 0.88. The proportion of methylation in each group was in inverse proportion to the corresponding HR. In our multivariate analysis of PFS, MGMT promoter methylation ratio of Asian groups is 0.29, the European is 0.53 and the American is 0.58. The HR of Asian groups is 0.49, the European is 0.44 and the American is 0.37. The proportion of methylation in each group was also in inverse proportion to the corresponding HR.

In our univariate analysis of OS, MGMT promoter methylation ratio of Asian groups is 0.50, the European is 0.46, the Australia is 0.36 and the American is 0.35. The HR of Asian groups is 0.73, the European is 0.47, the Australia is 0.51 and the American is 0.49. The proportion of methylation in most groups was in inverse proportion to the corresponding HR except for the Asian group. In our multivariate analysis...
of OS, MGMT promoter methylation ratio of Asian groups is 0.53, the European is 0.53 and the American is 0.72. The HR of Asian groups is 0.56, the European is 0.43 and the American is 0.36. The proportion of methylation in the European and American group was in inverse proportion to the corresponding HR but Asian group doesn’t follow the inverse relation.

Our meta-analysis with pooled data suggested that MGMT promoter methylation was associated with prolonged PFS in GBM patients according to both univariate analysis and multivariate analysis. From the perspective of PFS, the prognostic significance of MGMT promoter methylation is independent and basically equal in glioblastomas of different areas. Prolonged OS in GBM patients was also accompanied by MGMT promoter methylation through univariate analysis and multivariate analysis. However, from the perspective of OS, the prognostic significance of MGMT promoter methylation in the Asian group was not so important as in the European and American groups.

There are still two public questions. First, what is the most appropriate method for the assessment of methylation? The various technologies of measurement of MGMT promoter methylation sometimes show discrepant or even opposite results. It is originally regarded that MSP which evaluates the methylation status of the MGMT promoter is the best way to predict the MGMT expression of the tumor in a manner that also correlates with clinical prognosis.56 In the last 5 years, more and more studies have reported that a series of more accurate values have been obtained by PSQ compared to MSP.56 Studies with PSQ showed that this technique, having a higher reproducibility and sensitivity than MSP, is also a qualitative method. Therefore, besides MSP, our meta-analysis also absorbed measurement of MGMT promoter methylation from PSQ, which make our results more persuasive.

Second, what is the best threshold indicating methylated or unmethylated status? The definition of a prognostically relevant threshold for the percentage of MGMT methylation remains one of the most critical issues in the use of PSQ analysis. In 2015, the Receiver Operating Characteristics analysis from Villani et al showed that the best possible criteria for PSQ-detected percentage of MGMT methylation that predicted PFS and OS were 19% and 13%, respectively.23

This meta-analysis has several potential limitations that may be taken into account. First, only English and Chinese language literature studies were scanned for publication. If the search had included literature studies published in other languages, it is possible that more additional relevant trials may have been considered. Second, some ongoing studies, most of which being of high quality, were ineligible for inclusion. Therefore, limitations in quality cannot be excluded, and the pooled results of this meta-analysis may have been affected, more or less. Moreover, subgroup analysis still needs a larger number of trials to make results convincing. Additionally, we are unable to assess the effects of other clinically meaningful end points on PFS or OS, such as quality of life, patient and physician satisfaction with surgical resection and cytotoxic chemotherapy with the alkylating agent TMZ or concomitant radiotherapy, because of sparse and inconsistent reporting across studies. Finally, because all of the Asian studies included in the meta-analysis were carried out in Japan and South Korea, clinicians and pharmacists should carefully and judiciously assess the feasibility of applying the results in the clinical setting in China.

Conclusion
MGMT promoter methylation was an independent indicator of better prognosis for GBM and epigenetic MGMT gene silencing by promoter methylation associated with loss of MGMT expression may contribute to diminished DNA repair, which may be the potential mechanism that results in longer PFS and OS.71 From the perspective of PFS, the prognostic significance of MGMT promoter methylation is independent and basically equal in glioblastomas of different areas. However, from the perspective of OS, the proportion of methylation in the Asian group was not in basically inverse proportion to the corresponding HR as in European and American groups, in the univariate and multivariate analyses. The different prognosis might result from the intervention of age, percentage of MGMT methylation and the style of postoperative chemoradiation. More exploration is needed to investigate the clinical chemotherapy effect on MGMT promoter of the glioblastoma, screen a more sensitive alkylating agent combination for glioblastoma and apparent genetic targets for potential therapeutic value.

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Yangyang Jiang and Wei Meng independently reviewed and extracted the data needed. Disagreements were resolved through discussion with Professor Jie Ma. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.
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Significance of MGMT in GBM

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