REVIEW ARTICLE

IDH wild-type lower-grade gliomas with glioblastoma molecular features: a systematic review and meta-analysis

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Abstract

The WHO 2021 classification defines IDH wild type (IDHw) histologically lower-grade glioma (hLGG) as molecular glioblastoma (mGBM) if TERT promoter mutation (pTERTm), EGFR amplification or chromosome seven gain and ten loss aberrations are indicated. We systematically reviewed articles of IDHw hLGGs studies (49 studies, $N = 3748$) and meta-analyzed mGBM prevalence and overall survival (OS) according to the PRISMA statement. mGBM rates in IDHw hLGG were significantly lower in Asian regions (43.7%, 95% confidence interval [CI: 35.8–52.0]) when compared to non-Asian regions (65.0%, [CI: 52.9–75.4]) ($P = 0.005$) and were significantly lower in fresh-frozen specimen when compared to formalin-fixed paraffin-embedded samples ($P = 0.015$). IDHw hLGGs without pTERTm rarely expressed other molecular markers in Asian studies when compared to non-Asian studies. Patients with mGBM had significantly longer OS times when compared to histological GBM (hGBM) (pooled hazard ratio (pHR) 0.824, [CI: 0.694–0.98], $P = 0.03$)). In patients with mGBM, histological grade was a significant prognostic factor (pHR 1.633, [CI: 1.09–2.447], $P = 0.018$), as was age ($P = 0.001$) and surgical extent ($P = 0.018$). Although bias risk across studies was moderate, mGBM with grade II histology showed better OS rates when compared to hGBM.

Keywords IDH wild type · Lower-grade glioma · TERT promoter mutation · Molecular glioblastoma

Introduction

Diffuse gliomas with histologically lower-grade features (hLGG) are heterogeneous tumors with different clinical outcomes. Some patients may experience long stable disease, while others rapidly deteriorate with fatal outcomes. Classifications based on histological findings have been used to discriminate subgroups with distinct prognosis outcomes. Molecular studies have reported hLGG sub-classification into different molecular subgroups [13, 14, 17, 55]. The first group is *IDH* mutant-type (IDHm) and chromosome 1p/19q co-deleted tumors which correspond to oligodendrogliomas. These tumors generally have good prognoses.

The second group is IDHm with intact 1p/19q and alterations in *ATRX* and *TP53*, corresponding to astrocytomas. In contrast, *IDH* wild type (IDHw) hLGG are molecularly and clinically distinct [2, 13, 14, 55].

In adults, IDHw gliomas may contain several pediatric-type tumors [31]; these include biologically more favorable glial and glioneuronal tumors with BRAF alterations, those gliomas with altered MYB-/MYBL-1, and high-grade gliomas with H3F3A mutation or RTK2. The other IDHw hLGG, which mainly arise from the adult supratentorial brain, frequently have molecular features of glioblastomas; TERT promoter mutation (pTERTm), epidermal growth factor receptor amplification (EGFRamp), or chromosome 7 gain and 10 loss (CH7/10). New WHO guidelines have categorized such groups as glioblastoma, IDH wild type [11]. IDHw hLGGs with molecular features of glioblastomas are typically known as molecular glioblastoma (mGBM).

Recent studies have revealed that mGBM has specific clinical features; tumors often have diffuse infiltration patterns (gliomatosis), multicentric loci or gyriform spread [39, 57]. Consequently, patients are likely to undergo biopsy rather than resection. Furthermore, they were less likely to

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receive adjuvant radiochemotherapy. Thus, while most studies have suggested the prognostic correspondence between histological glioblastoma (hGBM) and mGBM, the equivalence has not been sufficiently demonstrated. Reports have indicated that mGBM may reflect under-sampling phenomena or early-stage hGBM [49, 65]. For the former, treatment outcomes are worse if adjuvant radiochemotherapy is withheld, while for the latter, the outcomes depend on lead-time to hGBM development.

Molecular marker frequency in IDHw hLGGs differ extensively between studies. pTERTm rates vary from 15 to > 70% in IDHw hLGGs [33, 57], while EGFRamp rates vary from 10 to > 50% [19, 34]. It is unclear if such differences are caused by methodological or other factors, however, differences may affect tumor classification and prognostication.

As IDHw hLGGs are relatively rare, large-scale studies are scarce. We systematically reviewed IDHw hLGG studies and performed a meta-analysis to explore the variability underlying molecular marker frequency and their prognostic implications for mGBM.

Methods

We conducted this study according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. It was not registered on The International Prospective Register of Systematic Reviews.

Literature search and data extraction

A PRISMA flow diagram is outlined (Fig. 1). From 2009 onward, we searched for relevant English studies using the keywords "glioma," "astrocytoma," AND "IDH" OR "isocitrate dehydrogenase" AND "TERT promoter" OR "EGFR" OR "chromosome 7" OR "chromosome 10" in PubMed, Ovid MEDLINR, Cochrane library and Scopus. Literature searches and data extraction were independently conducted by two study authors. EndoNote® (version 20) was used for data processing. Adult hemispheric IDHw LGG studies including ≥ 20 cases were incorporated if molecular testing in at least one of the followings was included; EGFRamp, pTERTm or CH7/10. Exclusion criteria: (1) molecular data could not be extracted, (2) studies with IDH1 data alone, (3) public database studies (e.g. The Cancer Genome Atlas, etc.), or (4) familial or pediatric cancers. For studies from the same institute, newer or relevant studies were selected. Finally, studies were selected by authors through discussion and consensus.

We collected patient age (mean or median) and sex information, molecular data, treatment-related factors, including tumor removal degree and adjuvant therapy,

and overall survival (OS). Molecular diagnosis methods and tissue types (formalin-fixed paraffin-embedded (FFPE) or fresh-frozen (FF)) were also recorded. Studies were discriminated into Asian or non-Asian regions. When only median values and ranges were available, the mean and standard deviation were calculated using the method of Hozo et al. [26]. Individual patient data (IPD) were recorded if available. We re-calculated relevant statistical data from IPD, whereas tumors with H3F3A or BRAF mutations were excluded where possible. We used hazard ratio (HR) to determine treatment effects. When HRs were unavailable, we calculated values according to the method by Tierney et al. [59] or from Kaplan–Meier curve data. We used WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) to extract survival data from Kaplan–Meier curves [43, 44].

Statistical analysis

We used the R software program (v4.03) (https://www.r-project.org/) to perform statistical analyses (Meta, Metafor and EZR packages). An inverse-variance approach, with a random-effects method, was applied. Studies were assessed for heterogeneity (I^2 statistic). A single-arm meta-analysis was performed to assess specific mutation rates using the metaprop function with a generalized linear mixed model. Meta-regression analyses were performed to identify heterogeneity related factors. Analyses were performed using the rma.uni function in Meta software package. In Kaplan–Meier curves from reconstructed data, log-rank and Cox-proportional hazard tests were used for survival analyses. Covariates of age, sex, type of surgery, adjuvant-treatment type, Karnofsky performance status score (KPS), and promoter methylation status of O^6-methylguanine-DNA methyltransferase (MGMT), in addition to molecular status, were included in multivariate analyses when applicable. Two-sided $P < 0.05$ values were statistically significant.

Risk of bias

We used the Joanna Briggs Institute's (JBI) critical appraisal checklist for case series (Supplementary Table 1) (https://jbi.global/critical-appraisal-tools) to evaluate risk of bias. Publication bias was evaluated using a funnel plot including > 10 studies. A linear regression analysis was also performed.

Ethics approval and informed consent

This review did not involve direct human investigations; therefore, no informed consent was required.

PRISMA Flow Diagram

Identification

Records identified through database searching
(PubMed n = 475, Ovid Medline = 359, Scopus= 521, Cochrane library=15)

Screening

Records after duplicates removed
(n = 688)

Records screened by title or abstract
(n = 688)

Records excluded
(n = 476)

Eligibility

Full-text articles assessed for eligibility
(n = 212)

Full-text articles excluded,
(n = 163)

Included

Studies included
(n = 49)

Studies included for comparison between molGBM and histGBM (n = 6). For other data analyses (n = 33). For both (n = 8). Prognostic factor analyses (n = 2).

Hand search or cross-reference
(n = 0)

PubMed Search result (Sept 4. 2022)
(((("glioma*"[All Fields] OR "astrocytoma*"[All Fields]) AND ("IDH"[All Fields] OR "isocitrate dehydrogenase"[All Fields]) AND ("erbb receptors"[MeSH Terms] OR ("erbb"[All Fields] AND "receptors"[All Fields]) OR "erbb receptors"[All Fields] OR "egfr"[All Fields] OR "epidermal growth factors receptor"[All Fields] OR "TERT"[All Fields] OR "chromosome 7"[All Fields] OR "chromosome 10"[All Fields])) NOT ("children"[Title] OR "pediatric"[Title] OR "infant*"[Title] OR "congenital"[Title] OR "neurofibromatosis"[Title] OR "spinal"[Title])) AND (english[Filter])   **475**

Ovid Medline

1. (glioma or astrocytoma).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]   83087

2. (IDH or "isocitrate dehydrogenase").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]   12358
3. (TERT or EGFR or "chromosome 7" or "chromosome 10").mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]   122597
1 AND 2 AND 3 AND limit 5 to (english language and humans and yr="2009 -Current") 359

Scopus
(TITLE-ABS-KEY (GLIOMA OR ASTROCYTOMA) AND TITLE-ABS-KEY (IDH OR "ISOCITRATE DEHYDROGENASE") AND TITLE-ABS-KEY (TERT OR EGFR OR "EPIDERMAL GROWTH FACTOR RECEPTOR" OR "CHROMOSOME 7" OR "CHRMOSOME10") AND NOT TITLE (CHILDREN OR INFANT OR PEDIATRIC OR NEUROFIBROMATOSIS OR SPINAL)) AND (LIMIT-TO (DOCTYPE , "AR")) AND (LIMIT-TO (EXACTKEYWORD , "HUMAN")) AND (LIMIT-TO (LANGUAGE , "ENGLISH")) AND (LIMIT-TO (SRCTYPE , "J")) 521
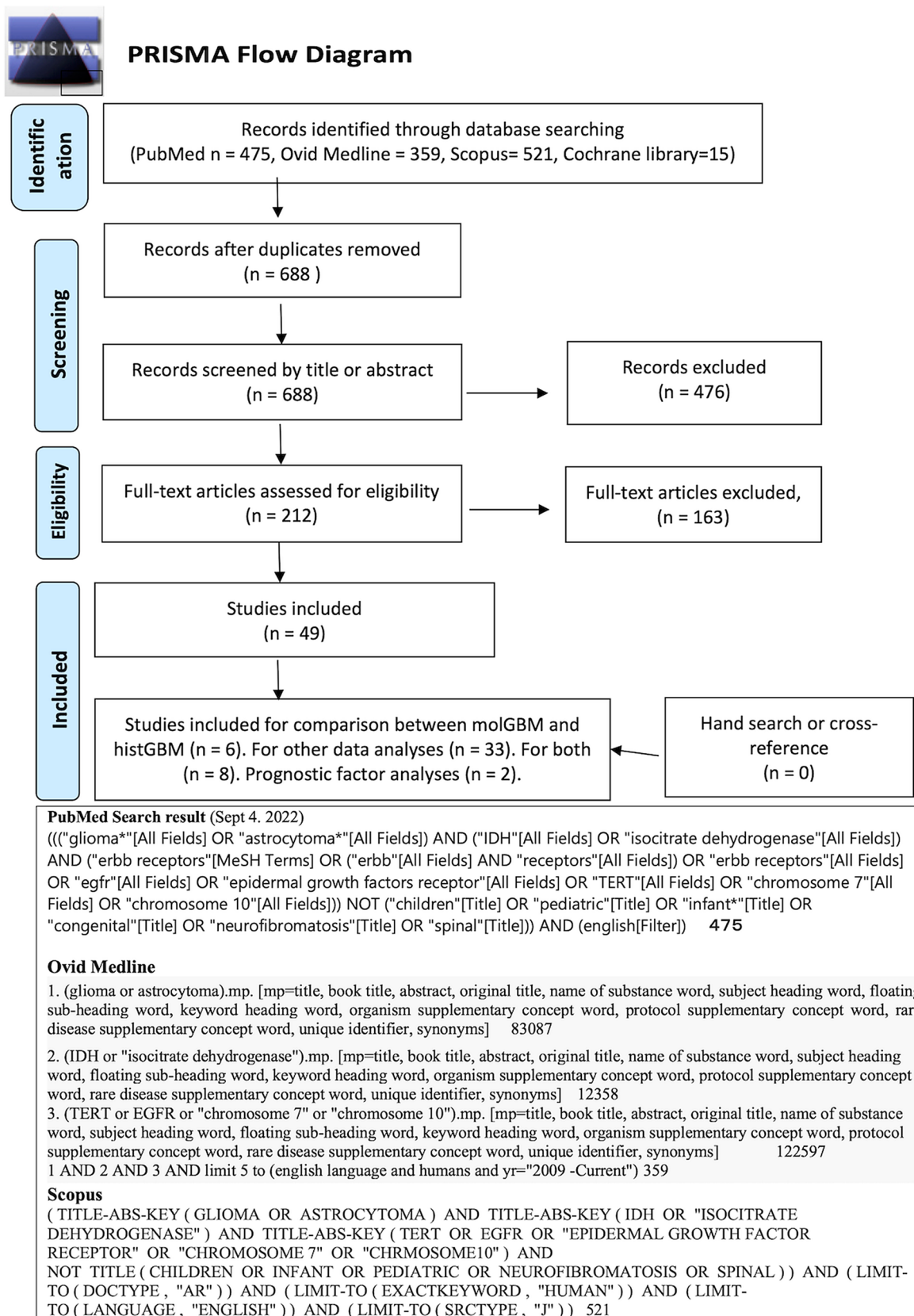
Fig. 1 PRISMA flow diagram and search strategy

Results

We performed our literature search on September 4th, 2022 and retrieved 212 studies out of 688 records for full-text assessment (Fig. 1). We excluded 163 studies (lack of relevant data = 64, < 20 case = 29, public database only = 27, review articles = 9, hGBM only = 8, overlapping data = 19, and other reasons = 7). Finally, 49 studies were selected: 6 studies for comparing mGBM with hGBM [3, 6, 15, 37, 50, 58], 33 studies for calculating molecular marker frequency [2, 4, 7–10, 12, 16–20, 23, 24, 29, 30, 33–36, 38–40, 45, 48, 51–54, 56, 60, 61, 63, 66], and 8 studies for both [25, 28, 32, 42, 46, 47, 57, 64]. Two studies were utilized for analyses of prognostic factor in mGBM [21, 62]. IPD were collected from 12 studies [2, 4, 6, 15, 19, 21, 23, 25, 51, 61, 62, 64].

Risk of bias

Almost all studies were retrospective case series' with low evidence levels. The JBI checklist for case series showed that most of them had one or two deficits (Supplementary Table 1).

mGBM marker frequency in IDHw hLGGs

In our analyses, 33 studies reported pTERTm rates in IDHw hLGG (Supplementary Table 2) [2–4, 8–10, 12, 18, 19, 24, 25, 28–30, 32, 33, 36, 38–40, 42, 45–48, 51, 52, 56, 57, 61, 63, 64, 66]. The pooled pTERTm proportion was 47.5% ([95% confidential interval (CI) 39.8–55.3]) ($N = 2044$, $I^2 = 86.2\%$) (Table 1) (Fig. 2A). A funnel plot showed no asymmetry ($P = 0.34$) (Fig. 2B). In subgroup analyses, the pooled proportion was significantly lower in studies from Asia when compared with non-Asian regions (36.2% [CI: 29.8–43.1] vs. 56.2% [CI: 45.2–66.5], $P = 0.002$), and significantly higher in studies using next generation sequencing (NGS) when compared with other methods (Sanger sequencing, Pyrosequencing or others) (68% [CI: 48.5–82.8] vs. 42.3% [CI: 35.5–49.3], $P = 0.015$), and significantly higher in studies using FFPE when compared with other methods

Table 1 Frequency of molecular markers in IDH wild-type histologically lower-grade gliomas

	TERT promotor mutation			EGFR amplification			Chromosome 7(+)/10(−)		
Pooled proportion	47.5% [39.8–55.3], $N = 2044$, $I^2 = 86.2\%$			23.6% [18.6–29.4], $N = 2225$, $I^2 = 83.1\%$			33.2% [21.5–47.4], $N = 1194$, $I^2 = 89.8\%$		
Subgroup analyses									
Region									
Asia	36.2% [29.8–43.1], $N = 867$			15.9% [10.6–23.2], $N = 683$			15.0% [6.7–30.4], $N = 317$		
Non-Asia	56.2% [45.2–66.5], $N = 1177$ $P = 0.02$			28.8% [22.9–35.6], N = 1542 $P = 0.008$			50.9% [42.9–58.9], $N = 857$ $P = 0.0003$		
Method									
NGS	68.0% [48.5–82.8], $N = 596$			26.8% [21.2–33.3], $N = 895$			48.0% [34.9–61.3], $N = 408$		
Others	42.3% [35.5–49.3], $N = 1448$ $p = 0.015$			23.0% [16.7–30.9], $N = 1350$ $P = 0.43$			28.5% [16.0–45.4], $N = 786$ $P = 0.073$		
Tissue sample									
FFPE	56.2% [45.1–66.7], $N = 1010$			29.6% [22.2–38.3], $N = 851$			53.9% [44.6–63.0], $N = 362$		
Frozen*	38.7% [28.5–50.0], $N = 894$ $P = 0.03$			17.1% [10.3–27.1], $N = 956$ $P = 0.047$			24.7% [12.4–43.4], $N = 786$ $P = 0.007$		
	Estimate	SE	P	Estimate	SE	P	Estimate	SE	P
Meta-regression									
Age	0.0728	0.0312	0.02	0.0325	0.0273	0.23	0.109	0.050	0.03
G3rate	1.29	0.708	0.068	1.363	0.646	0.035	3.098	1.554	0.046
Multiple meta-regression									
Region	0.724	0.341	0.034	0.710	0.281	0.012	1.374	0.215	< 0.0001
Age	0.367	0.028	0.19				0.0282	0.0301	0.35
G3rate				1.849	0.885	0.037	1.809	0.605	0.003
Method	− 0.395	0.434	0.36						
Tissue	0.598	0.343	0.08	0.590	0.268	0.028	1.174	0.177	< 0.0001
	Residual heterogeneity $I^2 = 84.8\%$			Residual heterogeneity $I^2 = 67.6\%$			Residual heterogeneity $I^2 = 0\%$		

Results of subgroup and meta-regression analyses. [] 95% confidence interval, G3rate, proportion of histologically grade III tumors, FFPE, formalin-fixed paraffin-embedded tissue; Frozen, fresh-frozen tissue, *including studies that using FFPE or Frozen, *SE* standard error, *N* total number of included patients

Fig. 2 **A** Forest plot of proportion for TERT promoter mutation (pTERTm) in IDH wild-type lower-grade gliomas. Subgroup analyses showing a higher frequency in Asian regions ($P = 0.0024$). **B** Funnel plot showing no asymmetry. **C** Forest plot showing molecular glioblastomas (mGBM) proportions for pTERTm rates. Subgroup analysis presenting a higher frequency in Asian regions ($P = 0.002$). **D** Kaplan–Meier curves from individual patient data showing overall survival in patients with mGBM and IDH wild-type lower-grade gliomas "not elsewhere classified" (NEC), in Asian and non-Asian regions
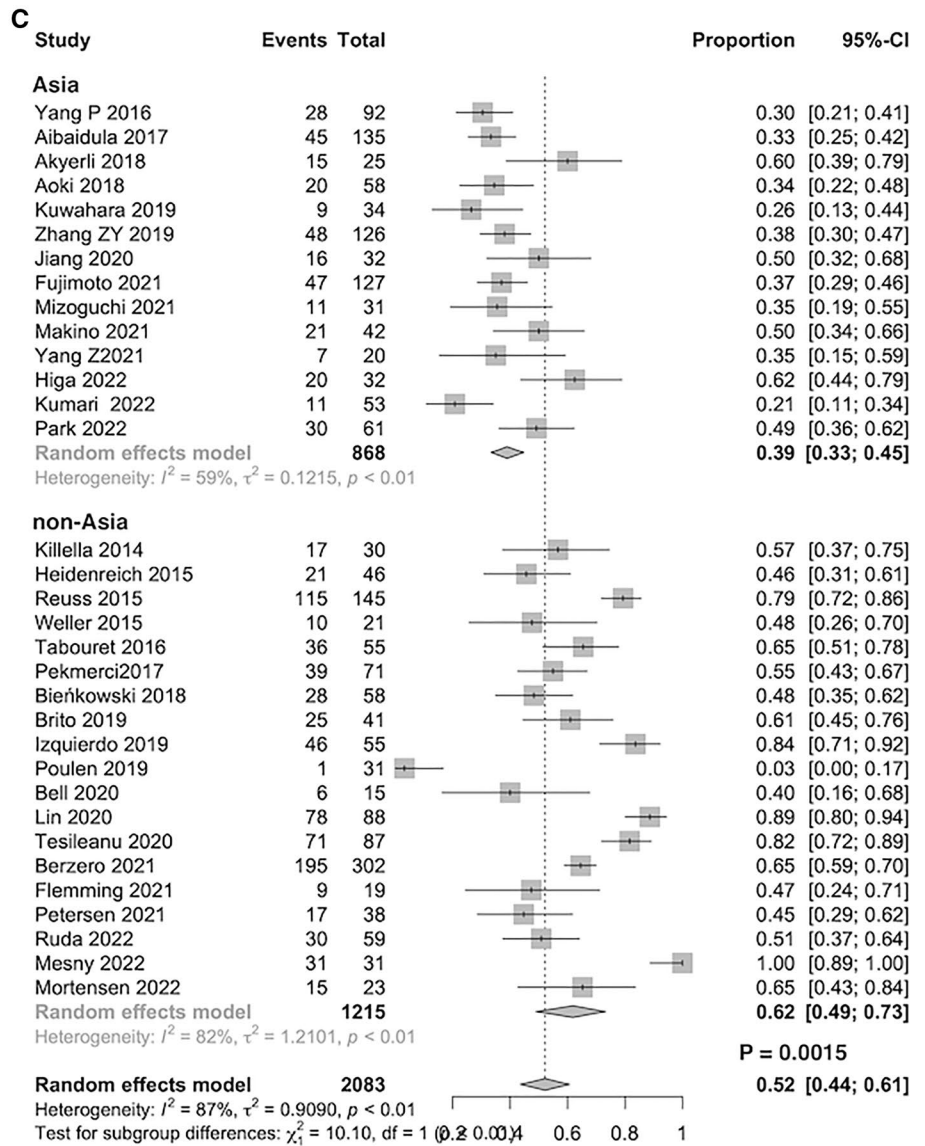
Study	Events	Total	Proportion	95%-CI
Asia				
Yang P 2016	28	92	0.30	[0.21; 0.41]
Aibaidula 2017	37	135	0.27	[0.20; 0.36]
Akyerli 2018	15	25	0.60	[0.39; 0.79]
Aoki 2018	17	58	0.29	[0.18; 0.43]
Kuwahara 2019	5	33	0.15	[0.05; 0.32]
Zhang ZY2019	48	126	0.38	[0.30; 0.47]
Jiang 2020	16	32	0.50	[0.32; 0.68]
Fujimoto 2021	46	127	0.36	[0.28; 0.45]
Mizoguchi 2021	11	31	0.35	[0.19; 0.55]
Makino 2021	18	42	0.43	[0.28; 0.59]
Yang Z2021	7	20	0.35	[0.15; 0.59]
Higa 2022	19	32	0.59	[0.41; 0.76]
Kumari 2022	9	53	0.17	[0.08; 0.30]
Park 2022	30	61	0.49	[0.36; 0.62]
Random effects model		867	0.36	[0.30; 0.43]
Heterogeneity: $I^2 = 68\%$, $\tau^2 = 0.2094$, $p < 0.01$				
non-Asia				
Killella 2014	17	30	0.57	[0.37; 0.75]
Heidenreich 2015	21	46	0.46	[0.31; 0.61]
Reuss 2015	83	127	0.65	[0.56; 0.74]
Weller 2015	10	21	0.48	[0.26; 0.70]
Tabouret 2016	24	40	0.60	[0.43; 0.75]
Pekmerci2017	39	71	0.55	[0.43; 0.67]
Bieńkowski 2018	28	58	0.48	[0.35; 0.62]
Brito 2019	25	41	0.61	[0.45; 0.76]
Izquierdo 2019	40	55	0.73	[0.59; 0.84]
Poulen 2019	1	31	0.03	[0.00; 0.17]
Bell 2020	6	15	0.40	[0.16; 0.68]
Lin 2020	70	89	0.79	[0.69; 0.87]
Tesileanu 2020	67	87	0.77	[0.67; 0.85]
Berzero 2021	174	275	0.63	[0.57; 0.69]
Flemming 2021	9	19	0.47	[0.24; 0.71]
Petersen 2021	16	59	0.27	[0.16; 0.40]
Ruda 2022	30	59	0.51	[0.37; 0.64]
Mesny 2022	30	31	0.97	[0.83; 1.00]
Mortensen 2022	12	23	0.52	[0.31; 0.73]
Random effects model		1177	0.56	[0.45; 0.67]
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 0.8290$, $p < 0.01$				
				$P = 0.0024$
Random effects model		2044	0.47	[0.40; 0.55]

Heterogeneity: $I^2 = 86\%$, $\tau^2 = 0.7359$, $p < 0.01$
Test for subgroup differences: $\chi_1^2 = 9.19$, df = 1 ($p < 0.01$)

Fig. 2 (continued)

C

Study	Events	Total	Proportion	95%-CI
Asia				
Yang P 2016	28	92	0.30	[0.21; 0.41]
Aibaidula 2017	45	135	0.33	[0.25; 0.42]
Akyerli 2018	15	25	0.60	[0.39; 0.79]
Aoki 2018	20	58	0.34	[0.22; 0.48]
Kuwahara 2019	9	34	0.26	[0.13; 0.44]
Zhang ZY 2019	48	126	0.38	[0.30; 0.47]
Jiang 2020	16	32	0.50	[0.32; 0.68]
Fujimoto 2021	47	127	0.37	[0.29; 0.46]
Mizoguchi 2021	11	31	0.35	[0.19; 0.55]
Makino 2021	21	42	0.50	[0.34; 0.66]
Yang Z2021	7	20	0.35	[0.15; 0.59]
Higa 2022	20	32	0.62	[0.44; 0.79]
Kumari 2022	11	53	0.21	[0.11; 0.34]
Park 2022	30	61	0.49	[0.36; 0.62]
Random effects model		**868**	**0.39**	**[0.33; 0.45]**
Heterogeneity: $I^2 = 59\%$, $\tau^2 = 0.1215$, $p < 0.01$				
non-Asia				
Killella 2014	17	30	0.57	[0.37; 0.75]
Heidenreich 2015	21	46	0.46	[0.31; 0.61]
Reuss 2015	115	145	0.79	[0.72; 0.86]
Weller 2015	10	21	0.48	[0.26; 0.70]
Tabouret 2016	36	55	0.65	[0.51; 0.78]
Pekmerci2017	39	71	0.55	[0.43; 0.67]
Bieńkowski 2018	28	58	0.48	[0.35; 0.62]
Brito 2019	25	41	0.61	[0.45; 0.76]
Izquierdo 2019	46	55	0.84	[0.71; 0.92]
Poulen 2019	1	31	0.03	[0.00; 0.17]
Bell 2020	6	15	0.40	[0.16; 0.68]
Lin 2020	78	88	0.89	[0.80; 0.94]
Tesileanu 2020	71	87	0.82	[0.72; 0.89]
Berzero 2021	195	302	0.65	[0.59; 0.70]
Flemming 2021	9	19	0.47	[0.24; 0.71]
Petersen 2021	17	38	0.45	[0.29; 0.62]
Ruda 2022	30	59	0.51	[0.37; 0.64]
Mesny 2022	31	31	1.00	[0.89; 1.00]
Mortensen 2022	15	23	0.65	[0.43; 0.84]
Random effects model		**1215**	**0.62**	**[0.49; 0.73]**
Heterogeneity: $I^2 = 82\%$, $\tau^2 = 1.2101$, $p < 0.01$				
			P = 0.0015	
Random effects model		**2083**	**0.52**	**[0.44; 0.61]**

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.9090$, $p < 0.01$
Test for subgroup differences: $\chi_1^2 = 10.10$, df = 1 ($p = 0.0014$)

D

(FF or either FFPE or FF) (30 studies; $N = 1904$: 56.2% [CI: 45.1–66.7] vs. 38.7% [CI: 28.5–50.0], $P = 0.03$). Meta-regression analyses also showed that the pooled pTERTm proportion increased by mean patient age ($P = 0.02$) and was possibly affected by grade III tumor rates (G3rate) ($P = 0.068$) (Table 1). Multiple meta-regression analyses showed that only regions (Asia or non-Asia) reached significance ($P = 0.03$) but FFPE exhibited borderline significance ($P = 0.08$). However, multiple meta-regression analyses still showed high residual heterogeneity ($I^2 = 84.8\%$). We hypothesized that undetermined factors may have affected our results. Such factors may have affected pTERTm rate in 1p/19q co-deleted gliomas (Codel). Indeed, we identified a significant correlation between pTERTm rates in IDHw LGG and Codel tumors ($R = 0.49$, $P = 0.012$) (Supplementary Fig.S1A). Moreover, a quantile–quantile (Q-Q) plot showed that distribution of pTERTm rates in Codel was normal when we excluded cases with rate < 90% (Supplementary Fig.S1B). For this reason, we selected 19 articles from institutes which reported ≥ 90% pTERTm rates in Codel for multiple meta-regressions. Then, the geographical region ($P < 0.001$) and method (NGS vs others, $P = 0.002$) were significant for the pTERTm proportion, and heterogeneity disappeared ($I^2 = 0\%$). The pooled pTERTm rate in IDHw hLGG was 41.1% [CI: 33.4–49.4] (7 studies, $N = 335$) in Asia but 64.1% [CI: 54.1–73.0] (12 studies, $N = 588$) in non-Asia regions ($P < 0.001$).

EGFRamp rates in IDHw hLGGs ($N = 2225$) (Table 1) were reported by 27 studies [2–4, 7, 9, 16, 17, 19, 20, 25, 28, 32, 34, 36, 38, 39, 42, 45, 47, 51–54, 56, 57, 60, 61]. The pooled EGFRamp proportion was 23.6% [CI: 18.6–29.4] ($I^2 = 83.1\%$). We did not identify publication bias ($P = 0.28$). It was low in Asia studies when compared with other regions (15.9% [CI: 10.6–23.2] vs. 28.8% [CI: 22.9–35.5], $P = 0.008$). Methodologies (NGS vs others (FISH, MLPA, array CGH etc.)) did not affect result ($P = 0.43$), but tissue type did and was significant (FFPE 29.6% [CI: 22.2–38.3] vs FF and FF or FFPE 17.1% [CI: 10.3–27.1], $P = 0.047$). Meta-regression analyses showed that G3rates were significant factors ($P = 0.035$), but mean age was not ($P = 0.23$). Multiple meta-regression analyses also revealed that geographical region ($P = 0.01$), tissue type ($P = 0.028$) and G3rates ($P = 0.037$) were significant factors impacting EGFRamp rates ($I^2 = 67.6\%$).

CH7/10 status was evaluated in 13 studies ($N = 1194$) (Table 1) [4, 9, 19, 23, 32, 35, 36, 38, 51, 54, 56, 57, 61], although definition were different (e.g. whole CH7/10, 7p(+)/10q(−), 7(+)/10q(−), or EGFR gain/PTEN loss) (Supplementary Table 1). The pooled proportion in IDHw hLGG was 33.2% [CI: 21.5–47.4] ($I^2 = 89.8\%$). A Funnel plot showed no publication bias ($P = 0.20$). The rate was also lower in Asian regions (15.0% [CI: 6.7–30.4]) when compared with non-Asian regions (50.9% [CI 42.9–58.9])

($P = 0.0003$). Methodologies (NGS vs. others) did not affect rates ($P = 0.07$), but tissue type did (FFPE 53.9% [CI: 44.6–63.0] vs. FF and FFPE or FF 24.7% [CI: 12.4–43.4] ($P = 0.007$). Meta-regression analyses showed that mean age ($P = 0.03$) and G3rate ($P = 0.046$) were significant factors. Multiple meta-regression analyses also revealed that geographical region ($P < 0.0001$), tissue type ($P < 0.0001$) and G3rate ($P = 0.0028$) significantly affected the CH7/10 rates. When evaluation was limited to studies using whole CH7/10 [9, 23, 32, 35, 36, 54, 56, 57], pooled proportion in IDHw hLGG was 34.8% [CI: 20.0–53.2], which is comparable to the abovementioned value. In this case, subgroup and meta-regression analyses did not reach significance except in terms of mean age ($P < 0.001$); however, they showed a tendency similar to the described analyses.

The prognostic implications of difference in mGBM marker rates

We calculated the pooled mGBM rate in IDHw hLGG studies examining pTERTm. The pooled mGBM rate in Asian regions (38.9% [CI: 33.4–44.8], 14 studies, $N = 868$) was lower than that in non-Asia regions (61.9% [CI: 49.0–73.2], 19 studies, $N = 1215$) ($P = 0.0015$) (Fig. 2C). Interestingly, the rate increased in studies examining multiple molecular markers (three markers 79.0% [CI: 68.9–86.5], two markers = 78.0% [CI: 50.3–92.5] vs. one marker (pTERTm) = 45.1% [CI: 34.2–56.4]) in non-Asian regions ($P < 0.0001$), while rates did not change in Asian regions (three markers = 39.6% [CI: 28.2–52.2], two markers = 32.0% [CI: 25.4–39.4], and one marker (pTERTm) = 41.1% [CI: 34.3–48.3]) ($P = 0.38$). This was true when we analyzed studies showing > 90% pTERTm rates in Codel tumors (Asian regions: $P = 0.94$ and non-Asian regions: $P < 0.0001$). Therefore, pTERT wild-type hLGGs in Asian regions rarely expressed other GBM molecular markers (4.1% when analyzed in IPD), whereas those in non-Asian did.

As molecular marker analyses showed, studies using FFPE showed a significantly higher mGBM rates (62.5% [CI: 49.5–74.0]) when compared with those using other tissue (FF or either FF or FFPE) (41.4% [CI: 31.4–52.1]) ($P = 0.014$).

We compared OS rates of IDHw hLGG tumors between Asian and non-Asian studies using IPD. The median OS rate in Asian mGBM tumors (21.1 months [CI: 16.1–24.7], $N = 185$) was similar to in non-Asian tumors (20.8 months [CI: 17.9–22.7], $N = 275$) ($P = 0.45$) (Fig. 2D). The median OS rate of IDHw hLGG tumors, "not elsewhere classified" (NEC) in Asian regions (38.1 months [30.4–46.8], $N = 304$), was also similar to non-Asian regions (35.2 months [CI: 26.4–53.3], $N = 123$) ($P = 0.6$).

Differences between mGBM and hGBM

mGBM and hGBM survival data were provided by 14 studies (Table 2) [3, 6, 15, 25, 28, 32, 37, 42, 46, 47, 50, 57, 58, 64]. Five showed that biopsied tumors were more frequent for mGBM when compared with hGBM [6, 37, 50, 57, 58] ($P < 0.001$ in each study, Fisher's exact tests), while two studies reported comparative total removal rates between the two [15, 32]. Eight studies described adjuvant radiochemotherapy frequency rates [6, 15, 32, 37, 42, 50, 57, 58]. Four studies reported that the patients with mGBM underwent radiotherapy less often when compared with patients with hGBM. Three studies reported that the patients with mGBM underwent chemotherapy less often when compared with patients with hGBM. Treatments frequency differences in other studies failed to reach significance.

While most studies showed that mGBM patients had comparable OS rates when compared with hGBM patients, the pooled HR value of mGBM against hGBM was 0.82 in univariate analyses ([CI: 0.69–0.98], $I^2 = 46\%$) ($P = 0.028$) (Fig. 3A). No publication bias was detected ($P = 0.92$) (Fig. 3B). Moderate heterogeneity improved in the pooled HR in multivariate analyses (including covariates of age (five studies), sex (four studies), surgery (four studies), radiotherapy and/or chemotherapy (three studies), KPS (three studies), MGMT (two studies) and CDKN2A/B (one study)), which showed a significantly better OS rate in mGBM (HR 0.61 [CI: 0.50–0.74], $I^2 = 0\%$) ($P < 0.0001$) (Fig. 3C). We identified no differences in pooled HR values between Asian and non-Asian regions (P = 0.80). Kaplan–Meier curves from IPD showed an identical OS rate between hGBM and mGBM with grade III histology ($P = 0.39$), but better OS for mGBM with grade II histology ($P = 0.014$) (Fig. 3D).

Prognostic factors in mGBM

We meta-analyzed prognostic factors related to OS rates in mGBM (16 studies) (Table 3) [3, 4, 9, 15, 19, 21, 25, 32, 38, 46, 47, 50, 51, 61, 62, 64]. A younger age (HR1.028 [CI: 1.011–1.045], $P = 0.001$) and extent of surgery (HR 0.643 [CI: 0.446–0.926], P = 0.018) were identified as significantly better prognostic factors. Although no molecular markers reached significance, patients with histologically grade III gliomas had worse OS rates when compared with grade II tumors in pooled results from both univariate (HR 1.58 [CI: 1.02–2.429], $P = 0.003$) and multivariate analyses (HR 1.314 [CI: 1.041–1.660], $P = 0.022$) (Supplementary Fig. S2A, B).

Discussion

mGBM has significantly better OS rates when compared with hGBM. Additionally, mGBM with grade II histological features had better OS rates when compared

with that with grade III histological features. Although mGBM rates in IDHw hLGG varied extensively among studies, differences were partly explained by geographical regions. Rates in Asia were significantly lower when compared with non-Asian regions. Interestingly, pTERT wild-type tumors in Asia rarely expressed other molecular markers, however, despite these differences, mGBM in Asian and non-Asian regions showed identical OS rates using IPD.

Diagnosis and frequency of mGBM

We identified one reason which possibly explained mGBM rate differences across studies, i.e. the geographical region. While low pTERTm frequency rates in glioblastomas in Asia were previously reported [5], this was also true for IDHw LGGs. Not only pTERTm, but also EGFRamp and CH7/10 also occurred less frequently in Asian regions. As lower-grade glioma incidences in Asia were lower when compared with eastern countries [41], mGBM incidence was assumed to be lower. We observed differences in molecular markers combination patterns between Asian and non-Asian regions. Fujimoto et al. [19] reported that pTERT mutation status was necessary and sufficient to diagnose IDHw hLGG with molecular features of glioblastoma. This appeared to be true for Asian but not in non-Asian regions. However, if only the test for pTERTm is used, approximately 4.1% of mGBM may be missed from the analyses even in Asia.

One substantial molecular diagnostic issue in this field is that TERT promotor areas have high guanine-cytosine content and easily form secondary structures which lead to a poor amplification [27]. Thus, a diagnosis may be misleading when tumor cell density is low. While it is generally accepted that FF tissues are better materials, our meta-regression analysis showed that pTERTm rates were higher in FFPE samples. EGFRamp and CH7/10 detection rates had similar frequencies. This was most likely due to sampling selection spots for molecular diagnostics. IDHw hLGGs sometimes grow invasively and adopt gliomatosis cerebri forms. In such cases, tumor cells may be sparse in tumor areas by preoperative imaging. A more appropriate area for molecular diagnoses may be selected in FFPE rather than FF samples. While different methodologies have different molecular diagnostic sensitivities [1, 22], specimen condition, especially tumor cell density, appears to be more important. To exclude the problems in material and methodological issues, we re-analyzed pTERTm data in studies that showed pTERTm > 90% of Codel tumors. This generated a small change in the pTERTm rates in mGBM but our overall conclusions were unaltered.

Table 2 Clinical and molecular features of IDH wild-type histological and molecular glioblastomas and "not elsewhere classified" lower-grade gliomas

Author year	Diagnosis	No	Age	Male/female	KPS	TERTm	EGFR amp	CH 7+/10−	Histological grade	Extent of resection	Radio-therapy	Chemo-therapy	M OS [95% CI]
Arita 2016* [6]	hGBM	301	M63	174/124	M80	181	NA	NA	IV 301	Bp32 Rx269	285/299	286/299	17.4 [16.2–19.6]
	mGBM	50	M66	25/25	M85	50	NA	NA	II 9 III 41	Bp17 Rx33	41/48	43/48	16.1 [12.6–23.4]
	Astro	87	M58	48/39	M90	0	NA	NA	II 24 III 63	Bp26 Rx61	73/86	69/86	34.8 [27.9–41.5]
Pekmezci 2017* [47]	hGBM	173	M57	NA	NA	117	NA	NA	IV 173	NA	NA	NA	15.8 [14.4–18.4]
	mGBM	39	M52	NA	NA	39	NA	NA	II 13, III 26	NA	NA	NA	22.2 [16.4–27.3]
	Astro	32	M39.5	NA	NA	0	NA	NA	II 12, II 20	NA	NA	NA	40.2 [21.3–181.5]
Akyerli 2018 [3]	hGBM	105	NA	NA	NA	NA	NA	NA	IV 105	NA	NA	NA	20.9 [18.0–25.0]
	mGBM	17	NA	NA	NA	17	NA	NA	II 4 III14	NA	NA	NA	25.9 [11.2–48.6]
	Astro	12	NA	NA	NA	0	NA	NA	II 8 III 4	NA	NA	NA	70.8 [10.2–NA]
Izquierdo 2019 [28]	hGBM	92	M66	44/48	NA	92	32/87	NA	IV 92	NA	NA	NA	13
	mGBM	40	M61	21/19	NA	40	9/39	NA	II 19 III 21	Bp34 PR5 GTR1	22	32	27
	astro	15	M40	8/7	NA	0	1/15	NA	II 7 III 8				58
Ma 2020 [37]	hGBM	345	M60	207,138	M80	151/167	112/256	NA	IV 345	Bp73 STR95 GTR177	345	308	13.5
	mGBM	22	M62.5	12/10	M90	16/17	6/21	NA	II 7 III 15	Bp13 STR4 GTR5	22	20	16.6
Tesileanu 2020 [57]	hGBM	197	M55	135/62	M90	NA	NA	NA	IV 197	Bp33 Rx164	184	181	19.2
	mGBM	71	M58	47/24	M90	67	17	42	II 45 III 16	Bp59 Rx12	48	44	23.8
	Astro	16	M45	8/8	M100	0	0	0	II 9 III 3	Bp9 Rx7	9	8	NR
Petersen 2021* [47]	hGBM	370	m63.4	229/141	NA	NA	NA	NA	IV 370	NA	313/362	213/362	11.4
	mGBM	17	m58.7	9/8	NA	13	8	NA	II 5, III 12	NA	14/25	4/25	10.0 [3.8–22.1]
	Astro	21	m59.7	14/7	NA	0	0	NA	II 11 III 10	NA	NA	NA	18.0 [7.5–23.5]
Yang 2021* [64]	hGBM	31	m54.5	17/14	NA	24	NA	NA	IVB 31	NA	NA	NA	18 [5-NR]
	mGBM	7	m54.7	3/4	NA	7	NA	NA	II 2 III 5	NA	NA	NA	NR [2-NR]
	astro	13	m44.6	4/9	NA	0	NA	NA	II 8 III 5	NA	NA	NA	NR [25-NR]
Ramos-Fresnedo 2022 [49]	hGBM	166	<65=120	100/65	>70=121	130	61	38	IV 166	Bp19, STR 44, GTR102	166	166	21
	mGBM	65	<65=43	43/22	>70=50	57	20	12	NA	Bp32, STR 22, GTR11	65	65	26

Table 2 (continued)

Author year	Diagnosis	No	Age	Male/female	KPS	TERTm	EGFR amp	CH 7+/10−	Histological grade	Extent of resection	Radio-therapy	Chemo-therapy	M OS [95% CI]
Higa 2022* [25]	hGBM	178	M66	106/72	NA	113	40	15	IV 178	NA	NA	NA	20
	mGBM	20	M64	11/9	NA	19	9	1	II5 III15	NA	NA	NA	51
Teske 2022 [58]	hGBM	224	M59	144/80	M90	NA	NA	NA	IV 224	GTR53 PTR 41, Bp130	216	223	19
	mGBM	57	M59	34/23	M80	57	NA	NA	II 19 III 38	GTR2 PTR 1 Bp54	25	33	19
Kumari 2022 [32]	hGBM	21	m48	13/8	NA	15	3	2	IV 21	GTR 21	21	21	19
	mGBM	11	m35.7	4/7	NA	9	3	1	II 8 III 3	GTR3 NTR5 STR1 Bp2	4	5	18
	Astro	42	m35.5	27/15	NA	0	0	0	II 23 III 19	GTR/NTR26 Lob14, Bp 1	31 radiotherapy and/or chemotherapy		GII 41.7, GIII 17
Mortensen 2022 [42]	hGBM	141	M65	91/50	NA	NA	NA	NA	IV141	NA	123	101	13.6
	mGBM	15	M67	9/6	NA	13	3	3***	NA	NA	14	11	18.3
Chan 2022** [15]	hGBM	319	m52.6	182/137	NA	153/315	40/135	NA	IV 319	GTR185 non-total 125	108/151	104/152	11.0 [9.96–12.2]
	mGBM	92	m50.7	55/37	NA	83	18/40	NA	II 36 III56	GTR 55 non-total 27	40/52	30/52	16.6 [12.6–27.8]

hGBM histological glioblastoma, mGBM molecular glioblastoma: astro IDH wild lower-grade gliomas not elsewhere classified, M median, m mean, TERTm TERT promoter mutation, EGFRamp amplification of epithelial growth factor receptor, CH7+/10− chromosome 7 gain and 10 loss, NA not available, NR not reached, OS overall survival, Bp biopsy, Rx resection, GTR gross total resection, NTR near total resection, STR subtotal resection, PR partial resection, Lob lobectomy astro IDH wild lower-grade glioma without molecular features of glioblastoma, *data re-calculated from individual patient data, **individual patient data obtained from https://www.surgery.cuhk.edu.hk/BTC/HSBC/molecular_grading_paper_data.pdf (Hong Kong & Shanghai Brain Consortium) but excluding cases with BRAF and H3F3A mutation, ***chromosome 7 gain and PTEN loss
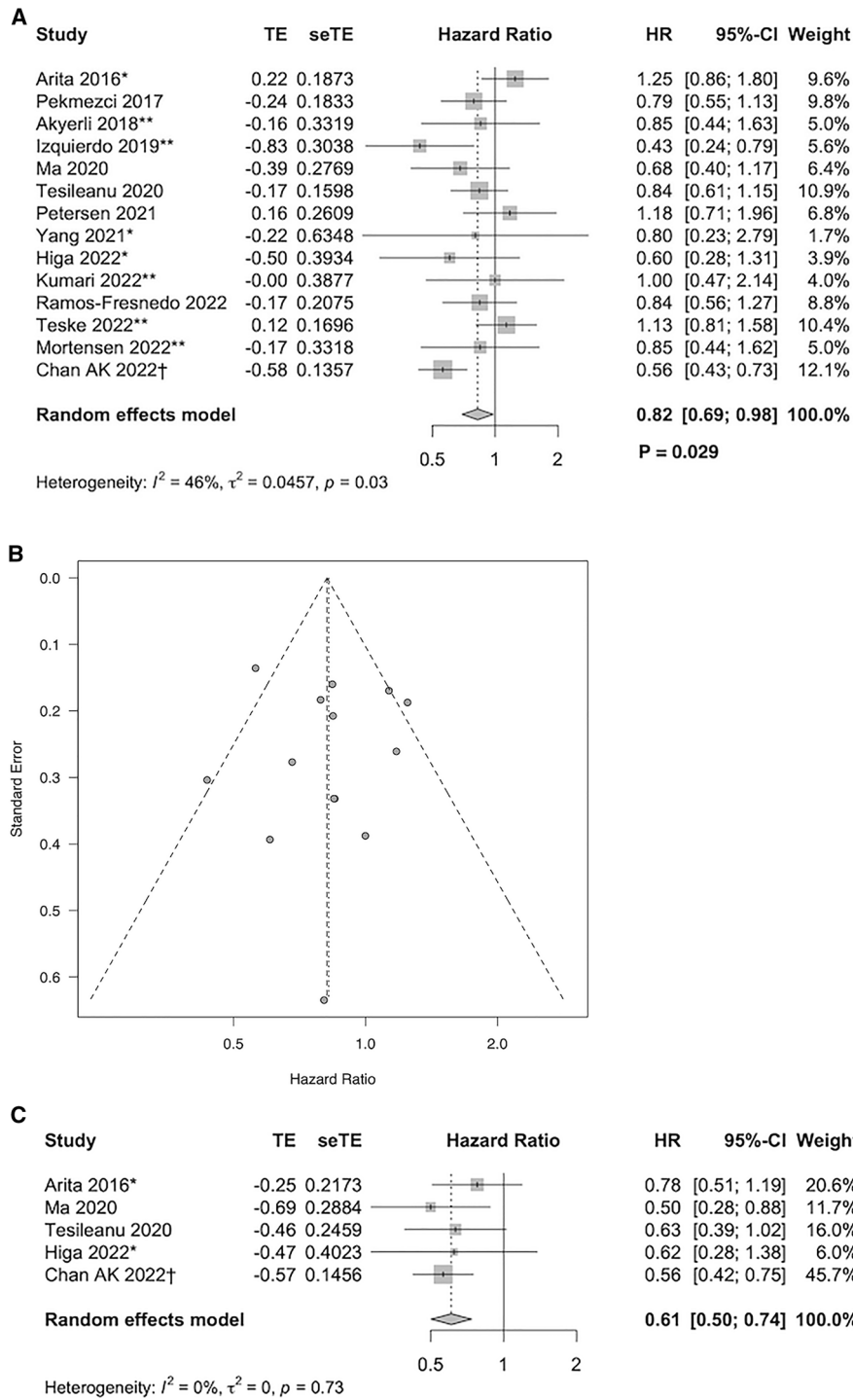
Fig. 3 A Forest plot showing hazard ratio (HR) values from overall survival analyses (univariate) between patients with molecular glioblastoma (mGBM) and histological glioblastoma (hGBM). **B** Funnel plot showing no asymmetry. **C** Forest plot (from multivariate analyses) showing significantly lower HR values in mGBM against hGBM (*P* < 0.0001), with low heterogeneity. *data from individual patient data (IPD):**extracted data from Kaplan–Meier curves: †data from https://www.surgery.cuhk.edu.hk/BTC/HSBC/molecular_grading_paper_data.pdf. **D** Kaplan- Meier curves of IPD showing better OS rates for mGBM with grade II histology when compared with mGBM with grade III histology or hGBM

D
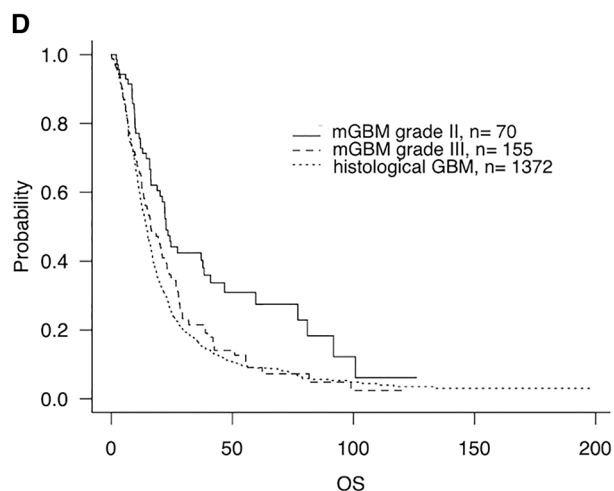
Fig. 3 (continued)

Prognostic factors in mGBM

Although mGBM in most studies exhibited similar OS rates to hGBM, pooled HR analyses showed better OS rates in mGBM when compared with hGBM. Furthermore, pooled HR values from multivariate analyses, including a covariate analysis of age, sex and surgery, showed a much better OS rates with lower heterogeneity (HR 0.61 [CI: 0.50–0.74], $I^2 = 0\%$). Berzero et al. [9] reported better OS rates in mGBM with grade II histology when compared with grade III, although their study lacked multivariate analyses. As mGBMs with grade III features showed worse OS rates when compared with grade II (HR 1.582 [CI:

1.030–2.429], $P = 0.003$), differences in OS rates between mGBM and hGBM appeared to be due to the grade II subgroup in mGBM, as indicated by Kaplan–Meier curves (Fig. 3D).

However, even mGBM in grade II histology sometimes shows rapid growth with new ring-like contrast enhancement by magnetic resonance imaging [28, 39], and hGBM transformation at recurrence [49, 52]. Thus far, specific molecular abnormalities showed no significant difference in OS rates [21, 50]. We also showed that no molecular markers significantly affected prognoses other than histological grade. The prognostic significance of the extent of mGBM surgery remains controversial. Ruda et al. [52] identified no survival benefit from gross total resection of mGBM with grade II histology (they did not include stereotactic biopsy cases). Ramos-Fresnedo et al. [50] did not demonstrate OS differences between biopsy and GTR ($P = 0.079$). Nevertheless, we showed that pooled HR favored more extensive surgery (HR 0.644 [CI: 0.420–0.990], $P = 0.045$). Zhang et al. [65] reported that the prospective identification of mGBM resulted in more aggressive patient management and improved clinical outcomes when compared with a biologically matched historical control patient cohort receiving standard-of-care therapy based on histomorphologic diagnoses alone. However, the effects of early aggressive treatment for mGBM must be examined in future studies.

Study limitations

Our study had several limitations. Firstly, most studies were retrospective and had low evidence levels. Consequently,

Table 3 Pooled results of prognostic factors in overall survival of molecular glioblastomas

Factors	Pooled hazard ratio [95% CI], I^2	P value	References
mGBM (hGBM = 1)	U: 0.824 [0.694–0.980], 46.1% M: 0.61 [0.502–0.738], 0%	0.03 <0.001	[3, 6, 15, 25, 28, 32, 37, 42, 46, 47, 50, 57, 58, 64]
Age (continuous)	U: 1.028 [1.011–1.045], 47.1% M: 1.054 [1.031–1.078]. 0%	0.001 <0.0001	[4, 15, 19, 21, 25, 46, 47, 51, 61, 62, 64]
Sex (Female = 1)	U: 0.992 [0.764–1.288], 0%	0.95	[4, 15, 19, 21, 25, 47, 50, 61, 62, 64]
Surgery (bp = 1)	U: 0.643 [0.446–0.926], 2.1% M: 0.45 [0.256–0.791], 34.0%	0.018 0.006	[4, 15, 19, 21, 50]
WHO grade (II = 1)	U: 1.633 [1.09–2.447], 56.4% M: 1.314 [1.041–1.660]. 28.9%	0.018 0.022	[3, 4, 9, 15, 19, 25, 32, 38, 46, 47, 51, 61, 62, 64]
pTERTm (mut = 1)	U: 0.812 [0.523–1.259], 0%	0.35	[4, 15, 19, 47, 51]
EGFR (amp = 1)	U: 0.823 [0.597–1.135], 6.7%	0.23	[15, 19, 21, 25, 47, 51]
CH7/10 (no = 1)	U: 0.785 [0.563–1.094], 0%	0.15	[4, 19, 21, 51, 62]
CDKN2A/B del (no = 1)	U: 1.352 [0.951–1.921], 0%	0.09	[4, 19, 21, 25, 47, 51]
MGMT (unmethyl = 1)	U: 0.645 [0.396–1.05], 0%	0.078	[19, 50, 61, 64]

bp biopsy or partial removal, *pTERTm* TERT promotor mutation, *CH7/10* chromosome 7 gain and 10 loss, *U* pooled hazard ratio of univariate analyses, *M* pooled hazard ratio of multivariate analyses, *mut* mutation, *amp* amplification, *del* homodeletion

heterogeneity was high in pooled data and multiple meta-regression analyses were required to identify reasons for this. Secondly, while we largely excluded tumors with BRAF or H3F3A mutation, some studies presented no information. Most of the studies had no data regarding other pediatric-type gene changes, such as altered MYB/MYB-L1. Therefore, NEC numbers in IDHw hLGG may have been overestimated in some studies. Thirdly, in some cases, we extracted survival data from Kaplan–Meier curves in figures of articles. Although we confirmed overlapping of original and extracted curves, measurement errors in graph line thickness may have inadvertently occurred. Fourthly, some multi-institutional studies may have had overlapping data with other studies. While we carefully selected studies, some duplicates data may have been included. Potential data overlaps are recorded in supplementary Table 1.

Conclusion

Patients with mGBM have better OS rates when compared with patients with hGBM, especially when grade II histology is indicated. We could not identify other molecular markers that differentiated mGBM prognosis, although patient age and surgical extent were prognostic factors. We identified differences between Asian and non-Asian regions in terms of molecular marker frequency pattern for mGBM in IDHw hLGG. However, OS rates in patients with mGBM were concordant between Asian and non-Asian cohorts. Although a considerable number of "NEC" in IDHw hLGGs were identified especially in Asian patients, further studies are warranted for their classification. Controversies continue to persist in the new WHO classification of IDHw hLGG. DNA methylation profiling is an evolving method that will further facilitate classification [31]. Prospective clinical studies in IDHw hLGG with DNA methylation profiling are necessary in the future.

Declarations

Conflicts of interest The authors declare none.

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