CIMP-positive glioma is associated with better prognosis
A systematic analysis

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Abstract
Background: CpG island methylator phenotype (CIMP) was closely related to the degree of pathological differentiation of tumors, and it's an important determinant of glioma pathogenicity. However, the molecular and pathological features of CIMP-positive glioma have not been fully elucidated. In addition, CIMP have been reported to be a useful prognostic marker in several human cancers, yet its prognostic value in gliomas is still controversial. Therefore, we aimed to evaluate gene mutations and pathological features of CIMP-positive glioma and explore the prognostic value of CIMP in gliomas.

Methods: We comprehensively searched PubMed, Embase, and MEDLINE for studies describing gene mutations, pathological features and overall survival of gliomas stratified by CIMP status. Odds ratios (OR), hazard ratios (HR), and their 95% confidence intervals (CI) were used to estimate the correlation between CIMP and the outcome parameters.

Results: Twelve studies with 2386 gliomas (1051 CIMP-positive and 1335 CIMP-negative) were included. Our results showed that CIMP was more frequent in isocitrinate dehydrogenase 1 (IDH1)-mutated gliomas (OR 229.07; 95% CI 138.72–378.26) and 1p19q loss of heterozygosity (LOH) gliomas (OR 5.65; 95% CI 2.66–12.01). Pathological analysis showed that CIMP was common in low-malignant oligodendroglioma (OR 5.51; 95% CI 3.95–7.70) with molecular features including IDH1 mutations and 1p19q LOH, but rare in glioblastoma (OR 0.14; 95% CI 0.10–0.19). However, CIMP showed no obvious correlation with anaplastic oligoastrocytomas (OR 1.57; 95% CI 1.24–2.00) or oligoastrocytomas (OR 0.79; 95% CI 0.35–1.76). Concerning the prognosis, we found that CIMP-positive gliomas had longer overall survival (HR 0.57; 95% CI 0.97–0.16) than CIMP-negative gliomas.

Conclusions: CIMP could be used as a potential independent prognostic indicator for glioma.

Abbreviations: AOA = anaplastic oligoastrocytoma, CI = confidence interval, CIMP = CpG island methylator phenotype, CNS = central nervous system, DNA = deoxyribonucleic acid, EGFR = epidermal growth factor receptor, GBM = glioblastoma, HR = hazard ratio, ICD-O = International Classification of Diseases for Oncology, IDH1 = isocitrate dehydrogenase 1, LGG = low-grade glioma, LOH = loss of heterozygosity, MGMT = O6-methylguanine-DNA methyltransferase, OA = oligoastrocytoma, OD = oligodendroglioma, OR = odds ratio, OS = overall survival, TCGA = The Cancer Genome Atlas, WHO = World Health Organization.

Keywords: CIMP (CpG island methylator phenotype), gene mutations, glioma, pathological features, prognosis, systematic review

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Glioma is the most common malignant tumor of the central nervous system (CNS) and adversely affects human health with poor overall survival.[1] In 2021, 24,530 new CNS cancers were reported in the United States, and 18,600 cases died of CNS cancer.[2] Surgery combined with postoperative radiotherapy and chemotherapy remains the standard treatment for glioma. However, the average survival time for high-grade gliomas is still only approximately 15 months.[3] With the development of molecular diagnosis and treatment technologies, prognostic markers play an increasingly important role in guiding clinical appropriate therapy and predicting tumor malignancy and prognosis.[4] In 2016, the World Health Organization (WHO) CNS classification used molecular biomarkers to classify gliomas for the first time, such as isocitrate dehydrogenase 1 (IDH1), 1p19q loss of heterozygosity (LOH), and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[5] In 2021, the WHO placed even more emphasis on molecular biomarkers.[6] Such molecular alterations are crucial in understanding the classification, diagnosis, management, and prognosis of gliomas.[7] However, the early diagnosis and prognosis of glioma are always a difficult point in the clinic. Thus, the identification of novel prognostic markers that are independent of the WHO molecular and histological tumor node metastasis staging systems for glioma are urgently needed.

CIMP, also called the CpG island methylator phenotype, has a high degree of methylation and is a distinct molecular characteristic of human cancer.[8] Frequent abnormal CpG island deoxyribonucleic acid (DNA) methylation in the promoter region of certain genes is an important mechanism of epigenetic suppression that silences tumor-suppressive genes, and affects normal functions of cell proliferation and apoptosis, DNA repair and cell cycle regulation.[9,10] Abnormal CIMP have been found in some aging normal cells and tumor cells such as gastric cancer and colorectal cancer.[11] Through broad-spectrum gene methylation analysis, it was found that the mutation of the above-mentioned molecular genes were closely related to DNA methylation alteration in gliomas. Although DNA methylation-induced epigenetic changes induce carcinogenesis, the prognostic value of CIMP in most human cancers remains unclear.

Many studies have reported that CIMP was closely related to the degree of pathological differentiation of tumors, suggesting that it may be a powerful determinant of tumor pathogenicity in glioma.[12,13] However, the molecular genetic characteristics, clinicopathological classification of CIMP-positive glioma have not been fully elucidated. Moreover, controversy surrounding the prognostic value of CIMP still exists in gliomas. Therefore, we aim to systematically analyze the relationship of between CIMP and gene mutations, pathological features, and prognosis in gliomas. To estimate the strength of this postulated relationship more accurately, the CIMP was determined to be either positive or negative, and we performed a systematic review and meta-analysis.

2. Methods

2.1. Search strategy

We performed a comprehensive literature search from the electronic databases, such as PubMed, Embase, and MEDLINE databases which focused on medicine, biomedical information and life science to identify relevant studies published up to February 2021. We utilized this search term combination: glioma and CIMP. Search results were combined in Endnote X8 to compile the reference manager database and duplicates were removed. Eligible studies were selected based on the inclusion and exclusion criteria. The reference lists of included studies were searched to identify other potential studies.

2.2. Study selection

The inclusion criteria were as follows: studies limited to human gliomas; studies evaluating the correlation between CIMP status and tumor node metastasis stage, gender, histology, molecular genes features or overall survival; sufficient published data to calculate the odds ratio (OR), hazard ratio (HR) and corresponding 95% confidence interval (CI). Furthermore, we excluded abstracts, editorials, letters, expert opinions, case reports, reviews, studies not written in English and impossible to extract the appropriate data.

2.3. Data extraction

Data extraction, based on the selection criteria, included the following information: 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, epidermal growth factor receptor (EGFR), MGMT, 1p19q LOH, gender, histology and overall survival in patients with and without CIMP. Outcomes were described as OR or HR with 95% CIs. We used the methods described by Tierney et al[12] and Guyot et al[13] to extract data from Kaplan-Meier curves.

2.4. Quality assessment

We assessed the quality of randomized and nonrandomized controlled trial studies using the Jadad Scale and the methodological index for non-randomized studies.[16,17] These criteria are not fully demonstrated in molecular studies, therefore, we set strict criteria for the included studies, for example, we did not exclude the single-aim study specimen of glioma, discussed tumors at all stages, and no exclusion based on molecular markers.

2.5. Statistical analysis

All statistical tests were performed using Stata Version 13.0 (Stata Corporation, College Station, TX). ORs and their 95% CIs were used to assess the relationship between the CIMP status and pathological and molecular parameters. For the quantitative aggregation of survival results, HRs and their 95% CIs were both used as the effective values. The HRs were calculated directly from the reported data by the number of events or from the Kaplan–Meier survival curve using Engauge Digitizer software (freely downloaded from http://sourceforge.net). $\chi^2$-based Q test ($P > .1$ was considered a lack of heterogeneity), and $I^2$ test ($I^2 \leq 50\%$ indicated low heterogeneity, and $I^2 > 50\%$ indicated substantial heterogeneity) was calculated for an objective measure of heterogeneity between studies. For low-heterogeneity group, each study was analyzed using the fixed-effects model. Otherwise, the random effects model was used. The significance of the pooled OR or HR was determined by Z test ($P < .05$ was considered statistically significant). Funnel plots were presented to estimate potential publication bias, and an asymmetric plot suggested possible publication bias. Funnel plot asymmetry was evaluated by Egger linear regression test, which is a linear regression approach measuring funnel plot asymmetry on the OR natural logarithm scale. As suggested by Egger, significance of the intercept was determined by the $t$ test ($P < .05$ considered representative of statistically significant publication bias).

3. Results

3.1. Study characteristics

The initial search from different 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 2386 patients with 1051 CIMP-positive and 1335 CIMP-negative, where CIMP was classified in a dichotomized fashion (CIMP-positive vs negative) (Table 1). Among the 12 studies, all reported IDH1 mutations, 3 reported 1p19q LOH, 2 reported EGFR mutations, 2 reported MGMT promoter methylation, 3 reported gender, nine reported histology, and 5 reported overall survival. Sample size in the studies ranged from 33 to 1122. Four studies used samples from The Cancer Genome Atlas (TCGA), [18,21,23,24] 2 from the Erasmus medical cancer brain tumor tissue bank, [20,23] 2 from the Spanish National Tumor Bank Network, [22,25] 2 from the Neurooncology Working Group trial in Germany, [19,27] and 1 from the Chinese Glioma Genome Atlas. [26] In addition, 1 study used data from a publicly available dataset [29] and another used mixed samples from 2 publicly available datasets and 1 newly generated dataset from MD Anderson. [28] For each included study, Figure 2 summarized the risk of bias from selection, exposure assessment, outcome assessment, other variable assessment, and confounding factors. Based on strict exclusion and inclusion criteria, studies with high risk in selection bias were excluded.

3.2. Gene mutations
The present research suggests that IDH1 mutation, 1p19q LOH, EGFR mutation and MGMT promoter methylation are newly added major molecular markers for genetic molecular typing of glioma. For the purpose 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; \( P < .00001 \); \( P_{\text{heterogeneity}} = .000 \)). Similarly, a higher risk of 1p19q LOH was observed in CIMP + glioma (OR 5.65; 95% CI 2.66–12.01; \( P = .01 \); \( P_{\text{heterogeneity}} = .040 \)), whereas EGFR mutation and MGMT promoter methylation did not show any differences between the 2 types of gliomas (OR 0.14; 95% CI 0.05–0.43; \( P = .35 \); \( P_{\text{heterogeneity}} = .002 \)) and (OR 3.01; 95% CI 0.79–11.48; \( P = .10 \); \( P_{\text{heterogeneity}} = .825 \)) (Fig. 3).

3.3. Pathological features
Extractable data related to pathological factors were gender and histopathology. The overall OR for the proportions of
**Table 1**
Summary of included study characteristics.

| Study | Country | Sample size, N | Stage | Male gender | Median | Gene panel | Lab method | CIMP classification | Marker threshold | CIMP prevalence, N (%) |
|-------|---------|----------------|-------|-------------|--------|------------|------------|---------------------|---------------------|------------------------|
| Houtan Noushmehr et al\[18\] | USA | 272 | II-IV | NR | mean 56 | DOCK5, ANKRD43, HFE, MAL, LGALS3, FAS-1, FAS-2, RHOF | MSP | CIMP± | CIMP+: ≥6/8 | 24 (8.8%) | OS |
| Martin J. van den Bent et al\[23\] | NR | 68 | NR | NR | 40 (58.5%) | PHC2, VM, KIAA0494, SLC20A1, FRD1, FABP5, DYNLT3, SPRY2, RUNX1, GRB10, SLC3A1, FNBP1, BCT1, C2orf13, ITOH, MBNL3, APNT12 | MartlyLight | CIMP± | HOPACH clustering red | 31 (45.6%) | OS |
| Sevin Turcan et al\[24\] | USA | 81 | II-IV | 48 (59.3%) | PHC2, VM, KIAA0494, SLC20A1, FRD1, FABP5, DYNLT3, SPRY2, RUNX1, GRB10, SLC3A1, FNBP1, BCT1, C2orf13, ITOH, MBNL3, APNT12 | MSP | CIMP± | K-means consensus clustering red | 49 (60.5%) | OS |
| Benedikt Wiestler et al\[19\] | German | 126 | NR | NR | >=65 | DOCK5, ANKRD43, HFE, MAL, LGALS3, FAS-1, FAS-2, RHOF | MSP | CIMP± | DOCK5 hypomethylated and ≥5/remaining 7 | 7 (5.6%) | OS, EFS |
| Nanne K. Kloosterhof et al\[20\] | NR | 138 | II-IV | 87 (63.0%) | mean 44 | IGS-16, IGS-18, IGS-23, IGS-17, IGS-9 | MSP | CIMP± | CIMP+: >5/remaining 7 | 85 (61.6%) | NR |
| Thoraia Shinawi et al\[21\] | NR | 35 | IV | 21 (60%) | NR | ANKRD43, DOCK5, LGALS3, FAS, HFE, MAL, RHOF | MSP | CIMP± | HOPACH clustering red | 5 (14.3%) | OS |
| Wei Zhang et al\[22\] | China | 33 | IV | 22 (59.42%) | ANKRD43, DOCK5, HFE, MAL, LGALS3, FAS-1, FAS-2, RHOF | MSP | CIMP± | CIMP+: ≥3/7 | 6 (18.2%) | NR |
| Benedikt Wiestler et al\[27\] | German | 115 | NR | NR | mean 42 | ANKRD43, DOCK5, HFE, MAL, LGALS3, FAS-1, FAS-2, RHOF | MSP | CIMP± | CIMP+: consensus cluster 1 (n = 12 tumors) red | 91 (79.1%) | OS, PFS |
| Xiaowei Guan et al\[28\] | USA | 716 | II-IV | NR | NR | The Verhaak 840-gene signature | MSP | CIMP± | CIMP+: DOCK5 hypomethylated and ≥5/remaining 7 | 208 (40.9%) | OS |
| Nduka M. Amankulor et al\[29\] | USA | 500 | II-III | NR | NR | DOCK5, ANKRD43, HFE, MAL, LGALS3, FAS-1, FAS-2, RHOF | MSP | CIMP± | CIMP+: 1503 CIMP classifier probes red | 419 (83.8%) | NR |
| Pilar Mur et al\[22\] | Spanish | 55 | II-III | 31 (56.4%) | TRPM4, DRG2, ASL, C1orf164, FLJ1286, ORELD1 | MethyLight | CD-CIMP+/CIMP+/CIMP− | CD-CIMP+: ≥24.7% total probes; CIMP+: ≥21.4% total probes | 38 (69.1%) | OS |
| Pilar Mur et al\[25\] | USA | 247 | II-IV | NR | <60y/o: N = 134; ≥60y/o: N = 53 | QpG165, QpG25, STP27 | MSP | CIMP± | QpG165 methylation | 88 (35.6%) | OS |

CD-CIMP+ = codeleted-CIMP+, CIMP = CpG island methylator phenotype, EFS = events-free survival, Hopach = hierarchical ordered partitioning and collapsing hybrid, MSP = methylation-specific polymerase chain reaction, NR = not reported, OS = overall survival, PFS = progression-free survival, y/o = years old.
males in CIMP + versus CIMP- gliomas was 1.60 (95% CI 0.98–2.62; \( P = .06 \); \( P_{\text{heterogeneity}} = 0.554 \); Fig. 4). The International Classification of Diseases for Oncology (ICD-O) is the most important standard classification in clinical medicine, and is used by all medical professionals. The ICD-O topography codes largely correspond to those in the tenth edition of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-10).\(^{[5,30]}\) WHO classified gliomas into low-grade gliomas (LGG) with low malignancy and high-grade gliomas. Compared to high-grade gliomas, such as anaplastic oligoastrocytomas (AOA, WHO Grade III, ICD-O 9382/3) or glioblastoma (GBM, WHO Grade IV, ICD-O 9440/3), LGG including oligoastrocytomas (OA, WHO Grade II, ICD-O 9382/3) and oligodendroglioma (OD, WHO Grade II, ICD-O 9450/3) had better overall survival prognosis.\(^{[30]}\) Our analysis showed that GBM and OD in the CIMP + and CIMP- groups achieved statistical significance [(OR 0.14; 95% CI 0.10–0.19; \( P = .005 \), \( P_{\text{heterogeneity}} = 0.000 \)] and [(OR 5.51; 95% CI 3.95–7.70; \( P = .003 \), \( P_{\text{heterogeneity}} = 0.000 \)], whereas no differences were shown for AOA and OA [(OR 1.57; 95% CI 1.24–2.00; \( P = .97 \), \( P_{\text{heterogeneity}} = 0.000 \)] and [(OR 0.79; 95% CI 0.35–1.76; \( P = .54 \), \( P_{\text{heterogeneity}} = 0.112 \); Fig. 5).  

### 3.4. Overall survival and publication bias

The prognostic role of CIMP status has been evaluated in various tumors, such as colorectal cancer, hepatocellular carcinoma and gastric cancer.\(^{[31–33]}\) In order to investigate whether CIMP status has prognostic value in glioma, we pooled 5 studies that has completed the correlation analysis between the overall survival of individuals and CIMP + or CIMP- gliomas. We found that CIMP + glioma was significantly associated with longer overall survival (HR 0.57; 95% CI 0.97-0.16; \( P = .003 \); \( P_{\text{heterogeneity}} = 0.000 \); Fig. 6).

Begg funnel plot was used to assess publication bias. Heterogeneity comparison of 12 combined studies showed that heterogeneity existed in certain analyses such as \( IDH1 \) 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).

### 4. Discussion

Epigenetic alterations have been reported to be involved in the process of tumor carcinogenesis through various mechanisms such as histone modifications, DNA methylation, small and long noncoding ribonucleic acid, and chromatin architecture remodeling.\(^{[34]}\) With the unclear significant impact of aberrant DNA sequence changes in human cancers and the irreversible and hereditary characteristics of epigenetic alterations,\(^{[35]}\) the presence of epigenetic alterations in noncancerous tissues suggests that epigenetic alterations are involved in the field of carcinization. CIMP is 1 of the most reported epigenetic alterations and is recognized as a major event in the origin of many cancers.\(^{[8,34]}\) Prognostic value of CIMP in a variety of tumors has been reported.\(^{[36,37]}\) For example, global genome hypermethylation, resulting in the switch off of tumor suppressor genes, indicated as CIMP, which is closely associated with a worse outcome in colorectal cancer.\(^{[31,38]}\) In addition, CIMP, an indicator of poor prognosis, is related to a higher mutation burden of \( bromo-domain-containing protein, DNA damage-induced apoptosis suppressor, and nicotinamide adenine dinucleotide phosphate oxidase 1 \) in hepatocellular carcinoma patients.\(^{[32]}\) CIMP is also a potential biomarker for the treatment of patients with gastric cancer.\(^{[33]}\) However, the prognostic role of the CIMP status in gliomas is uncertain. In this study, we expanded upon previous tumor-associated research on the prognostic value of CIMP to examine CpG islands associated with glioma. Several researches have suggested that the potential cancer-specific mutated driver genes include \( IDH1/2 \) and \( H3 histone \) \( (H3F3A) \).\(^{[39]}\) It has been well documented that CIMP of genes is associated with survival in glioma patients. The ADP-ribosylation factor family plays an oncogenic role in the development of gliomas. One study showed that AL9R hypermethylation can predict...
Figure 3. Meta-analysis of studies to investigate the molecular features of glioma patients associated with CIMP. CI = confidence interval, CIMP = CpG island methylator phenotype, EGFR = epidermal growth factor receptor, IDH1 = isocitrate dehydrogenase 1, LOH = loss of heterozygosis, MGMT = O6-methylguanine-DNA methyltransferase, OR = odds ratio.

Figure 4. Meta-analysis of studies to investigate the gender of glioma patients associated with CIMP. CI = confidence interval, CIMP = CpG island methylator phenotype, OR = odds ratio.
favorable OS and progression-free survival in patients with LGG and it could be as a prognostic biomarker for LGG.[40] In addition, the TP73 gene encodes protein 73. Chen et al confirmed that 8 methylation sites of TP73 gene CpG island were significantly positively associated with better OS and progression-free survival of patients diagnosed with grade II/III glioma.[41] EMILIN2 is an extracellular matrix protein, and LGG data from TCGA discovered that the EMILIN2 expression, negatively correlated to the EMILIN2 methylation, could predict a poor prognosis.[42] However, another research found that the inhibition of methylated miR-338-5p in the promoter region was related to AOA invasion.[43] It was because of these inconsistent prognostic results that we further used a meta-analysis to research the prognostic value of CIMP in gliomas.

We identified 12 published studies, including 2386 glioma patients to assess the correlation between CIMP and gene mutations or pathological features in gliomas. More IDH1 mutations, 1p19q LOH and OD, and less GBM were found in CIMP-positive glioma than in CIMP-negative glioma. Moreover, we also identified 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 in glioma patients.

Heterogeneity in the relationship between the CIMP status and certain pathological features was significant in this study. One of the main confounding factors of 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 each study. Until 2010, Noushmeh[18] reported that in 272 gliomas in the context of TCGA, 3 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 as the glioma-CIMP (G-CIMP). Further, Noushmeh and colleagues validated that 8 genes were formed at the G-CIMP loci. A sample was considered G-CIMP-positive when 7 loci (ANKRD43, HFE, MAL, LGALS3, FAS-1, FAS-2, and RHO-F) were hypermethylated and 1 locus, DOCK5, was hypomethylated. Moreover, they also demonstrated that the G-CIMP status was more common in the grade II and III glioma with improved survival. Until recently, classifications based on CIMP-positive versus CIMP-negative, as well as classifications based on IDH1-mutant (G-CIMP-high, G-CIMP-low subgroups), were widely used in a variety of studies for glioma. Further studies are needed to verify a consistent CIMP definition.

So far, the value of CIMP as a predictive biomarker to guide the 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. Malta reported that glioma were divided into 2 clinically relevant subsets (CIMP-high, CIMP-low subgroups), were widely used in a variety of studies for glioma. Further studies are needed to verify a consistent CIMP definition.

5. Conclusions
In conclusion, this meta-analysis highlights that there are specific molecular (such as IDH1 mutations and 1p19q LOH) and pathological features and a better prognosis in CIMP-positive gliomas, suggesting that CIMP could be used as an independent prognostic marker for glioma.

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