IDH1/IDH2 Mutations Define the Prognosis and Molecular Profiles of Patients with Gliomas: A Meta-Analysis

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Abstract

Background: Isocitrate dehydrogenase isoforms 1 and 2 (IDH1 and IDH2) mutations have received considerable attention since the discovery of their relation with human gliomas. The predictive value of IDH1 and IDH2 mutations in gliomas remains controversial. Here, we present the results of a meta-analysis of the associations between IDH mutations and both progression-free survival (PFS) and overall survival (OS) in gliomas. The interrelationship between the IDH mutations and MGMT promoter hypermethylation, EGFR amplification, codeletion of chromosomes 1p/19q and TP53 gene mutation were also revealed.

Methodology and Principal Findings: An electronic literature search of public databases (PubMed, Embase databases) was performed. In total, 10 articles, including 12 studies in English, with 2,190 total cases were included in the meta-analysis. The IDH mutations were frequent in WHO grade II and III glioma (59.5%) and secondary glioblastomas (63.4%) and were less frequent in primary glioblastomas (7.13%). Our study provides evidence that IDH mutations are tightly associated with MGMT promoter hypermethylation (P < 0.001), 1p/19q codeletion (P < 0.001) and TP53 gene mutation (P < 0.001) but are mutually exclusive with EGFR amplification (P < 0.001). This meta-analysis showed that the combined hazard ratio (HR) estimate for overall survival and progression-free survival in patients with IDH mutations was 0.33 (95% CI: 0.25–0.42) and 0.38 (95% CI: 0.21–0.68), compared with glioma patients whose tumours harboured the wild-type IDH. Subgroup analyses based on tumour grade also revealed that the presence of IDH mutations was associated with a better outcome.

Conclusion: Our study suggests that IDH mutations, which are closely linked to the genomic profile of gliomas, are potential prognostic biomarkers for gliomas.

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Introduction

Gliomas, which are the most common primary intracranial tumours, are classified as grade I to grade IV, according to the 2007 WHO Classification of Tumours of the Central Nervous System [1]. Despite advances in diagnostic and therapeutic techniques, the prognosis for most glioma patients remains dismal. Histomorphological criteria alone are not sufficient to predict the clinical outcome of gliomas. Thus, new avenues must be taken to integrate the molecular advances with the histological assessment of gliomas.

Recently, the sequencing of human gliomas has identified gene mutations in the isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) genes [2–4]. IDH mutations are relatively glioma-specific. However, IDH1 and IDH2 mutations are also found in acute myeloid leukaemia (AML) [5]. The IDH1 gene mutations are found frequently in malignant gliomas and are likely to be involved in the early stage of gliomagenesis, even before TP53 mutations or loss of 1p and 19q [6]. The IDH1 mutations occur in the highly conserved residue R132, which is in the catalytic domain, where it binds to its substrate. The mutations in IDH2 consistently occur at the analogous amino acid R172 [7], which is functionally equivalent to amino acid 132 of IDH1. IDH1 mutations have been found in approximately 80% of grades II-III gliomas and secondary glioblastomas but have been found in less than 10% of primary glioblastomas [2,4,6]. The IDH2 mutations have also been described in gliomas, although at a lower frequency [4,8]. The IDH1 and IDH2 enzymes catalyse oxidative decarboxylation of isocitrate into α-ketoglutarate (aKG), thereby reducing NADP to NADPH [9,10]. The tumourigenic potential of a mutant IDH protein is under intense investigation. First, a heterozygous point mutation in codon 132 impairs the interaction of the enzyme with isocitrate both sterically and electrostatically, and the mutant IDH1 molecules dominantly inhibit the activity of wild-type IDH1 by forming a catalytically inactive heterodimer [11]. Second, the mutations cause reduced formation of aKG and decreased
cytoplasmic levels of aKG increase levels of hypoxia-inducible factor subunit HIF-1-alpha [11–13], a component of the hypoxia-responsive transcription factor complex that facilitates tumour angiogenesis and growth. Third, heterozygous IDH mutations confer neomorphic enzyme activity rather than inactivating the enzyme; the mutant enzyme converts aKG to 2-hydroxyglutarate (2-HG) in the process of consuming NADPH [14]. The excess accumulation of 2-HG has been shown to be associated with tumour progression and leads to an elevated risk of malignant gliomas [14,15].

Recently, an increasing number of studies have evaluated the relative prognostic impact of IDH mutations and the clinical outcome of gliomas [16–25], with conflicting results due to the relatively small sample sizes in the studies. Here, we performed a meta-analysis to further clarify the prevalence of IDH mutations, their relationship to other genetic alterations and their impact on prognosis for glioma patients.

Methods

Identification of relevant studies

A comprehensive literature search of the PubMed and Embase databases (last search updated in October 2012) was conducted to identify all studies that analysed the prognostic role of IDH mutations in patients with gliomas. The following keywords were used in various combinations: ‘prognosis’, ‘prognostic’, ‘survival’, ‘IDH1’ and ‘IDH2’. The reference lists from the relevant original articles and review articles were also examined for additional relevant publications.

Study eligibility

The studies eligible for inclusion in this meta-analysis had to meet the following criteria: (1) proven diagnosis of gliomas in humans; (2) evaluate the association between IDH mutations and the prognosis of glioma patients, e.g., progression-free survival (PFS) and overall survival (OS); (3) have a hazard ratio (HR) for OS or PFS, according to IDH mutations, either reported directly in the study or calculated from the data presented; (4) be the most recent or complete report if the same author or group reported results obtained from the same patient population in more than one article; and (5) be written in English.

Reports considered ineligible for the meta-analysis were (1) reviews; (2) case reports; (3) about the association between another marker and outcome and data for IDH was not presented; and (4) lacking key information such as hazard ratio (HR), 95% confidence interval (CI) or survival curve.

Definitions and Data Extraction

The PFS was defined as the time interval between the date of surgery and the date of tumour progression or the end of follow-up. The OS was defined as the time interval between the date of surgery and the end of follow-up or death. The following data from all eligible publications were extracted: the first author’s name, year of publication, country, patient ethnicity, sample size, tumour grade, mutations and prognostic outcomes (PFS and OS). Any discrepancies were resolved through discussion amongst the authors.

Statistical Analysis

The correlations of IDH1/2 mutations with MGMT promoter hypermethylation, EGFR amplification, codelletion of chromosomes 1p/19q and TP53 gene mutation in gliomas were analysed using a two-sided \( \chi^2 \) test. To estimate the overall effects, the outcomes were calculated as hazard ratios (HRs) with their respective 95% confidence intervals (CIs). Subgroup analyses were performed according to tumour grade. The impact of IDH1/2 mutations on survival was considered statistically significant if the 95% CI for the summary HR did not overlap 1.0. By convention, an observed HR greater than 1 implied a worse prognosis for the group with IDH mutations. The statistical significance of the pooled HR was determined using the \( z \) test \(( P<0.05 \) was considered statistically significant). When HRs were not provided in a paper, the estimated value was derived from other data using the methods described by Tierney et al. [26]. Moreover, when univariate and multivariate analyses of PFS and/or OS were available, the multivariate analyses were combined because the survival response was influenced by multiple factors. The heterogeneity between the studies was tested using the Q statistic. When the Q-test reported a \( P \) value greater than 0.05, the fixed-effects model (Mantel–Haenszel method) was used; otherwise, the random effects model was chosen, according to the DerSimonian–Laird method. The \( F \)-statistic was also calculated to efficiently test heterogeneity \(( F<25\%, \) no heterogeneity; \( F=25–50\%, \) moderate heterogeneity; and \( F>50\%, \) large or extreme heterogeneity). Finally, a funnel plot and Egger’s linear regression test were used to assess the potential publication bias [27,28]. All \( P \) values were two-sided. Statistical calculations were all performed using STATA version 11.0 software (Stata Corporation, College Station, TX).

Results

Studies included in the meta-analysis

Figure 1 shows the study selection procedure. By the initial literature search, 253 studies were relevant to the search terms. Of which, 175 were excluded because of obvious irrelevance by the step of screening the title and abstract. By reading through the full texts of the remaining and 68 studies were excluded (27 articles lacked usable data, 2 studies were overlapping data sets, 20 studies were not directly related to specific outcomes, 19 articles were not about IDH mutations). Overall, 10 articles, including 12 studies, published between 2009 and 2012 were used in the pooled analysis. Table 1 lists the studies and their main characteristics. In the 12 studies, the range of the sample size was 49 to 407 patients. The 12 studies collected in this meta-analysis included 6 studies on Asians and 6 studies on Caucasians. One study examined grade II tumours, four studies examined grade III tumours, four studies examined grade IV tumours, one study examined grades II-IV tumours and two studies examined tumours of all grades. An HR for PFS and OS could be extracted from 7 and 11 of the studies, respectively. All survival data were available through multivariate analysis.

Correlation of IDH mutations with genetic aberrations and grade of the gliomas

The \( \chi^2 \) test were carried out to analyze the significance of the correlation of IDH mutations with other genetic alterations and glioma grade.

The frequencies of MGMT promoter hypermethylation, EGFR amplification, codelletion of chromosomes 1p/19q and TP53 gene mutation and their relationship with IDH mutations are shown in Table 2. We provide evidence that IDH mutations are closely associated with 1p/19q codelletion \(( P<0.001 \) ), TP53 gene mutation \(( P<0.001 \) ), and MGMT promoter hypermethylation \(( P<0.001 \) ), but they are mutually exclusive with EGFR amplification \(( P<0.001 \) ). These data indicate that the IDH mutation rate is linked to the genomic profile of gliomas.
We found a strong correlation of IDH mutations with tumour grade. The IDH mutations were present in the majority of grades II and III glial tumours (59.5%) but were rare in primary GBM (7.13%, \( P = 0.001 \); Table 2). A higher rate of IDH mutations were found in secondary GBM (63.4%) than in primary GBM (7.13%, \( P = 0.001 \); Table 2).

**Prognostic value of IDH mutations**

The pooled results of the meta-analysis showed that the IDH mutations were independent prognostic markers for improved OS (HR = 0.33, 95% CI: 0.25–0.42, \( P_{\text{heterogeneity}} = 0.204 \); Figure 2) and PFS (HR = 0.38, 95% CI: 0.21–0.68, \( P_{\text{heterogeneity}} = 0.000 \); Figure 3) in gliomas (Table 3). The subgroup analysis was performed according to tumour grade and ethnicity. In grades III and IV gliomas with IDH mutations, the overall HR for OS was 0.19 (95% CI: 0.11–0.35, \( P_{\text{heterogeneity}} = 0.579 \) and 0.39 (95% CI: 0.27–0.56, \( P_{\text{heterogeneity}} = 0.065 \)), respectively, compared with wild-type IDH (Table 3). IDH mutations were a significant prognostic marker for PFS in grade III (HR = 0.17, 95% CI: 0.03–0.58, \( P_{\text{heterogeneity}} = 0.000 \)) and grade IV gliomas (HR = 0.67, 95% CI: 0.40–1.13, \( P_{\text{heterogeneity}} = 0.000 \); Table 3). In Asians and Caucasians, the overall HR for OS was 0.37 (95% CI: 0.25–0.56, \( P_{\text{heterogeneity}} = 0.066 \)) and 0.30 (95% CI: 0.21–0.41, \( P_{\text{heterogeneity}} = 0.684 \)), respectively (Table 3). IDH mutations were a significant prognostic marker for PFS in Asians (HR = 0.11–0.34, \( P_{\text{heterogeneity}} = 0.000 \); Table 3) and Caucasians (HR = 0.52, 95% CI: 0.37–0.74, \( P_{\text{heterogeneity}} = 0.512 \); Table 3).

**Table 1. Characteristics of studies included in the meta-analysis.**

| First Author | Year | Country | Ethnicity | Case | Grade | Mutations | OS HR(95%CI) | PFS HR(95%CI) |
|--------------|------|---------|-----------|------|-------|-----------|--------------|--------------|
| Yan          | 2012 | China   | Asian     | 118  | IV    | IDH1      | 0.62(0.32–1.22) | 0.62(0.34–1.11) |
| Mukasa       | 2012 | Japan   | Asian     | 61   | II    | IDH1/2    | 0.33(0.07–1.53) | 0.60(0.17–2.15) |
| Mukasa       | 2012 | Japan   | Asian     | 49   | III   | IDH1/2    | 0.32(0.10–0.95) | 0.06(0.01–0.24) |
| Mukasa       | 2012 | Japan   | Asian     | 125  | IV    | IDH1/2    | 0.91(0.26–2.42) | 0.90(0.26–2.43) |
| Li           | 2012 | China   | Asian     | 77   | III   | IDH1      | 0.15(0.04–0.66) | NA            |
| Shibahara    | 2011 | Japan   | Asian     | 115  | III   | IDH1/2    | 0.16(0.07–0.37) | 0.11(0.06–0.23) |
| Christensen  | 2011 | America | Caucasian | 131  | I-IV  | IDH1/2    | 0.27(0.10–0.72) | NA            |
| Bleeker      | 2010 | Netherland | Caucasian | 109  | IV    | IDH1      | 0.21(0.09–0.47) | NA            |
| Wick         | 2009 | Germany | Caucasian | 318  | III   | IDH1/2    | NA            | 0.47(0.30–0.77) |
| Sanson       | 2009 | France  | Caucasian | 404  | II–IV  | IDH1      | 0.30(0.16–0.56) | 0.59(0.36–0.96) |
| Nobusawa     | 2009 | Switzerland | Caucasian | 407  | IV    | IDH1/2    | 0.29(0.16–0.51) | NA            |
| Gravendeel   | 2009 | Netherland | Caucasian | 276  | I-IV  | IDH1      | 0.55(0.21–1.45) | NA            |

Abbreviations: OS, overall survival; PFS, progression-free survival. 

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gliomagenesis and patient prognosis. IDH1 is localised to the cytoplasm and peroxisome, whereas IDH2 resides in the mitochondria. The \textit{IDH} genes encode redox enzymes that decarboxylate isocitrate to \( \alpha \)-ketoglutarate (aKG), resulting in the production of NADPH and participation in cellular metabolic processes such as glucose sensing, lipid metabolism, and oxidative

| Parameters | IDH mutation/wild type | Total (%) | \( P \) |
|------------|------------------------|-----------|---------|
| Yan, 2012 | NA 6/109 | 4/15 | 10/75 | NA 11/172 | 14/363 | 64/833 | 7.13 |
| Mukasa, 2012 | NA 6/13 | 6/1 | 8/5 | NA 10/3 | 22/8 | 52/30 | 63.4 | <0.001 |
| Li, 2012 | NA 62/110 | 25/22 | 76/39 | 47/22 | NA 133/62 | 144/77 | NA 487/332 | 59.5 | <0.001 |
| Shibahara, 2011 | NA 6/13 | 6/1 | 8/5 | NA 10/3 | 22/8 | 52/30 | 63.4 | <0.001 |
| Christensen, 2011 | NA 62/110 | 25/22 | 76/39 | 47/22 | NA 133/62 | 144/77 | NA 487/332 | 59.5 | <0.001 |
| Bleeker, 2010 | NA 6/13 | 6/1 | 8/5 | NA 10/3 | 22/8 | 52/30 | 63.4 | <0.001 |
| Wick, 2009 | NA 62/110 | 25/22 | 76/39 | 47/22 | NA 133/62 | 144/77 | NA 487/332 | 59.5 | <0.001 |
| Sanson, 2009 | NA 6/13 | 6/1 | 8/5 | NA 10/3 | 22/8 | 52/30 | 63.4 | <0.001 |
| Nobusawa, 2009 | NA 62/110 | 25/22 | 76/39 | 47/22 | NA 133/62 | 144/77 | NA 487/332 | 59.5 | <0.001 |

Genetic aberrations

| Parameters | MGMT methylated | Total (%) | \( P \) |
|------------|-----------------|-----------|---------|
| + | 8/17 | 35/38 | NA 69/18 | NA NA 70/63 | NA 182/176 | 57.2 | <0.001 |
| – | 4/48 | 7/52 | NA 7/21 | NA NA 16/45 | NA 34/176 | 17.0 |

| Parameters | EGFR amplification | Total (%) | \( P \) |
|------------|---------------------|-----------|---------|
| + | 9/74 | NA 8/13 | 0/5 | NA NA 1/89 | 2/115 | 20/296 | 6.33 | <0.001 |
| – | 10/22 | NA 68/26 | 27/28 | NA NA 154/160 | 29/214 | 288/450 | 39.0 |

| Parameters | 1p19q codeletion | Total (%) | \( P \) |
|------------|------------------|-----------|---------|
| + | NA 33/3 | NA 30/4 | NA NA 45/5 | NA 108/129 | 90.0 | <0.001 |
| – | NA 42/173 | NA 46/35 | NA NA 110/244 | NA 198/452 | 30.5 |

| Parameters | TP53 mutation | Total (%) | \( P \) |
|------------|--------------|-----------|---------|
| + | 18/66 | 27/29 | NA 36/15 | 11/5 | NA 9/31 | 26/88 | 127/234 | 35.2 | <0.001 |
| – | 1/30 | 48/147 | NA 40/24 | 16/27 | NA 23/55 | 6/243 | 134/526 | 20.3 |

NA: not available.
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Figure 2. A forest plot of HR and 95% CI of the association between \textit{IDH} mutations and OS of gliomas calculated from the multivariate Cox regression analyses.
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Study | HR(95%CI) | %Weight
---|----------|-----
Yan (2012) | 0.62 (0.32, 1.22) | 14.61
Mukasa (2012) | 0.33 (0.07, 1.53) | 2.75
Mukasa (2012) | 0.32 (0.10, 0.95) | 5.16
Mukasa (2012) | 0.91 (0.26, 2.42) | 5.26
Li (2012) | 0.15 (0.04, 0.66) | 3.33
Shibahara (2011) | 0.16 (0.07, 0.37) | 9.44
Christensen (2011) | 0.27 (0.10, 0.72) | 6.71
Bleeker (2010) | 0.21 (0.09, 0.47) | 9.58
Sanson (2009) | 0.30 (0.16, 0.56) | 16.67
Nobusawa (2009) | 0.29 (0.16, 0.51) | 19.47
Gravendeel (2009) | 0.55 (0.21, 1.45) | 7.01
Overall (I-squared = 25.2%, \( p = 0.204 \)) | 0.33 (0.25, 0.42) | 100.00
The mutated IDH have a strongly decreased enzymatic activity, leading to lower αKG production, thereby increasing HIF-1alpha levels. In addition, IDH mutations cause a loss of native enzymatic activities and thus increase the ability to reduce α-ketoglutarate to 2-hydroxyglutarate [14]. The information on the relationship of IDH mutations to other genetic alterations and prognostic values is still limited. In our present study, we investigated molecular and prognostic features of gliomas with and without IDH mutations.

We found IDH mutations were significantly correlated with glioma grade. IDH mutations were frequent in WHO grades II and III gliomas (59.5%) and in secondary glioblastomas (63.4%), but they only occur in a small fraction of primary glioblastomas (7.13%). The low frequency of IDH mutations in the gliomas with EGFR amplification most likely accounts for the low IDH mutations rate in primary glioblastomas compared with secondary glioblastomas [2]. This meta-analysis indicated that lower-grade gliomas had a different genetic aetiology from high-grade tumours and that IDH mutations occurred early in tumour development from a stem cell that can give rise to both astrocytes and oligodendrocytes.

Our study suggested that IDH mutations were closely linked to the genomic profile of the gliomas. There were significant associations between IDH mutations and 1p/19q codeletion (P<0.001), TP53 gene mutation (P<0.001) and MGMT promoter...

### Table 3. Main results of eligible studies evaluating IDH mutations and OS/PFS in gliomas.

| Study          | HR(95%CI) | %Weight |
|----------------|-----------|---------|
| Yan (2012)     | 0.62 (0.34, 1.11) | 17.01   |
| Mukasa (2012)  | 0.60 (0.17, 2.15)  | 10.55   |
| Mukasa (2012)  | 0.06 (0.01, 0.24)  | 8.27    |
| Mukasa (2012)  | 0.90 (0.26, 2.43)  | 11.84   |
| Shibahara (2011)| 0.11 (0.06, 0.23) | 16.21   |
| Wick (2009)    | 0.47 (0.30, 0.77)  | 18.14   |
| Sanson (2009)  | 0.59 (0.36, 0.96)  | 17.97   |
| Overall (I-squared = 77.7%, p = 0.000) | 0.38 (0.21, 0.68) | 100.00 |

NOTE: Weights are from random effects analysis.

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Figure 3. A forest plot of HR and 95% CI of the association between IDH mutations and PFS of gliomas calculated from the multivariate Cox regression analyses.
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Figure 4. A Begg’s funnel plot for the publication bias test of the IDH mutations and OS of human gliomas.
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Figure 5. A Begg's funnel plot for the publication bias test of the IDH mutations and PFS of human gliomas. doi:10.1371/journal.pone.0068782.g005

hypermethylation (P<0.001), whereas an inverse association was observed between IDH mutations and EGFR amplification (P<0.001). The DNA-repair enzyme MGMT removes alkyl groups from the O6 position of guanine, which is the site of several chemotherapy-induced DNA alkylations, and the epigenetic silencing of the MGMT gene by promoter hypermethylation is associated with diminished DNA-repair enzyme activity and increased sensitivity to alkylating agents such as nitrosourea and temozolomide [30–32]. In the present meta-analysis, mutated IDH were strongly correlated with a higher MGMT promoter hypermethylation. Promoter hypermethylation of the MGMT could explain the high percentage of the IDH1 codon 132 G395A transition because MGMT promoter methylation has been demonstrated to be linked to the appearance of G to A mutations in TP53 and K-Ras [33–35]. Therefore, MGMT promoter hypermethylation could explain the high rate of the IDH1 codon 132 G395A transition. EGFR activation by amplification or mutation is one of the most frequent genetic lesions in gliomas, and higher-grade gliomas are genetically characterised by EGFR amplification [36]. The overexpression of EGFR has been shown to promote glioma cell motility and invasion [37]. Our meta-analysis has shown an inverse association between IDH mutations and EGFR amplification. Therefore, the low proliferation rate accompanying IDH mutations can explain the correlation between IDH mutations and a favourable prognosis in glioma patients. The tumour protein p53 responds to diverse cellular stresses to regulate target genes that induce cell cycle arrest, apoptosis, DNA repair and genome stability, and p53 mutants often lead to cancer development and poor outcome [38]. TP53 mutations are one of the most crucial factors in the development of malignant gliomas [39]. Considering the IDH1 mutations correlated with mutant P53 protein, the inherent mechanism of a better prognosis for patients with IDH mutations requires further investigation. Co-deletion of chromosome 1p/19q, which is commonly observed in oligodendrogial tumours, is associated with a good prognosis and increased responsiveness to chemotherapy [13,40]. These genetic changes often occur in a staged order during malignant transformation.

Watanabe et al. [6] dissected multiple biopsies from the same glioma patients and found that there was no case in which IDH mutations had occurred after the acquisition of either a TP53 mutation or 1p/19q codeletion, suggesting that IDH mutations were early events occurring during gliomagenesis and may affect a common glial precursor cell population. Our meta-analysis has found that IDH mutations carry a very strong prognostic significance for PFS and OS. Subgroup analyses according to tumour grade also revealed that the presence of IDH mutations was associated with a better outcome. For patients with IDH mutations, longer OS was observed in patients with grades III and IV gliomas. The PFS in patients with mutated IDH and grades III or IV gliomas had a better prognosis, but this observation had no statistical significance in grade IV gliomas. In our meta-analysis all the survival data were available in the form of a multivariate analysis. Therefore, IDH mutations seem to be an independent favorable prognostic marker in glioma patients. The reasons for an improved outcome could potentially be related to the biological results of mutant IDH. First, mutant IDH1R132H overexpression in stably transfected glioma cell lines in vitro resulted in a markedly decreased proliferation rate, decreased Akt phosphorylation, altered morphology, and a more contact-dependent cell migration. The reduced proliferation is a consequence of the D-2-HG produced by IDH1R132H. Mice injected with IDH1R132H-GFP-expressing cells have prolonged survival compared to mice injected with cells expressing either IDH1wt-GFP or GFP [41]. Second, the IDH1 codon 132 mutations consume rather than produce NADPH. NADPH plays an important role in detoxification processes and scavenging oxygen radicals; the low NADPH levels may be less resistant to irradiation and chemotherapy, thus explaining the prolonged survival of patients with mutated glioblastoma [20]. Third, the substitution of R132 with any one of the six amino acids observed in gliomas (His, Ser, Gly, Cys, Val, and Leu) may have a dramatically reduced affinity for isocitrate and dominantly inhibit wild-type IDH1 activity through the formation of catalytically inactive heterodimers, making the cell more susceptible to the oxidative stress induced by chemotherapy and radiotherapy [42].

The current meta-analysis has several limitations. First, because of limited data, we did not perform the stratification analyses with other variables. Second, the number of included studies was not sufficiently large enough for a comprehensive analysis. Therefore, a larger and well-designed study should be performed to further confirm the results.

Our findings strongly suggest that IDH mutations are associated with other genetic alterations and carry a very strong prognostic significance for PFS and OS. Further studies on the biological results of mutant IDH should lead to a more comprehensive understanding of the association between IDH mutations and their impacts on the outcome of gliomas.

Author Contributions
Conceived and designed the experiments: P. Zou AG P. Zhao. Performed the experiments: P. Zou HX. Analyzed the data: P. Zou PC QY. Contributed reagents/materials/analysis tools: P. Zhao LZ. Wrote the paper: P. Zou AG P. Zhao.

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