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SYSTEMATIC REVIEW AND META-ANALYSIS

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Isocitrate Dehydrogenase (IDH)1/2 Mutations as Prognostic Markers in Patients With Glioblastomas

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Abstract: The purpose of this study was to perform a meta-analysis examining the association of isocitrate dehydrogenase (*IDH*)*1/2* mutations with overall survival (OS) and progression-free survival (PFS) in patients with glioblastomas.

Medline, Cochrane, EMBASE, and Google Scholar were searched from inception to January 28, 2015, using combinations of the following keywords: IDH mutation, brain tumor, glioma, glioblastoma, oligodendroglioma, prognosis. Randomized controlled trials, and prospective and retrospective studies of patients with glioblastomas that provided IDH mutation and survival data were included. OS and PFS were used to evaluate the association of *IDH1* and *IDH1/2* mutations and prognosis. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for OS and PFS were calculated and compared between patients with and without mutations.

Of 165 studies that were identified, 136 nonrelevant studies were excluded. Twenty-nine full-text articles were assessed, and of these, 5 were excluded as they did not provide a quantitative outcome. Therefore, 24 studies were included in the qualitative synthesis. The pooled HR of 0.358 (95% CI 0.264–0.487, $P < 0.001$) indicated that IDH mutations were associated with better OS. Similarly, the pooled HR of 0.322 (95% CI 0.24200.455, $P < 0.001$) indicated that IDH mutations were associated with better PFS. When patients were stratified by surgery versus no surgery or IDH1 versus IDH1/2 mutations, the results also indicated that the presence of IDH mutations was associated with better OS and PFS.

The IDH mutations are associated with improved survival in patients with glioblastomas.

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Abbreviations: CI = confidence interval, GBM = glioblastoma multiforme, HR = hazard ratio, IDH = isocitrate dehydrogenase 1, OS = overall survival, PCV = procarbazine, lomustine, and vincristine, PFS = progression-free survival, RCT = randomized controlled trial, WHO = World Health Organization.

INTRODUCTION

Glioblastomas (glioblastoma multiforme [GBM]) are the most common and aggressive malignant brain tumor, with a median survival from diagnosis of approximately 12 to 14 months.[1] The majority of glioblastomas (~90%) occur without evidence of a less malignant precursor lesion (primary glioblastomas) in older patients, whereas secondary glioblastomas progress from low-grade diffuse astrocytoma or anaplastic astrocytoma, and occur in younger patients.[2] Secondary glioblastomas have a significantly better prognosis than primary glioblastoma.[2]

Approximately 70% to 80% of secondary glioblastomas have somatic mutation in the isocitrate dehydrogenase 1 (*IDH1*) gene, which are absent in primary glioblastoma.[3–5] Wild-type IDH1 protein is found in the cytoplasm, peroxisomes, and endoplasmic reticulum, and catalyzes the oxidative decarboxylation of isocitrate to α-ketogluterate.[6–8] Mutations in *IDH1* associated with glioblastomas map to the highly conserved residue R132 in the enzyme active site, and usually result in an Arg to His substitution, although other substitutions can also occur.[8–12] The *IDH1 R132* mutation occurs in 55% to 80% of grade II and III oligodendrogliomas and astrocytomas, but is rare in primary glioblastomas.[12] To a lesser extent, glial tumors have somatic mutations in the corresponding codon (codon R172) of the *IDH2* gene.[9] The IDH2 protein has a similar function to IDH1, but is found in the mitochondria. Both the *IDH1-R132* and *IDH2-R172* mutations are thought to result in an accumulation of the oncometabolite 2-hydroxyglutarate instead of α-ketogluterate.[13,14]

It is unclear how a tumor's biology is affected by *IDH1/2* mutations. *IDH1/2* mutations may result in genome-wide epigenetic changes in human gliomas.[4] Another hypothesis is that the mutations reduce the capacity of cells to produce NADPH, and consequently lowers the ability of the cell to scavenge oxygen species, making the tumor cells more susceptible to irradiation and chemotherapy. This increased sensitivity to treatments may result in increased patient survival.[15]

A number of studies have found that *IDH1-R132* and *IDH2-R172* mutations are linked to the genomic profile of the tumor, and are important prognostic markers in grade II to IV gliomas.[16–20] However, other studies have not found an association of *IDH1/2* mutations with prognosis in low-grade tumors.[18,21] Therefore, the prognostic value of these genetic markers for survival is not clear.

The purpose of the current study was to perform a meta-analysis to examine the association of *IDH1/2* mutations with overall survival (OS) and progression-free survival (PFS) in patients with glioblastomas.

METHODS

Literature Search Strategy

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines.[22] Medline, Cochrane, EMBASE, and Google Scholar were searched from inception to January 28, 2015, using combinations of the following keywords: IDH mutation, brain tumor, glioma,

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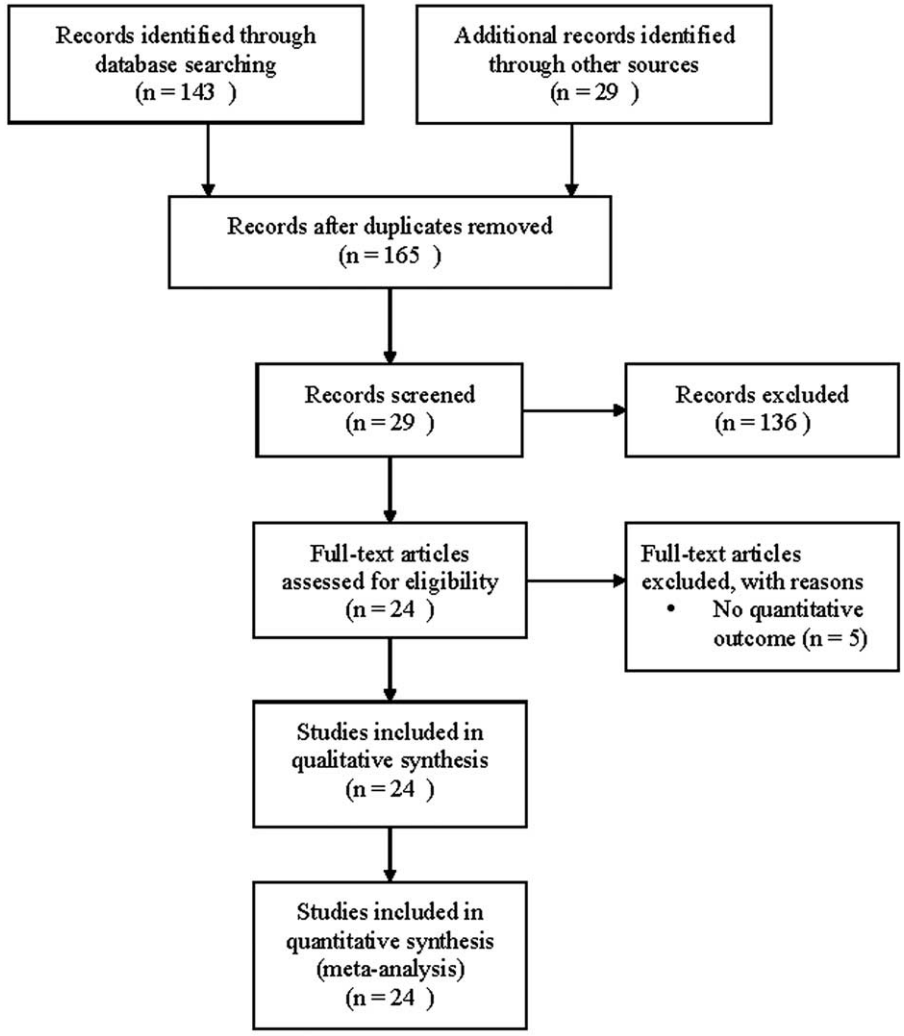


FIGURE 1. Flow diagram of study selection.

glioblastoma, oligodendroglioma, prognosis. Reference lists of relevant studies were hand-searched. Meta-analyses do not involve humans and do not require Institutional Review Board approval.[23]

Study Selection and Data Extraction

Inclusion criteria were as follows: randomized controlled trials (RCTs) and prospective and retrospective studies; patients with a malignant brain tumor (glioma, glioblastoma, anaplastic oligodendroglioma, etc); provided IDH mutation data; and contained survival analysis data. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded, as were studies in which no survival analysis was performed. Studies were identified by the search strategy by 2 independent reviewers. When there was uncertainty regarding eligibility, a third reviewer was consulted.

The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and sex, diagnostic criteria, tumor type and World Health Organization (WHO) grade, treatments, and survival data.

Quality Assessment

The quality of the included studies was assessed using the modified 18-items Delphi checklist, which is designed for assessing the quality of single-arm clinical studies.[24] The quality assessment was also performed by 2 independent reviewers, and a third reviewer was consulted for any uncertainties.

Outcome Measures and Data Analysis

Overall survival and PFS were used to evaluate the association of *IDH1* and *IDH1/2* mutations, and prognosis for patients with malignant brain tumors. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for OS and PFS were calculated and compared between patients with and without mutations. Pooled HRs and 95% CIs were calculated for all studies combined, and for given subgroups (e.g., *IDH* mutation type or surgery vs no surgery). A HR value <1 indicates that mutations may prolong OS or PFS, whereas a HR value >1

TABLE 1. Study Characteristics

1st Author (y)	Type of Study	Diagnosis of Malignant Progression	Number of Patients	Age, y	Men, %	Tumor Type	WHO Tumor Grade	Treatments	Time-point for Evaluation of OS and PFS
Cairncross (2014)	Retrospective	Histological	291	≥18	60	Anaplastic oligodendroglioma, anaplastic oligoastrocytoma		CHT, RT	n/a
Hatanpaa (2014)	Retrospective	High nestin protein expression is a strong adverse prognostic factor	50	Median = 37.5 (range 20–66)	52	Astrocytomas, oligodendrogliomas, oligoastrocytoma	II, III	Surgery, CHT, RT	After diagnosis
Polivka (2014)	Retrospective	Neomorphic function of the mutated enzyme	44	Median = 64.3 (range 35–87)	50	Glioblastoma	IV	Surgery, CHT, RT+CHT	Time after diagnosis
Frenel (2013)	Retrospective	n/a	43	Median = 51 (range 25–78)	65	Anaplastic oligodendroglioma	n/a	Surgery, RCT, CHT, RT	Time after diagnosis
Gorlia (2013)	RCT	Signs of clinical or radiological progression	368	Median = 49.5 (range 18.6–68.7)	57.6	Oligodendroglioma or oligoastrocytoma	n/a	RT, RT + CHT	OS: the time from randomization until death regardless of cause. PFS: time from randomization until clinical or radiological progression or death
Ohno (2013)	Retrospective	Histopathologically progressed from lower-grade gliomas	18	Median = 30.5 (range 20–64)	66.7	Diffuse astrocytoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma	II, III	Surgery	n/a
Yao (2013)	Retrospective	n/a	53	Mean = 39.5; median = 38 (range 5–67)	54.7	Gliomas	II (n = 29), III (n = 16), IV (n = 8)	CHT, surgery	OS: time between the diagnosis and death or last follow-up. PFS: time between the diagnosis and first unequivocal clinical or radiological sign of progressive disease
Ahmadi (2012)	Retrospective	Malignant progression towards anaplastic astrocytomas of WHO grade III and secondary glioblastomas	100	Median = 37 (range 19–72)	55	WHO grade II astrocytomas	II	Surgical resection or biopsy, RT, CHT	Time first symptoms appeared
Juratli (2012)	Retrospective	n/a	99	Mean = 37.5	55.6	Oligodendroglioma or oligoastrocytoma	II (n = 35), diffuse astrocytomas (n = 64)	CHT, RT	OS: time interval from LGG diagnosis to death or censor. Secondary PFS: the time between first diagnosis of a HGG and first tumor recurrence or tumor progression
Leibetseder (2013)	Retrospective	MRI	47	Median = 32 (range 18–39)	59.5	GBM	n/a	Surgery, CHT, RT	Time after surgery
Mukasa (2012)			250	Range 12-80	40–100	GBM (glioblastoma) primary (grade IV), 109 (43%); GBM secondary (grade IV), 13 (5.2%); GBM (grade IV), 3 (1.2%); anaplastic astrocytoma (grade III), 29 (11.6%); anaplastic oligoastrocytoma (grade III), 5 (2%); anaplastic oligodendroglioma (grade III), 15 (6%); diffuse astrocytoma (grade II), 29 (11.6%); oligoastrocytoma (grade II), 7 (2.8%); oligodendroglioma (grade II), 25(1%); pilocytic astrocytoma (grade I), 9 (3.6%); ganglioglioma (grade I), 6 (2.4%)	I, IV	Surgical resection	From date of surgical procedure

1st Author (y)	Type of Study	Diagnosis of Malignant Progression	Number of Patients	Age, y	Men, %	Tumor Type	WHO Tumor Grade	Treatments	Time-point for Evaluation of OS and PFS
Thon (2012)	Retrospective	Multilocular tumor appearance/contrast enhancement of an initially nonenhancing lesion combined with rapid tumor growth	127	Median = 37.0 (range 18.0–75.0)	47	Astrocytoma: fibrillary astrocytoma, 118 (93%); gemistocytic astrocytoma, 8 (6.2); protoplasmatic astrocytoma, 1 (0.78%)	II	RT, CHT, surgery	From date of first surgical procedure
Okita (2012)	Retrospective	MRI (Gd-DTPA) showed a new enhancing lesion	72	Median = 39 (range 21–75)	55.6	Gliomas	II	CHT, RT, surgery	After surgery
SongTao (2012)	Retrospective	>25% increase in T2 hypersignal or contrast enhancement, or tumor-related neurologic deterioration	86	Median = 40 (range 20–72)	54.7	Astrocytoma, oligoastrocytoma, anaplastic astrocytoma, anaplastic oligoastrocytoma	Low-grade glioma High-grade glioma High-grade glioma	CHT	After diagnosis
Takano (2012)	Retrospective	n/a	164	Mean = 48.6 ± 14.3 (range 18–83)	Male predominant		Grade IV	glioblastomas, 52 (41 primary, 11 secondary); grade III, 66 (32 anaplastic astrocytomas, 10 anaplastic	oligodendrogliomas, 24 anaplastic oligoastrocytomas); grade II, 46 (42 diffuse astrocytomas, 4 oligodendrogliomas)
II, III, IV	Primary surgery	Time of surgery							
Hartmann (2011)	Cohort	n/a	89 (cohort A) 50 (cohort B)	Median = 36.7 (range 17.4–75.7)	67.4 (cohort A); 58 (cohort B)	Diffuse astrocytoma, mixed oligoastrocytoma, oligodendroglioma	II	Surgical resection,no CHT, no RT (cohort A); RT, CHT, surgical resection (cohort B)	From day of first surgery
Ohka (2011)	Retrospective	n/a	57 (grade 2 glioma) 54 (GBM)	Median = 42.0 (range 21–72) for grade 2 glioma; median = 59.0 (range 12–84) for GBM	63 (grade 2 glioma); 61 (GBM)	Astrocytoma, oligodendroglioma, oligo-astrocytoma (grade II glioma), primary GBM, secondary GBM	II	CHT, RT, surgery	From day of initial surgery
SongTao (2011)	Retrospective	>25% increase in T2 hypersignal or contrast enhancement, or tumor-related neurologic deterioration	203	Median = 36.4 (range 2–78)	55.7	Pilocytic astrocytoma, ganglioglioma, diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic oligodendroglioma, primary glioblastoma, secondary glioblastoma	n/a	CHT, RT, CHT + RT, surgery	After surgery
Bleeker (2010)	Retrospective	n/a	98	Mean = 58 for no mutation; mean = 41 for mutation	54.1	n/a	n/a	CHT, RT, surgery	After surgery

1st Author (y)	Type of Study	Diagnosis of Malignant Progression	Number of Patients	Age, y	Men, %	Tumor Type	WHO Tumor Grade	Treatments	Time-point for Evaluation of OS and PFS
Christensen (2010)	Retrospective	n/a	131	Median = 49 (range 17–78) for no mutation; median = 35 (range 20–59) for mutation	57	Primary glioblastoma, 20; secondary glioblastoma, 12; grade 3 astrocytoma, 9; grade 2 astrocytoma, 20; grade 3 oligoastrocytoma, 9; grade 2 oligoastrocytoma, 22; grade 2 oligodendroglioma, 20; ependymoma, 15; pilocytic astrocytoma, 4	II, III	n/a	n/a
Houillier (2010)	Retrospective	Greater than 25% increase in T2 hypersignal or contrast enhancement, or tumor-related neurologic deterioration	271	Median = 39 (range 18–78)	58	Astrocytoma, oligodendroglioma, oligoastrocytoma	n/a	CHT, RT	After diagnosis
Metellus (2010)	Retrospective	n/a	47	Mean = 41 ± 13.2 (range 21–71)	46.8	Oligodendrogliomas, oligoastrocytomas, astrocytomas	II	RT, CHT, CHT + RT	From the day of diagnosis
van den Bent (2010)	RCT	n/a	159	Range 16-70	n/a	Anaplastic oligodendroglioma	n/a	RT + PCV	PFS and OS were measured from the day of randomization
Kim (2010)	Retrospective	Histological	360	Mean = 42.1 ± 12.3	n/a	Diffuse astrocytoma, oligoastrocytoma, oligodendroglioma	II	Surgery, RT, CHT	Date of the first biopsy

CHT = chemotherapy, GBM = glioblastoma multiforme, HGG = high-grade glioma, LGG = low-grade glioma, n/a = not available, OS = overall survival, PCV = procarbazine, lomustine, and vincristine, PFS = progression-free survival, RCT = randomized control trials, RT = radiotherapy.

indicates the absence of mutations may decrease OS or PFS. A HR value equal to 1 indicates there was no significant association of *IDH1* or *IDH1/2* mutations with OS or PFS.

Heterogeneity among the studies was evaluated by the Cochran Q and the I^2 statistic. A Q statistic, with a $P < 0.10$, was considered to indicate statistically significant heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, and a value >50% was considered to indicate significant heterogeneity. Random-effects models (DerSimonian–Laird method) were used if heterogeneity was detected ($I^2 >$ 50% or Q statistics $P < 0.1$). Otherwise, fixed-effects models (Mantel–Haenszel method) were utilized. Sensitivity analysis was performed using the leave-one-out approach. Publication bias was assessed by constructing funnel plots and by Egger test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution, and a 1-tailed significance level of $P > 0.05$ (Egger test). All statistical assessments were 2-sided, and a value of $P < 0.05$ was considered as statistically significant. Statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Search Results and Study Characteristics

A flow diagram of study selection is shown in Figure 1. A total of 165 studies were identified in the database search. After a review of the abstracts, 136 studies were excluded because they did not match the topic of the current analysis. Thus, 29 full-text articles were assessed for eligibility, and of these, 5 were excluded as they did not provide a quantitative outcome. Therefore, 24 studies were included in the qualitative synthesis.[3,13,16–18,21,25–42] The characteristics and populations of the included studies are summarized in Table 1, and OS and PFS data are summarized in Table 2. Studies that reported median OS or PFS time were not considered for the analysis because most of the included studies were presented as HR. The study by Mukasa et al[21] was not included in the analysis because the HRs were reported by tumor stage.

Association of IDH1 or IDH2 Mutations With OS

A total of 15 studies with completed data of OS were included in the analysis.[3,13,16,18,25–29,32–34,36,37,42] Significant heterogeneity was noted ($I^2 = 59.23\%$, Q statistic = 34.336, $P = 0.002$); therefore a random-effects model was used. The pooled HR of 0.358 (95% CI 0.264–0.487, $P < 0.001$) indicated that *IDH1* or *IDH1/2* mutations were associated with better OS (Figure 2). When patients were stratified by surgery versus no surgery or *IDH1* versus *IDH1/2* mutations, the results also indicated that the presence of *IDH* mutations was associated with better OS.

Association of IDH1 or IDH2 Mutations With PFS

A total of 10 studies with completed data of PFS were included in the analysis.[13,16,25–29,32,36,37] Significant heterogeneity was noted ($I^2 = 53.53\%$, Q statistic = 19.369, $P = 0.022$); therefore a random-effects model was used. The pooled HR of 0.322 (95% CI 0.242–0.455, $P < 0.001$) indicated that *IDH1* or *IDH1/2* mutations were associated with better PFS (Figure 3). When patients were stratified by surgery versus no surgery or *IDH1* versus *IDH1/2* mutations, the results also indicated that the presence of *IDH* mutations was associated with better PFS.

TABLE 2. Overall Survival and Progression-free Survival in Patients With and Without *IDH1/IDH2* Mutations

1st Author (y)	IDH Mutation	Number of Patients	Surgery	Mutation Rate (%)	Hazard Ratio (95% CI) for OS	Hazard Ratio (95% CI) for PFS
Cairncross (2014)	IDH1/IDH2	291	No	74	0.41 (0.27- 0.63) ref. no mutation	n/a
Hatanpaa (2014)	IDH1/IDH2	50	Yes	84	RR = 6.99 (1.91–25.66) ref. mutation	n/a
Polivka, (2014)	IDH1	44	Yes	45	Median: 270 d (139–400) mutant/ 130 d (87–172) wild type	Median: 136 d (22–249)/51 d (19–82) wild type
Frenel (2013)	IDH1/IDH2	43	No	54	0.1 (0–0.7) ref. no mutation	0.1 (0–0.3) ref. no mutation
Gorlia (2013)	IDH1/IDH2	368	No	45.6	0.478 (0.334–0.682) ref. no mutation	0.422 (0.291–0.610) ref. no mutation
Ohno (2013)	IDH1/IDH2	18	Yes	44.4	Wild-type IDH1: 2, 6.8 vs mutant IDH1: 2, 6.75 mo: $P = 0.93$	n/a
Yao (2013)	IDH1	53	Yes	60.4	4.74 (1.73–12.98) ref. Mutation	3.60 (1.45–8.95) ref. mutation
Ahmadi (2012)	IDH1	100	Yes	79	Median 81.4 (range 5.5–274.8) mutation; median 80.2 (range 12.4–192) wild type	Median 44.6 (range 1–267) mutation; median 67.4 (range 7.9–116.9) wild type
Juratli (2012)	IDH1/IDH2	99	No	75.7	0.5 (0.3–0.9) ref. no mutation	0.5 (0.3–0.8) ref. no mutation
Leibetseder (2012)	IDH1	47	Yes	43.4	Median 28 mo (24–31.6)	Median 12 m (9.5–14)
Mukasa (2012)	IDH1/IDH2	250	Yes	II: 65.6; III: 44; primary GBM: 5.5	Grade II: 0.329 (0.0728–1.5270); grade III: 0.319 (0.0985–0.9519); primary GBM: 0.905 (0.2609–2.4203)	Grade II: 0.602 (0.1678–2.1535) ref. no mutation; grade III: 0.059 (0.0086–0.2395) ref. no mutation; primary GBM: 0.898 (0.2575–2.4255)
Thon (2012)	IDH1	127	Yes	78	1.30 (0.72–2.33) ref. mutation	2.17 (1.26–3.74) ref. mutation
Okita (2012)	IDH1/IDH2	72	Yes	58.3	0.365 (0.155–0.819) ref. no mutation	0.558 (0.289–1.068) ref. no mutation
SongTao (2012)	IDH1/IDH2	86	No	73.4	HR = 0.110, $P \leq 0.001$	HR = 0.110, $P \leq 0.001$
Takano (2012)	IDH1	164	Yes	47.3	0.256 (0.068–0.959) adjusted multivariable	0.088 (0.023–0.333) adjusted multivariable
Hartmann (2011)	IDH1	89 (cohort A) 50 (cohort B)	Yes	81.8 (cohort A); 20 (cohort B)	Cohort A: mutated median 10.5 y (5.1–15.9) Cohort B: mutated median 50.0 y (0–100)	Cohort A: 4.5 (4.0–5.1); cohort B: 6.7 (1.6–11.7)
Ohka (2011)	IDH1/IDH2	57grade 2 glioma; 54 GBM	Yes	82.4	6.433 (0.522–79.280) ref. mutation	1.886 (0.571–6.886) ref. mutation
SongTao (2011)	IDH1/IDH2	203	Yes	41	IDH mutant: median 57.34 mo; IDH wild type: median 21.30 mo	IDH mutant: median 56.87 mo IDH wild type: median 13.70 mo
Bleeker (2010)	IDH1	98	Yes	18	0.209 (0.093–0.471) ref. no mutation	n/a
Christensen (2010)	IDH1/IDH2	131	No	60	0.27 (0.10–0.72) ref. no mutation	n/a
Houillier (2010)	IDH1/IDH2	271	No	69.8	HR = 0.32, $P = 0.003$	HR = 0.92, $P = 0.7$
Metellus (2010)	IDH1/IDH2	47	No	85	40.9 (2.89–578.49) ref. mutation	6.79 (2.12–21.77) ref. mutation
van den Bent (2010)	IDH1/IDH2	159	No	45.9	0.24 (0.15–0.38) ref. no mutation	0.27 (0.18–0.40) ref. no mutation
Kim (2010)	IDH1/IDH2	360	Yes	89.2	1.047 (0.593–1.850) ref. mutation	n/a

CI = confidence interval, GBM = glioblastoma multiforme, HR = hazard ratio, IDH = isocitrate dehydrogenase, n/a = not available, ref. = reference group.

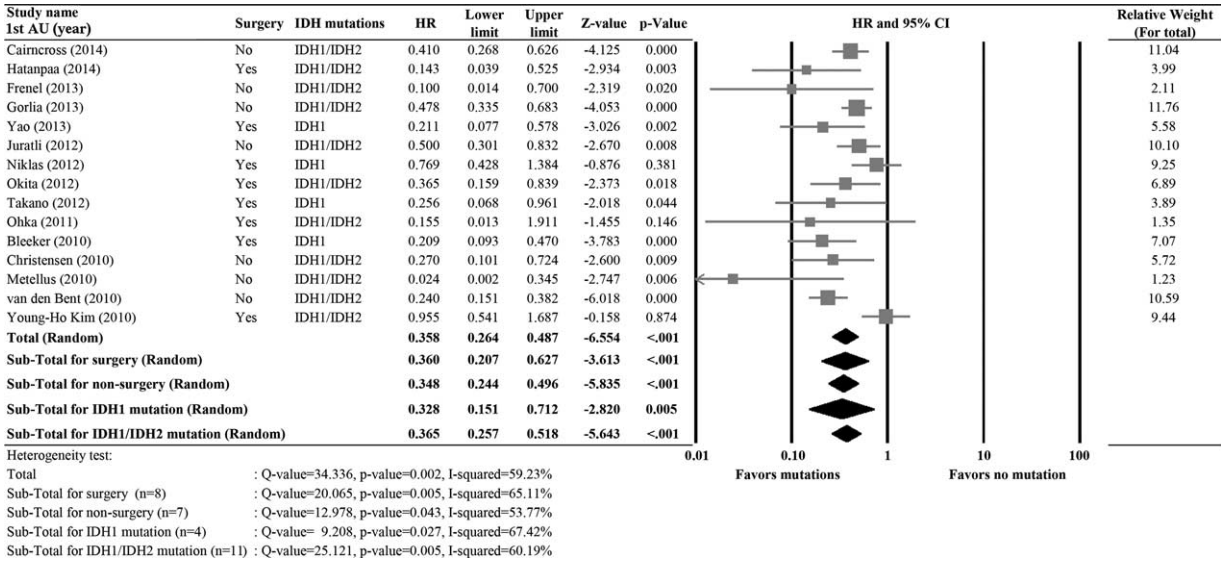


FIGURE 2. Meta-analysis for the association of IDH1/IDH2 mutations versus overall survival (OS). 1st AU = first author, 95% CI = 95% confidence interval, HR = hazard ratio, IDH = isocitrate dehydrogenase, lower limit, upper limit of HR.

Sensitivity Analysis

Results of the sensitivity analysis using the leave-one-out approach for OS and PFS are shown in Figure 4. For both OS and PFS, the pooled estimates with each of the studies removed in turn remained statistically significant, indicating that the meta-analysis had good reliability for both measures (HRs for OS: range 0.33–0.38, all P values < 0.001; HRs for PFS, range 0.31–0.37, all P values < 0.001).

Publication Bias Analysis

Results of the evaluation of publication bias for OS and PFS are shown in Figure 5. For both measures, the funnel plots were symmetric (both $P < 0.001$; classic fail-safe test). However, Egger test indicated that the intercepts of the funnel plots did not obtain statistical significance (OS: 1-tailed, $P = 0.037$; PFS: 1-tailed, $P = 0.075$, respectively). Hence, publication bias may exist with respect to OS.

Quality Assessment

Results of the quality assessment using the modified 18-item Delphi checklist are shown in Table 3. All of the included studies clearly stated the aim of the study in the abstract or introduction, and described the characteristics of the included participants. The eligibility criteria of all the studies were explicit and appropriate, and outcome measures were all well-defined. The final total Delphi checklist scores of the studies ranged from 9 to 15 (maximum possible score of 18). Overall, the results indicate the studies are of good quality.

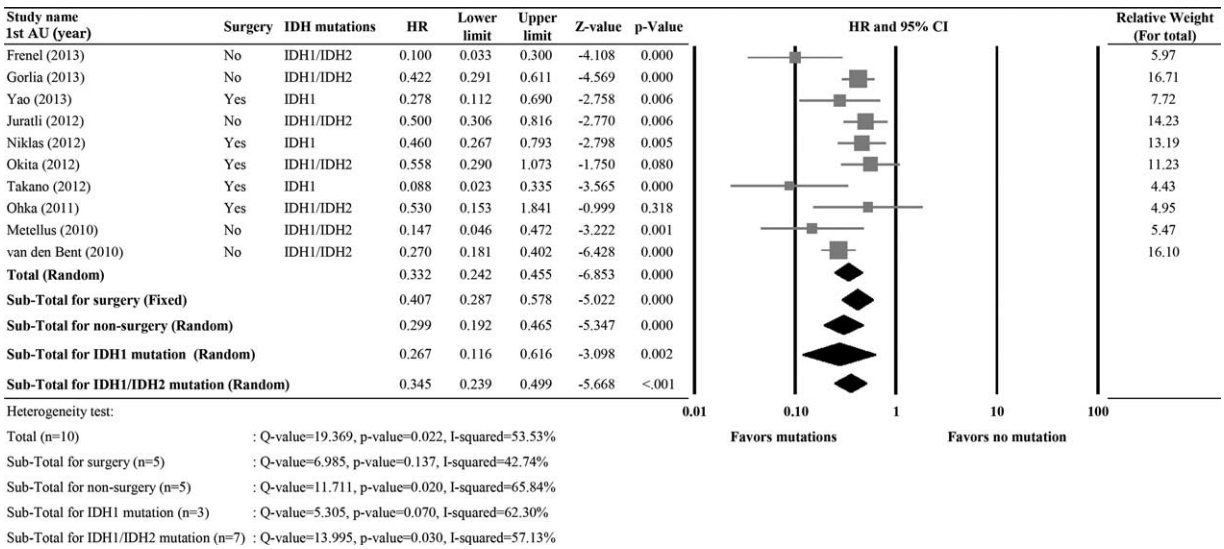
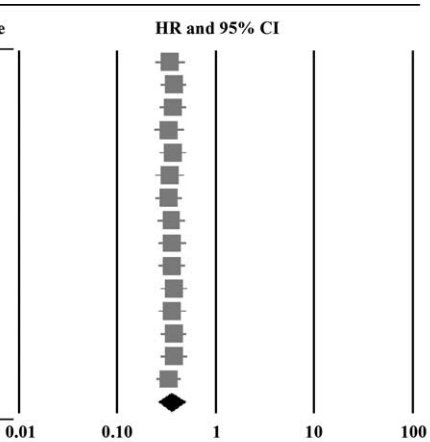


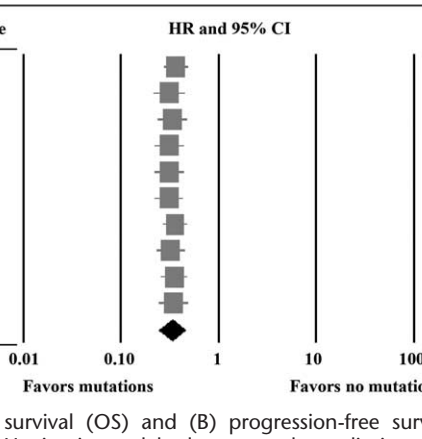
FIGURE 3. Meta-analysis for the association of IDH1/IDH2 mutations versus progression-free survival (PFS). 1st AU = first author, 95% CI = 95% confidence interval, HR = hazard ratio, lower limit, upper limit of HR.

Removed study 1st AU (year)	Surgery	IDH mutations	HR	Lower limit	Upper limit	Z-value	p-Value
Cairncross (2014)	No	IDH1/IDH2	0.344	0.243	0.489	-5.963	<.001
Hatanpaa (2014)	Yes	IDH1/IDH2	0.374	0.275	0.508	-6.266	<.001
Frenel (2013)	No	IDH1/IDH2	0.369	0.272	0.502	-6.372	<.001
Gorlia (2013)	No	IDH1/IDH2	0.337	0.237	0.480	-6.036	<.001
Yao (2013)	Yes	IDH1	0.370	0.269	0.507	-6.171	<.001
Juratli (2012)	No	IDH1/IDH2	0.340	0.242	0.478	-6.225	<.001
Niklas (2012)	Yes	IDH1	0.334	0.245	0.457	-6.875	<.001
Okita (2012)	Yes	IDH1/IDH2	0.355	0.255	0.492	-6.194	<.001
Takano (2012)	Yes	IDH1	0.362	0.263	0.497	-6.272	<.001
Ohka (2011)	Yes	IDH1/IDH2	0.362	0.265	0.494	-6.397	<.001
Bleeker (2010)	Yes	IDH1	0.374	0.273	0.513	-6.109	<.001
Christensen (2010)	No	IDH1/IDH2	0.363	0.263	0.500	-6.182	<.001
Metellus (2010)	No	IDH1/IDH2	0.375	0.279	0.502	-6.566	<.001
van den Bent (2010)	No	IDH1/IDH2	0.379	0.277	0.520	-6.026	<.001
Young-Ho Kim (2010)	Yes	IDH1/IDH2	0.334	0.251	0.445	-7.503	<.001
Total (Random)			0.358	0.264	0.487	-6.554	<.001



A

Removed study 1st AU (year)	Surgery	IDH mutations	HR	Lower limit	Upper limit	Z-value	p-Value
Frenel (2013)	No	IDH1/IDH2	0.365	0.274	0.484	-6.960	<.001
Gorlia (2013)	No	IDH1/IDH2	0.310	0.213	0.453	-6.064	<.001
Yao (2013)	Yes	IDH1	0.335	0.238	0.470	-6.304	<.001
Juratli (2012)	No	IDH1/IDH2	0.309	0.217	0.438	-6.583	<.001
Niklas (2012)	Yes	IDH1	0.313	0.219	0.446	-6.403	<.001
Okita (2012)	Yes	IDH1/IDH2	0.311	0.222	0.435	-6.794	<.001
Takano (2012)	Yes	IDH1	0.358	0.267	0.479	-6.893	<.001
Ohka (2011)	Yes	IDH1/IDH2	0.322	0.231	0.449	-6.687	<.001
Metellus (2010)	No	IDH1/IDH2	0.350	0.255	0.479	-6.531	<.001
van den Bent (2010)	No	IDH1/IDH2	0.342	0.240	0.489	-5.899	<.001
Total (Random)			0.332	0.242	0.455	-6.853	<.001



B

FIGURE 4. Sensitivity analysis using the leave-one-out approach for (A) overall survival (OS) and (B) progression-free survival (PFS). 1st AU = first author, 95% CI = 95% confidence interval, HR = hazard ratio, IDH = isocitrate dehydrogenase, lower limit, upper limit of HR.

DISCUSSION

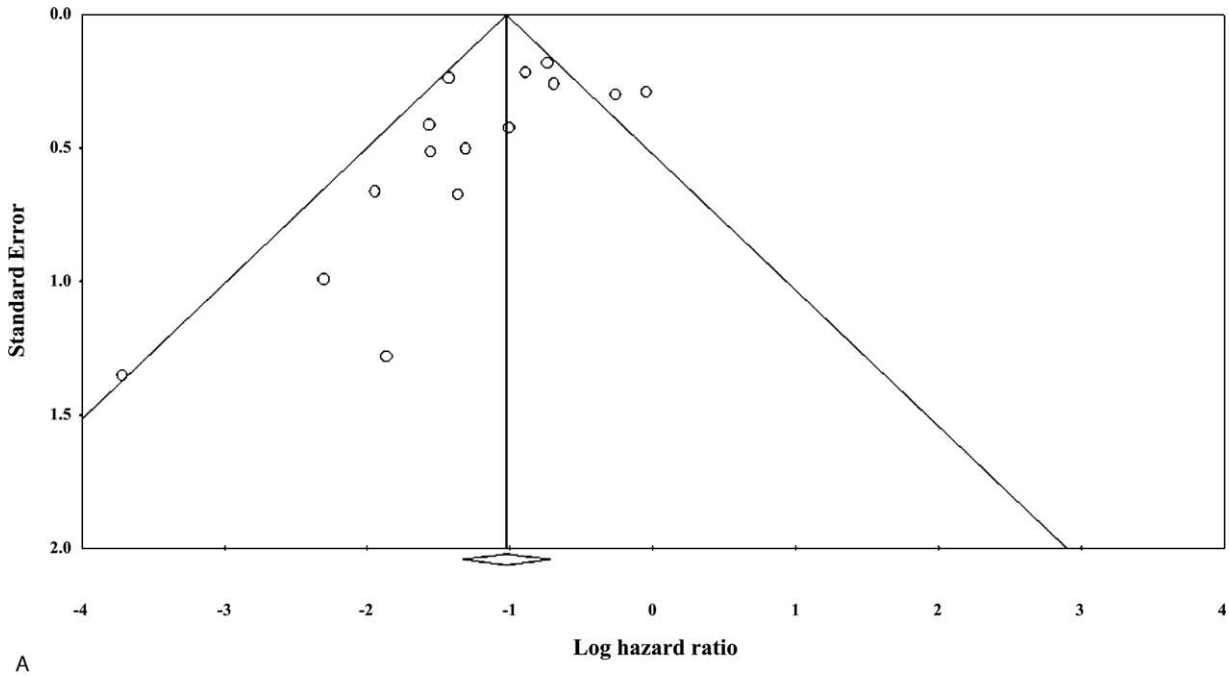
The purpose of this meta-analysis was to evaluate the prognostic value of *IDH1/2* mutations with respect to OS and PFS in patients with glioblastoma. The results showed that the presence of *IDH1/2* mutations was associated with longer OS and PFS, and this result was seen in both patients treated with surgery and those treated nonsurgically (e.g., radiotherapy), as well as in patients with *IDH1* and *IDH1/2* mutations.

IDH1 mutations have been reported in secondary GBM, diffuse astrocytoma, oligodendrogliomas, anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas, and rarely in primary GBM, and have not been reported in pilocytic astrocytomas, ependymonmas, and medulloblastomas.[43] Mutations have also been reported in other cancers including acute myeloid leukemia and colorectal and prostate cancer.[43]

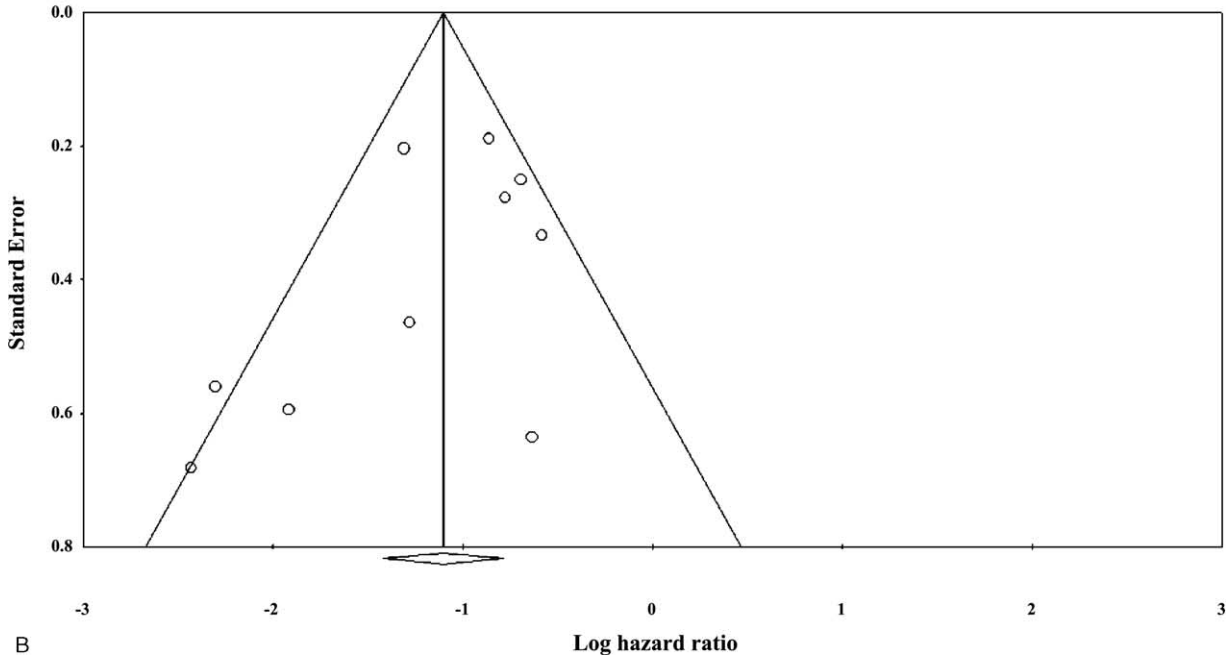
Prior studies have found that *IDH1/2* mutations may influence the prognosis of patients with secondary or greater than grade II gliomas; however, these studies have differed in design and the results have not always been consistent.[16–21,44]

Evidence has generally shown that *IDH1* mutations are associated with improved OS and PFS, particularly in patients with high-grade gliomas.[9,13,27] The prognostic value in low-grade gliomas is, however, less clear. For example, Sanson et al[19] showed that the *IDH1* mutation had a significant prognostic value for OS in gliomas, whereas Kim et al[18] reported the *IDH1/IDH2* mutation was of no prognostic value in 360 low-grade gliomas. Interestingly, although *IDH1* mutations have generally been shown to be a prognostic indicator, their presence is not necessarily predictive of response to therapy.[9,13,19,40] Reasons for these findings may have to do with the association of *IDH1* mutations with O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.[42] For example, Molenaar et al[45] reported that the combination of *IDH1* mutations and MGMT methylation status predicted survival in patients with glioblastomas better than either *IDH1* or MGMT status alone. Though the reasons for the associations between survival, and *IDH1* and MGMT methylation status remain to be determined, it has been suggested there may be mechanistic link between *IDH1* mutations and MGMT methylation.[46]

Prior studies have suggested that chemoradiotherapy may be effective for a subset of patients with gliomas, as the addition of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy conferred a significant increase in OS and PFS.[47,48] Among the studies included in the current analysis, Okita et al[28] suggested *IDH1/2* mutations were predictive for response to chemoradiotherapy, but not radiotherapy alone in patients with grade II gliomas. However, van den Bent et al[13]



A



B

FIGURE 5. Evaluation of publication bias by funnel plot and the Egger test for (A) overall survival (OS) and (B) progression-free survival (PFS).

TABLE 3. Quality Assessment Results

1st Author (Publication Year)	Cairncross (2014)	Hatanpaa (2014)	J. Polivka, (2014)	Frenel (2013)	Gorlia (2013)	Ohno (2013)	Yao (2013)	Ahmadi (2012)	Juratli (2012)	Leibetseder (2012)	Niklas (2012)	Okita (2012)	SongTao (2012)	Takano (2012)	Hartmann (2011)	Ohka (2011)	SongTao (2011)	Bleeker (2010)	Christensen (2010)	Houillier (2010)	Metellus (2010)	van den Bent (2010)	Kim (2010)
Is the hypothesis/aim/ objective of the study clearly stated in the abstract, introduction, or methods section?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are the characteristics of the participants included in the study described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the cases collected in more than 1 center?	Y	N	Y	N	Y	N	Y	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N	Unknown	Y
Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were participants recruited consecutively?	N	N	N	Y	Y	N	Unknown	N	Y	N	Y	Y	N	N	N	N	N	N	N	N	Y	N	N
Did participants enter the study at a similar point in the disease?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the intervention clearly described in the study?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were additional interventions (cointerventions) clearly reported in the study?	N	N	N	N	Y	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N
Are the outcome measures clearly defined in the introduction or methods section?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were relevant outcomes appropriately measured with objective and/or subjective methods?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were outcomes measured before and after intervention?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Were the statistical tests used to assess the relevant outcomes appropriate?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the length of follow-up reported?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Was the loss to follow-up reported?	N	N	N	Y	N	Y	N	Y	N	Y	Y	N	N	N	Y	N	N	N	N	N	N	Y	N

1st Author (Publication Year)	Cairncross (2014)	Hatanpaa (2014)	J. Polivka, (2014)	Frenel (2013)	Gorlia (2013)	Ohno (2013)	Yao (2013)	Ahmadi (2012)	Juratli (2012)	Leibetseder (2012)	Niklas (2012)	Okita (2012)	SongTao (2012)	Takano (2012)	Hartmann (2011)	Ohka (2011)	SongTao (2011)	Bleeker (2010)	Christensen (2010)	Houillier (2010)	Metellus (2010)	van den Bent (2010)	Kim (2010)
Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Are adverse events reported?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Are the conclusions of the study supported by results?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are both competing interest and source of support for the study reported?	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N	N	Y	Y	N	N	N	Y	N	Y	Y	N
Total score	13	12	13	13	14	12	11	13	13	13	15	12	9	11	13	12	11	11	12	11	13	12	12

reported that *IDH1* mutations were predictive of both OS and PFS for patients treated with radiotherapy and radiotherapy/PVC. It has also been reported that patients with low-grade gliomas were sensitive to temozolomide.[17] In the current meta-analysis, we did not evaluate the predictive value of *IDH1/2* mutations with respect to radiotherapy, chemotherapy, or chemoradiotherapy. This was due to the heterogeneity across the studies, and because few studies directly evaluated this question.

Other prior meta-analyses have evaluated the association of *IDH* mutations and survival in patients with glioblastomas. An analysis by Cheng et al[49] included 9 studies with a total of 1669 patients with glioblastomas, and, similar to our results, found that *IDH1* mutations were associated with improved OS. Zou et al[50] performed a meta-analysis including 12 studies with a total of 2190 patients, and reported HRs for OS and PFS in patients with *IDH* mutations were 0.33 (95% CI 0.25–0.42) and 0.38 (95% CI 0.21–0.68), respectively, as compared with glioma patients with the wild-type *IDH* gene. Subgroup analyses based on tumor grade also showed that the presence of *IDH* mutations was associated with better outcomes.

There are several limitations to this analysis that should be considered when interpreting the results. We did not evaluate whether the histological subtype or tumor grade influenced the association of *IDH1/2* mutations with the survival outcomes of patients with secondary GBM. As mentioned above, we also did not evaluate whether the type of treatment regimen influenced the prognostic value of *IDH1/2* mutations of patients with secondary GBM. Furthermore, significant heterogeneity was present among the studies for both OS and PFS with respect to tumor type and grade, treatments, method for calculating endpoints, and method for determining the presence of mutations. Publication bias may be present as well, for those studies without significance might not be submitted or published.

CONCLUSIONS

In summary, the results of this meta-analysis indicate that *IDH1/2* mutations are associated with improved survival in patients with glioblastomas.

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