Tracking the Features of CIMP-positive Glioma: A Systematic Review and Meta-Analysis

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Abstract

Backgrounds

Controversy surrounding CpG island methylator phenotype (CIMP) in glioma exists with regard to its prognostic value.

Methods

PubMed, EMBASE, and Cochrane Library databases were searched for studies describing molecular and clinicopathological features, and overall survival of gliomas stratified by CIMP status. Associations of CIMP with outcome parameters were estimated using odds ratio (OR) or hazard ratios (HRs) with a 95% confidence interval (CI) using a fixed or random effects model.

Results

A total of 12 studies involving 2386 gliomas (1051 CIMP-positive and 1335 CIMP-negative) were included. Molecular analysis showed that CIMP is more frequent in IDH1-mutated gliomas (OR 229.07; 95% CI 138.72–378.26) and 1p19q LOH gliomas (OR 5.65; 95% CI 2.66–12.01), though CIMP was not associated with EGFR mutation (OR 0.14; 95% CI 0.05–0.43) or MGMT promoter methylation (OR 3.01; 95% CI 0.79–11.48). Clinicopathological analysis showed that CIMP is more frequent in oligodendroglioma (OR 5.51; 95% CI 3.95–7.70), but less frequent in glioblastoma (OR 0.14; 95% CI 0.10–0.19). However, CIMP was not associated with anaplastic oligoastrocytomas (OR 1.57; 95% CI 1.24-2.00) or oligoastrocytoma (OR 0.79; 95% CI 0.35–1.76). We found that CIMP-positive glioma was associated with a longer overall survival (HR -0.57; 95% CI -0.97– -0.16).

Conclusions

A CIMP-positive glioma has better prognosis and its own molecular features (such as IDH1 and 1p19q LOH mutations) and clinicopathological features. These conditions suggest CIMP could be used as an independent prognostic marker for glioma.

Background

Glioma is the most common malignant tumor of the central nervous system (CNS) and adversely affects human health with a poor overall survival rate (1). In 2018 within the United States, 23,880 new CNS cancer patients were reported and 16,830 patients died of CNS cancers (2). Surgery combined with postoperative radiotherapy and chemotherapy remains the main treatment with curative potential, yet the average survival time for high-grade glioma patients is still only approximately 15 months (3). Novel prognostic markers that may improve prognosis, independent of the WHO molecular and histological TNM staging systems for glioma, are urgently needed and may promote the discovery of new therapeutic targets.

CIMP, also called the CpG island methylator phenotype, has high degrees of methylation and is a distinct molecular characteristic of human cancer (4). DNA methylation-induced epigenetic changes induce carcinogenesis, but the prognostic value of CIMP in human cancer is still unclear. The promoter region of certain genes is known to have frequent aberrant DNA methylation of the CpG island, an important mechanism of the epigenetic suppression that silences tumor-suppressive genes (5).

Many studies reporting promoter-associated CpG island hypermethylation in human glioma have shown it to be a powerful determinant of tumor pathogenicity (6,7), but the relationship of CIMP with other molecular events, clinicopathological features, and prognosis in gliomas remains unresolved. To determine a more precise estimate of the strength of this postulated relationship, we performed a systematic review and meta-analysis.

Methods

Search strategy

We performed a comprehensive literature search from the electronic databases PubMed, EMBASE and Cochrane Library to identify relevant studies published up to April 2019. We used this search term combination: glioma and ((CpG island methylator phenotype) or CIMP). Search results were combined in Endnote X8 to compile the reference manager database and duplicates were removed. Eligible studies were selected following inclusion and exclusion criteria. Reference lists in the included studies were searched to identify other potential studies.

Study selection

We selected studies on glioma patients with molecular and clinicopathological features in different CIMP status, and studies from which hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) could be calculated. We excluded abstracts, letters, editorials, expert opinions, reviews, case reports and studies not written in English.

Data extraction

Data extraction, based on the selection criteria, included the following items: last name of the first author, publication year, sample size, number of patients with positive CIMP, number of patients with negative CIMP, number of patients with IDH1, EGFR, MGMT promoter methylation, 1p19q LOH, gender, histology and overall survival in those with and without CIMP. Outcomes were described as HRs with 95% CIs. Methods described by Tierney JF et al. (8) and Guyot P et al. (9) were used to extract data from Kaplan–Meier curves.

Quality assessment

We assessed the quality of randomized and nonrandomized controlled trial studies using the Jadad Scale and MINORS (10,11). These criteria are insufficiently validated for molecular studies, so we defined

strict criteria for included studies, such as no exclusion in specimen for a single-aim study of glioma, discussion of all stage of tumors, and no exclusion based on molecular marker.

Statistical analysis

All statistical tests were performed with Stata Version 13.0 (Stata Corporation, College Station, TX, USA). ORs and 95% CI were used to assess the relationship between CIMP status and clinicopathological and molecular parameters. For quantitative aggregation of survival results, HRs and their 95% CIs were combined as the effective value. The HRs were calculated directly from the reported data by number of events or calculated from Kaplan–Meier survival curve using Engauge Digitizer software (freely downloaded from http://sourceforge.net). Heterogeneity between studies was analyzed using a X^2 -based Q-test ($P > 0.1$ was considered a lack of heterogeneity) and an I^2 test ($I^2 < = 50\%$ indicated low heterogeneity, and $I^2 > 50\%$ indicated substantial heterogeneity). For the low heterogeneity group, each study was analyzed using the fixed effects model. Otherwise, the random effects model was used. Significance of the pooled OR or HR was determined by a Z-test, with $P < 0.05$ considered statistically significant. An estimate of potential publication bias was carried out using a funnel plot, with an asymmetric plot suggesting possible publication bias. Funnel plot asymmetry was assessed using Egger's linear regression test, a linear regression approach measuring funnel plot asymmetry on the natural logarithm scale of the OR. As suggested by Egger, significance of the intercept was determined by a t-test (with $P < 0.05$ considered representative of statistically significant publication bias).

Results

Study characteristics

The electronic search from three databases yielded 121 potential articles. After title screening, abstract screening and full-text evaluation, 109 articles were excluded (Fig. 1). The 12 remaining studies included 2,386 patients with 1,051 CIMP positive samples and 1,335 CIMP negative samples, where CIMP was classified in a dichotomized fashion (CIMP-positive vs. negative) (Table 1). Among the 12 studies, all reported IDH1 mutations, three reported 1p19q LOH (loss of heterozygosity), two reported EGFR mutations, two reported MGMT promoter methylation, three reported gender, nine reported histology, and five reported overall survival. Sample size in the studies ranged from 33 to 1,122. Four studies used samples from TCGA (The Cancer Genome Atlas) (12,13,14,17), two from the Erasmus medical cancer brain tumor tissue bank (13,16), two from the Spanish National Tumor Bank Network (18,19), two from the NOA trial in Germany (15,21), and one from the Chinese Glioma Genome Atlas (CGGA) (20). In addition, one study used data from a publicly available dataset (23) and another used mixed samples from two publicly available datasets and one newly generated dataset from MD Anderson (22). For each included study, Fig. 2 lists the risk of bias from selection, exposure assessment, other variable assessment, outcome assessment, and confounding factors. Based on a strict exclusion and inclusion criteria, studies with high risk in selection bias were not included.

Molecular features

For the purposes of pooled analysis, CIMP+ (CIMP-positive) glioma was compared with CIMP- (CIMP-negative) glioma. The pooled OR for IDH1 mutation in the CIMP + versus CIMP- glioma revealed a significantly higher risk of IDH1 mutation in the CIMP + glioma (OR 229.07; 95% CI 138.72–378.26; P < 0.00001, $P_{heterogeneity}$ 0.000). Similarly, a higher risk of 1p19q LOH was observed in CIMP + glioma (OR 5.65; 95% CI 2.66–12.01; P = 0.01, $P_{heterogeneity}$ 0.040), whereas EGFR mutation and MGMT promoter methylation did not show any differences between the two types of gliomas [(OR 0.14; 95% CI 0.05–0.43; P = 0.35; $P_{heterogeneity}$ 0.002) and (OR 3.01; 95% CI 0.79–11.48; P = 0.10; $P_{heterogeneity}$ 0.825)] (Fig. 4).

Clinicopathological features

Extractable data related to clinicopathological factors were gender and histopathology. The overall OR for the proportions of males in CIMP + vs. CIMP- gliomas was 1.60 (95% CI 0.98–2.62; P = 0.06; $P_{heterogeneity}$ 0.554; Fig. 3). Both glioblastoma (GBM) and oligodendroglioma (OD) in the CIMP + and CIMP- groups achieved statistical significance [(OR 0.14; 95% CI 0.10–0.19; P = 0.005, $P_{heterogeneity}$ 0.000) and (OR 5.51; 95% CI 3.95–7.70; P = 0.003, $P_{heterogeneity}$ 0.000)], whereas no differences were shown for anaplastic oligoastrocytomas (AOA) and oligoastrocytoma (OA)[(OR 1.57; 95% CI 1.24-2.00; P = 0.97; $P_{heterogeneity}$ 0.000) and (OR 0.79; 95% CI 0.35–1.76; P = 0.54; $P_{heterogeneity}$ 0.112; Fig. 5)].

Overall survival and publication bias

In total, five studies compared the overall survival of individuals with CIMP + and CIMP- gliomas. Our pooled analysis showed that CIMP + glioma was significantly associated with longer overall survival (HR -0.57; 95% CI -0.97– -0.16; P = 0.003; $P_{heterogeneity}$ 0.000; Fig. 6).

Begg’s funnel plot was performed to assess publication bias. Heterogeneity tests for comparing the 12 combined studies showed heterogeneity in certain analyses such as those of IDH1 mutation, 1p19q LOH, EGFR mutation, AOA, OD, GBM and overall survival. However, no single study influenced the pooled OR qualitatively as indicated by the sensitivity analyses (data not shown).

Discussion

Epigenetic alterations have been reported to be involved in human cancerization through various mechanisms such as DNA methylation, histone modifications, small and long noncoding RNA, and chromatin architecture remodeling (27). With unclear significant influence of aberrant DNA sequence changes in human cancers and the irreversible and hereditary nature of epigenetic alterations (28), the presence of epigenetic alterations in noncancerous tissue suggests epigenetic alterations are involved in the field for cancerization. CpG island methylator phenotype (CIMP) is one of the most reported epigenetic alterations and is recognized as a major event in the origin of many cancers (27).

Prognostic value of CIMP has been reported for a variety of tumors. For example, CIMP + phenotype is significantly associated with a worse outcome in colorectal cancer (24) and is a predictor of poor prognosis to esophageal adenocarcinoma (25). CIMP is also a promising biomarker for the management of patients with gastric cancer (26). However, the prognostic role of CIMP status in glioma is unclear. In this study, we expanded upon previous tumor-associated studies of the prognostic value of CIMP to examine CpG islands associated with glioma.

We identified 12 published studies that included 2386 glioma patients in order to estimate the association between CIMP and other molecular and clinicopathological features in glioma. We found a trend toward more IDH1 mutations and 1p19q LOH and OD, and less GBM in CIMP-positive glioma than in CIMP-negative glioma. Moreover, we also demonstrated that CIMP did not show a correlation with MGMT promoter methylation, EGFR mutation, AOA, OA or gender, but CIMP-positive was significantly associated with longer overall survival. Taken together, these results suggest that CIMP may be used as an independent prognostic marker.

Heterogeneity in the relationship between CIMP status and certain clinicopathological features was significant in this study. One of the major confounding factors in the significant heterogeneity may be the lack of a standardized definition of CIMP, with the number, type and identity of genes employed in the selection panel different in every study. Until 2010, Noushmeh and colleagues (12) reported that in 272 gliomas in the context of The Cancer Genome Atlas (TCGA), three DNA methylation clusters were identified by GoledenGate and Infinium data. Cluster 1 formed a highly characteristic DNA methylation profile, showing GBM-specific methylation changes at a subset of loci, which was designated a glioma CpG island methylator phenotype (G-CIMP). Further, Noushmeh and colleagues validated that eight genes were formed at the G-CIMP loci. A sample was considered G-CIMP-positive when seven loci (ANKRD43, HFE, MAL, LGALS3, FAS-1, FAS-2 and RHO-F) were hypermethylated and one locus, DOCK5, was hypomethylated (28). Moreover, they also demonstrated that G-CIMP status was more common in the grade II and III glioma with improved survival (28). Until recently, classifications based on CIMP-positive vs. CIMP-negative, as well as classifications based on numbers of CIMP markers (CIMP-positive, CIMP-intermediate, CIMP-negative), were widely used in a variety of studies for glioma (29). Further studies are needed to validate a consistent CIMP definition.

So far, the value of CIMP as a predictive biomarker to guide prescription of neoadjuvant or adjuvant chemotherapy in glioma is uncertain. However, considering the influence of CIMP in therapeutic and clinical trial strategy may be necessary. It is clear that there is heterogeneity, even within other molecule biomarker combinations, which is likely to lead to potential prognostic value for individualized therapy. Aldap and colleagues (29) reported that glioma were divided into 3 distinct survival groups based on CIMP markers (CIMP-positive, CIMP-intermediate and CIMP-negative). Multivariate analysis showed that both IDH1 mutation and CIMP were independent predictors of outcome, suggesting CIMP and IDH1 mutation are potential prognostic biomarkers in glioma. Furthermore, G-CIMP tumor-related genes exhibited a demethylated pattern, and reversing the methylated pattern of G-CIMP tumor-related genes

may be a potential solution for glioma. Further work should be conducted to verify and confirm the clinical value of CIMP in glioma patients.

The main limitation of our study the spectrum of gene panel markers used for CIMP. Unfortunately, this is a common finding in CIMP studies, and other systematic reviews and meta-analyses in colorectal cancer (30) and gastric cancer (31,32) have accepted this relative limitation when performing pooled analyses. This study has significant strength in that it is a systematic review and meta-analysis of the currently available literature regarding the prognostic value of CIMPs in glioma.

Conclusions

In conclusion, this meta-analysis highlights that CIMP-positive glioma have their own molecular (such as IDH1 mutations) and clinicopathological features and a better prognosis for CIMP-positive glioma, suggesting CIMP could be used as an independent prognostic marker for glioma.

Abbreviations

CIMP, CpG island methylator phenotype; DNA, Deoxyribonucleic Acid; RNA, Ribonucleic Acid; LOH, 1oss of heterozygosis; GBM, Glioblastoma; OD, oligodendroglioma; AOA, anaplastic oligoastrocytomas; OA, oligoastrocytoma; MGMT, O6-methylguanine-DNA methyltransferase; EGFR, epidermal growth factor receptor; IDH1, isocitrate dehydrogenase 1;MINORS, Methodological Index for Non-Randomized Studies; CNS, central nervous system; WHO, World Health Organization; TNM, tumor–node–metastasis; TCGA, The Cancer Genome Atlas; NOA, Neurooncology Working Group; CGGA, Chinese Glioma Genome Atlas; OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HX: acquisition, analysis and interpretation of data, manuscript drafting; ST: analysis and interpretation of data; YX, HS, WL, PC, GY, CR and LS: manuscript revising; DY: drafting and critical appraisal of manuscript; LZ: study design, data interpretation, final approval of the manuscript. All authors have given final approval to this version of the manuscript to be published.

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Authors' information

As previously declared.

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Table

Due to technical limitations, Table 1 is provided in the Supplementary Files section.

Figures

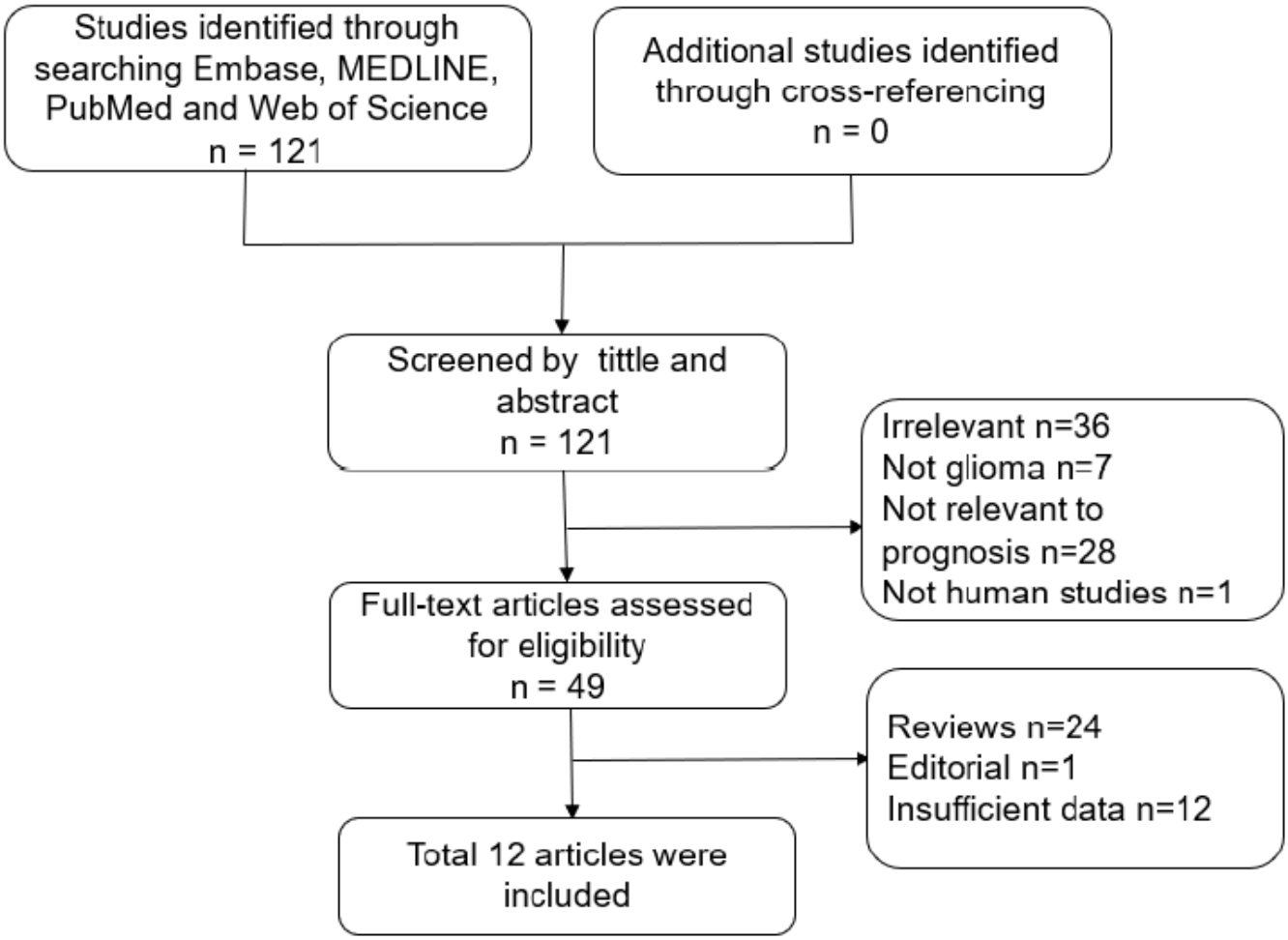

Figure 1

Flowchart of literature selection.

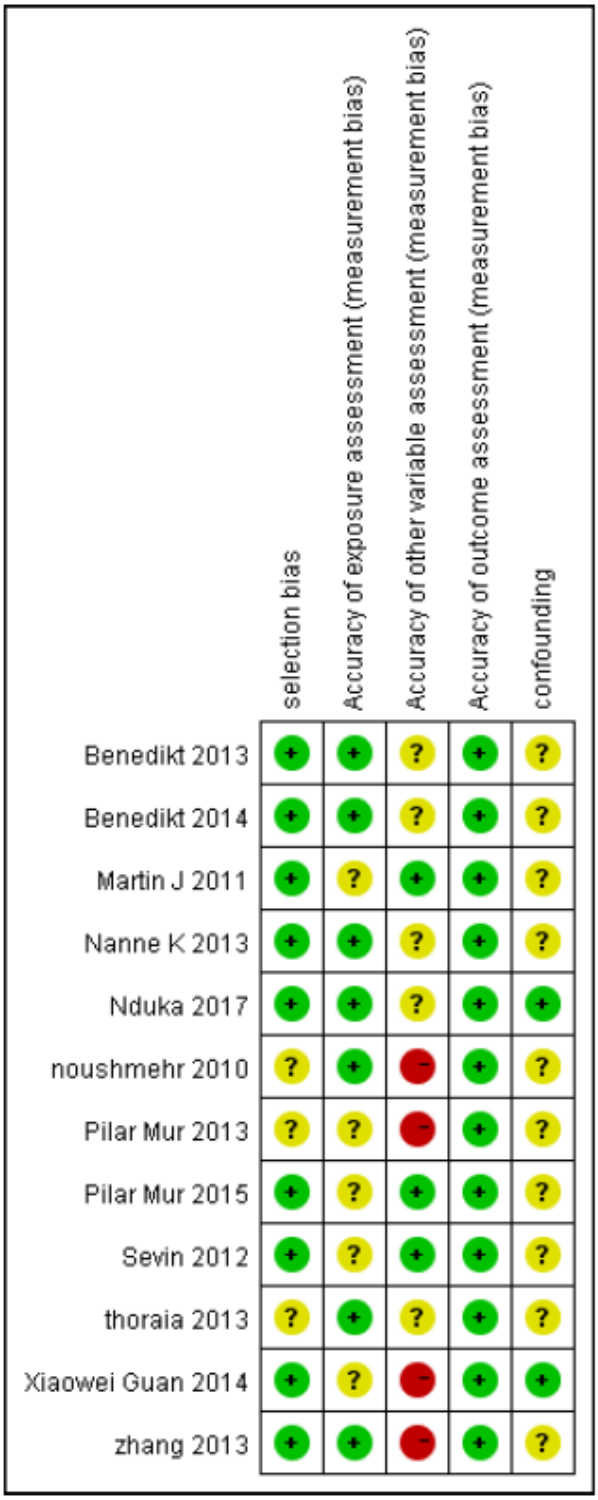

Figure 2

Risk of bias of each included study. Red cycle: study with high risk of bias; green cycle: study with low risk of bias; yellow cycle: study with insufficient information for assessing risk of bias.

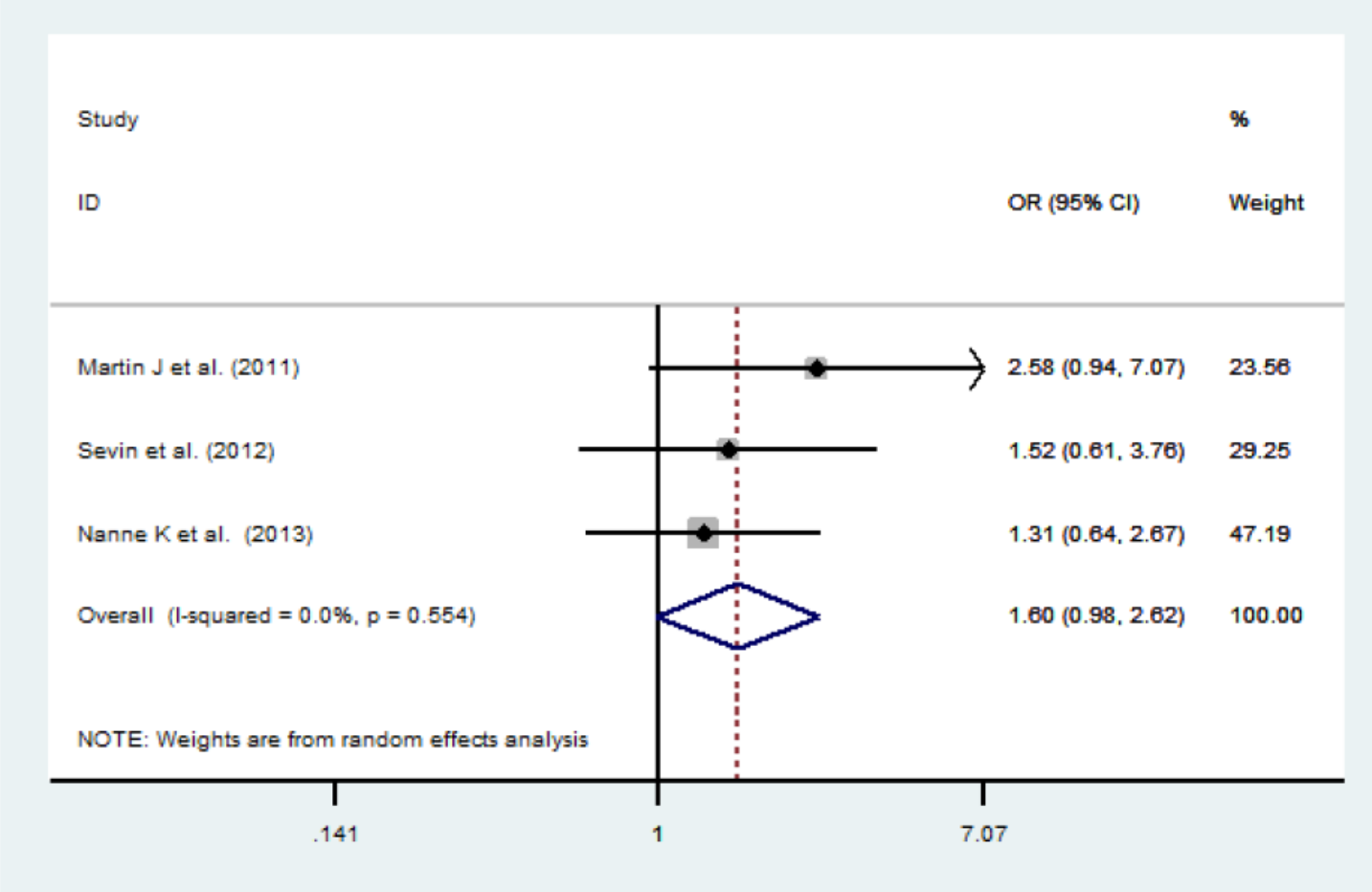

Figure 3

Meta-analysis of studies to investigate the gender in studies of glioma patients associated with CpG island methylator phenotype (CIMP). Random effect meta-analysis showing no significant difference in male gliomas.

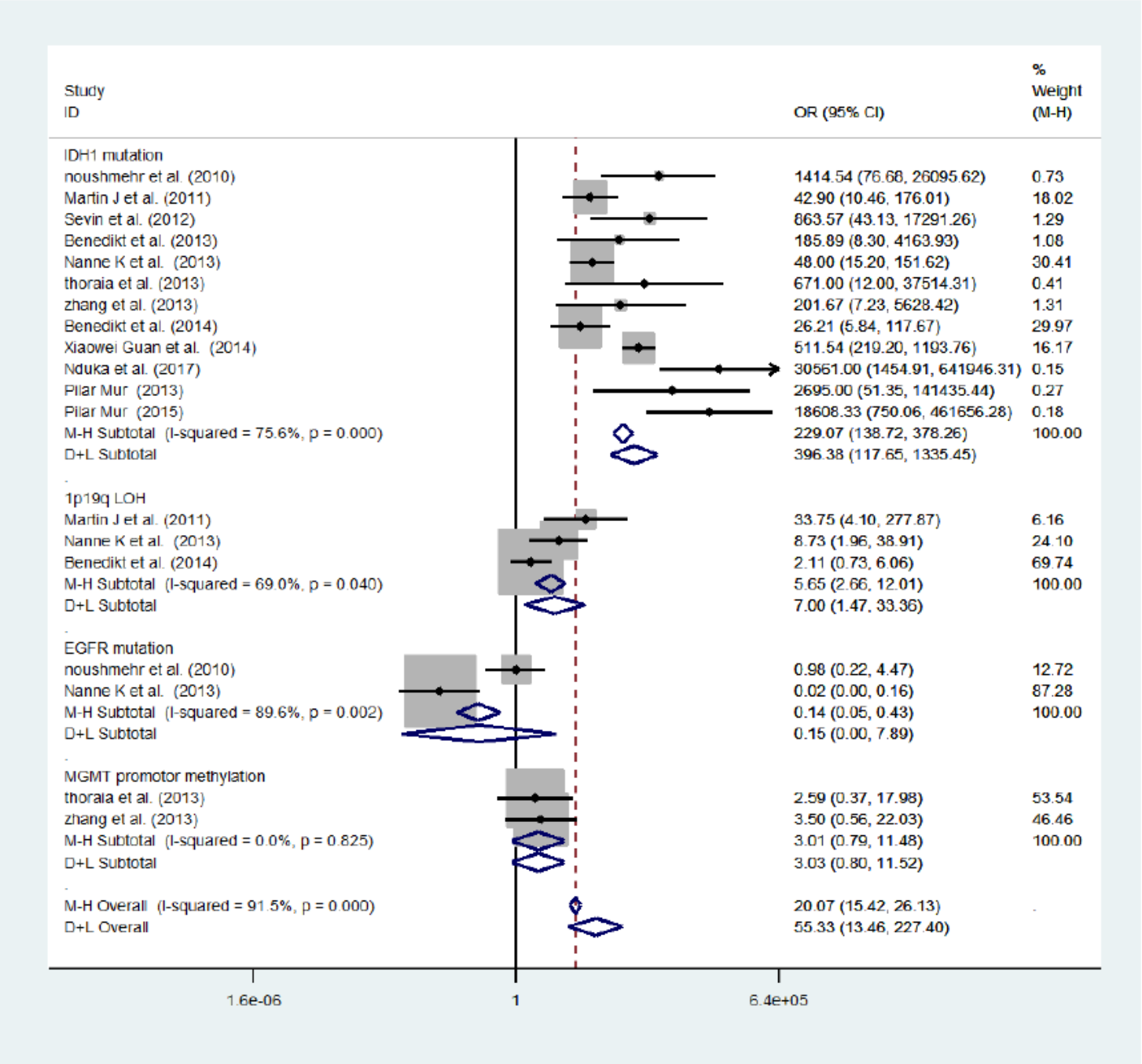

Figure 4

Meta-analysis of studies to investigate the molecular features in studies of glioma patients associated with CpG island methylator phenotype (CIMP). (a) Random effect meta-analysis showing more IDH1 mutations in CIMP-positive gliomas. (b) Random effect meta-analysis showing more 1p19q LOH in CIMP-positive gliomas. (c) Random effect meta-analysis showing no significant difference in EGFR mutation gliomas. (d) Fixed effect meta-analysis showing no significant difference in MGMT promoter methylation gliomas.

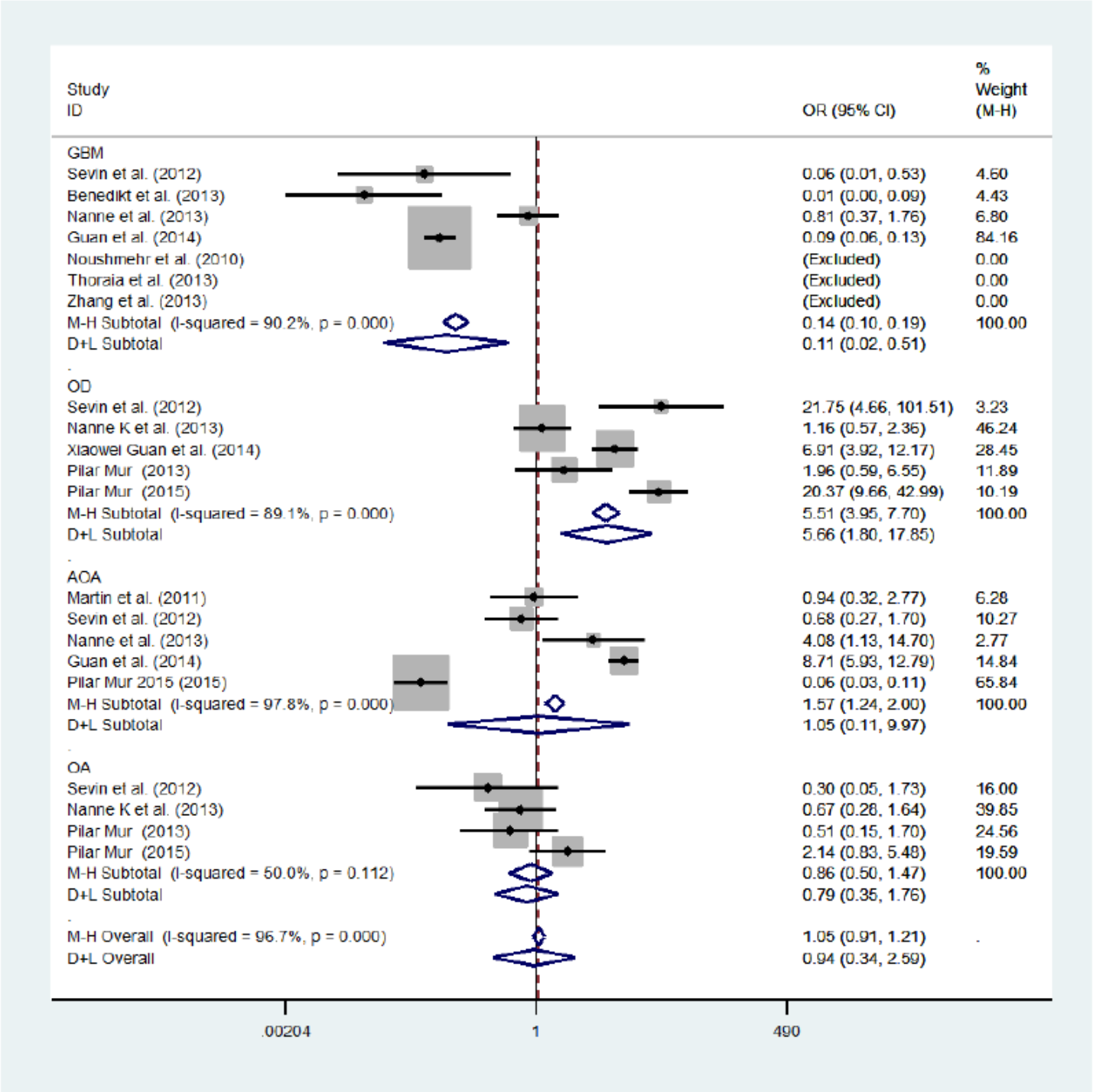

Figure 5

Meta-analysis of studies to investigate the histopathology features in studies of glioma patients associated with CpG island methylator phenotype (CIMP). (a) Random effect meta-analysis showing less GBM in CIMP-positive gliomas. (b) Random effect meta-analysis showing more OD in CIMP-positive gliomas. (c) Random effect meta-analysis showing no significant difference in oligoastrocytomas (AOA) gliomas. (d) Fixed effect meta-analysis showing no significant difference in oligoastrocytoma (OA) gliomas.

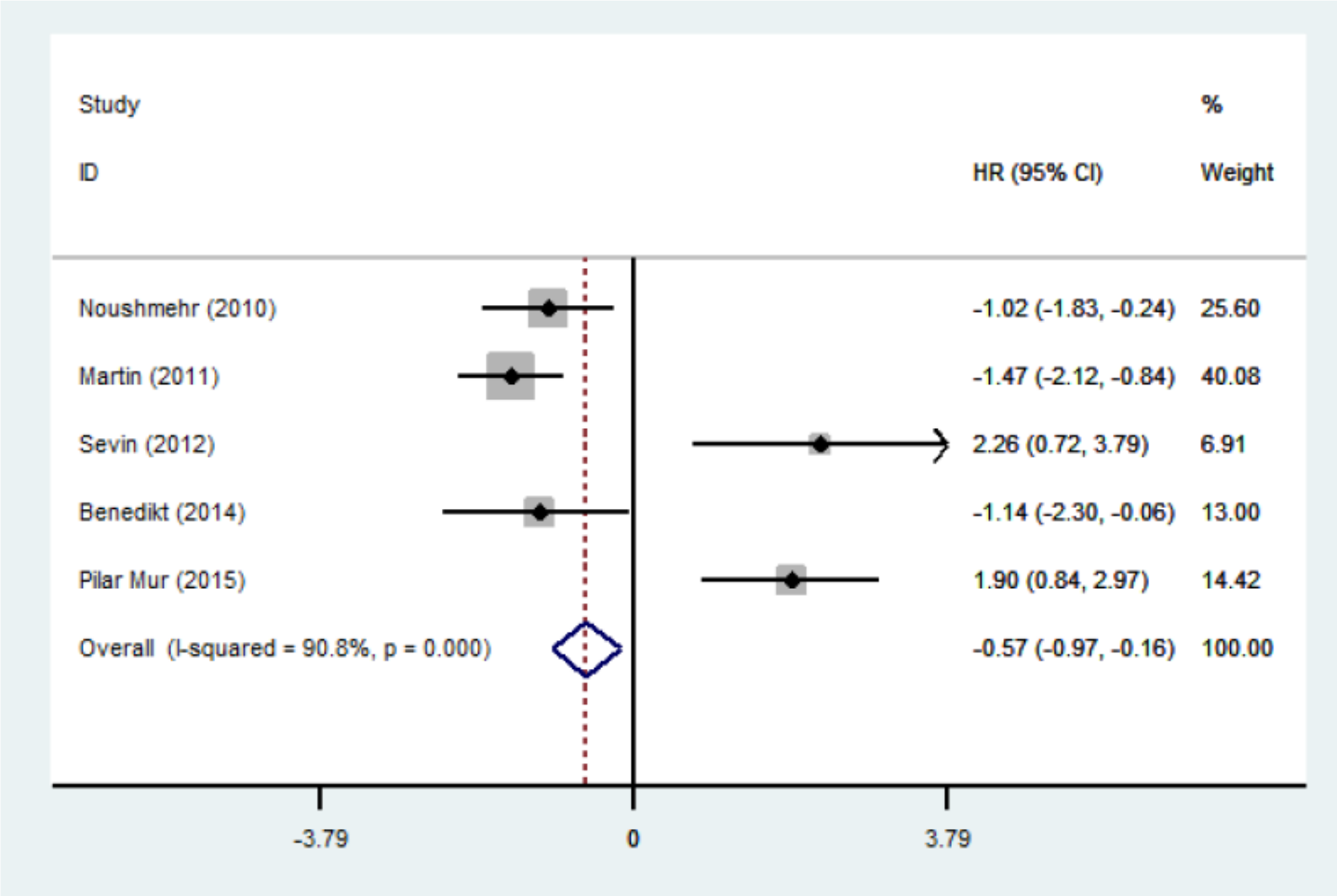

Figure 6

Meta-analysis of overall survival (OS) in studies of CIMP-positive vs CIMP-negative gliomas. Random effect meta-analysis showing longer OS in CIMP-positive gliomas.

Supplementary Files

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- table.docx