Review Article

Association of human telomerase reverse transcriptase promoter mutation with unfavorable prognosis in glioma: A systematic review and meta-analysis

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Background: Glioma is one of the most malignant and aggressive tumors, with an extremely poor prognosis. Human telomerase reverse transcriptase (hTERT) promoter mutation is regarded as a risk factor in tumor growth. Although the prevalence of hTERT promoter (pTERT) mutation in gliomas has been investigated, the results are inconsistent. This meta-analysis aims to investigate the prognostic value of hTERT in glioma patients and its interaction with other biomarkers. **Materials and Methods:** We searched 244 citations from four databases: PubMed (2000–2021), Web of Science (2000–2021), Embase (2010–2021), and Cochrane Library (2000–2021) with 28 articles included. **Results:** We calculated hazard ratios (HRs) using the random effect model and the pooled result suggested that TERT promoter mutation predicted poorer overall survival (HR: 1.53, 95% confidence interval [CI]: 1.34–1.75, $P < 0.001$, I2: 49.9%, pheterogeneity:0.002) and progression-free survival (HR: 1.55, 95% CI: 1.27–1.88, $P < 0.001$, I2: 0.0%, pheterogeneity: 0.473). For subgroup analysis, we analyzed multiple factors including iso-citrate dehydrogenase (IDH) genotype, age, diagnosis, pTERT region, so as to locate the sources of heterogeneity. Interestingly, in IDH mutant subgroup, pTERT mutation became a beneficial prognostic factor (HR: 0.73, 95% CI: 0.57–0.93, I2: 22.3%, pheterogeneity: 0.277), which is contrary to the results in pooled analysis. **Conclusion:** In general, pTERT mutation may result in shorter survival time in glioma patients, but longer survival time when glioma patients are combined with IDH mutation.

Key words: Glioma, human telomerase reverse transcriptase, iso-citrate dehydrogenase, meta-analysis, prognosis

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INTRODUCTION

There is an urgent need to address the healthy problems caused by glioma, a malignant tumor in central nervous system, which is a growing public health concern worldwide for its 40% of primary brain tumors accompanied by a poor prognosis. Gliomas can be classified into astrocytic, oligodendroglial, and other neuroepithelial tumors, of which glioblastoma (GBM) has the worst prognosis and is most common in primary brain tumors.[1,2] A growing body of literature hint at the importance of the telomerase reverse transcriptase (human telomerase reverse transcriptase [hTERT]) in oncogenesis. In broad terms, hTERT is understood as a reverse transcriptase with high specificity that adds repeats to 3′ end of chromosomes with key role in maintaining chromosomes integrity,[3]

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which has a sharp positive correlation between repeated cell replication and oncogenesis.[4] Tremendous research has been published, suggesting pTERT mutation in glioma patients, with mainly two types of mutation in hTERT promoter (pTERT) region: C228T and C250T,[4] desired molecules into a new binding section for transcriptional enhancers,[4] which in turn upregulates TERT. Since TERT expression in body cells is extremely low, a pTERT mutation is generally thought to be a hallmark of oncogenesis. Recently, a considerable amount of literature has been published suggesting a worse survival in pTERT mutated glioma patients. However, interestingly, some studies indicated differently with adverse ratios (hazard ratio [HR] <1) in their results. Due to this inconsistency, the aim of our research is to conduct a meta-analysis seeking for the correlation of pTERT mutation and survival of glioma patients, which contribute to prognosis and develop targeted drug that can lead to new curative therapies.

METHODS

Searching strategy

Pertinent publications that concentrate on the subject of glioma more frequently adopt a historical or chronological approach were carried out based on four databases: PubMed, Web of Science, Embase, and Cochrane Library from 2000 to January 26, 2022. The studies were restricted to humans and there were no place and publication status limitations. The broad use of the key term "glioma," "hTERT," and "prognosis" is sometimes broadened to include (hTERT) AND (glioma OR glial cell tumor OR astrocytoma OR GBM) AND (prognosis OR prognostic OR prognoses). The search volume with high correlation on databases and some articles related to the searched keywords was also viewed for potential studies. The functional information of regularly imported data was all from the electronic databases into EndNote with duplicates deleted. Articles were independently assessed by two reviewers (Rongxuan Hua and Qiuxuan Li) using predesigned eligibility forms, according to defined inclusion criteria and exclusion criteria. Any disagreement between investigators was resolved by consensus.

Inclusion and exclusion criteria

Although extensive research has been carried out on glioma, no single study has analyzed the complex clinical manifestations and possible mechanisms. Analysis was based on the conceptual framework proposed by following standards listed as follows: First, there are investigations on TERT promoter mutation in glioma patients; second, they evaluated the survival outcomes including overall survival (OS) or progression-free survival (PFS) in glioma patients; third, HRs and 95% confidence interval (CI) are available or able to be calculated with enough data. Last but not least, the studies about TERT expression affects the survival rate in glioma patients were also taken into consideration.

Exclusion were as follows: (i) are about other tumors but glioma; (ii) without successive records of following-up; (iii) were no enough data for HRs and 95% CIs calculation; (iv) the data are from neither clinical nor experimental studies, but from other sources such as reviews, posters, conference papers, letters, etc.; and (v) a clear benefit of factor in the prevention of glioma could not be identified in this analysis.

Quality assessment

To evaluate the quality and methodological appropriateness of included articles, provide guidance for future research as well, a wide variety of relevant parameters for disease evaluation have been proposed, including the Newcastle–Ottawa Scale in the meta-analysis.[5] Two reviewers independently awarded stars and studies can receive a maximum score of nine stars. Studies awarded more than five stars regarded to be of high-quality and low-quality are awarded a star.

Data extraction

All data were extracted using Microsoft Office Excel 2019 as dichotomous outcomes (primary outcome: OS and secondary outcome: PFS). All of the content related to the research is extracted, including the names of the first author, publication years, ethnicity, diagnosis group, stages of tumors, sample size, numbers of male and female, mean age, cutoff values, outcomes, HRs combined with 95% CIs, therapy methods, variable types, and investigation design including prospective and retrospective studies to corroborate the initial diagnosis and study designs (retrospective or prospective). For several studies that did not offer HRs and 95% CIs, we extracted them from Kaplan − Meier curves in original articles. In order to make the obtained data have more objectivity and accuracy, all the related data were extracted by two independent authors (Rongxuan Hua and Qiuxuan Li) and discussed with a third author (Han Gao) if disagreement occurs.

Statistical analysis

HRs and 95% CIs were directly extracted from included articles if the data was straightly given, if not, Engauge Digitizer Software version 4.1 (Mark Mitchell, Baurzhan Muftakhidinov and Tobias Winchen *et al*.URL: http://markummitchell.github.io/engauge-digitizer) was used for retrieving the HRs and the 95% CIs from the Kaplan-Meier curves. When a HR >1, it indicates a worse prognosis in glioma patients with mutant pTERT. StataSE version 12.0 (Stata Corp, College Station, TX, USA) was used for the following statistical analyses. HRs and 95% CIs were combined in analyzing the association of pTERT mutation with the prognosis of glioma patients. Cochran's

Q test and Higgins I^2 statistic were conducted to evaluate the heterogeneity. For $P_{heterogeneity}$ <0.10 or I^2 >50% in the literature,[6] which indicates a significant heterogeneity, we use random-effect model (DerSimonian–Laird method). Otherwise, the fixed-effects model (Mantel–Haenszel method) was undertaken. Subgroup analysis was conducted to investigate the sources of heterogeneity among included studies. We separately categorized 28 studies into Subgroup 1-6 based on following stratification: iso-citrate dehydrogenase (IDH) genotype (wildtype/mutant), age (adult/adult and children), diagnosis (astrocytoma/GBM), pTERT region (C228T/C250T), ethnicity (Asian/Caucasian), and TERT evaluation type (promoter mutation/protein expression). Publication bias was assessed by Begg's funnel. Sensitivity analysis was conducted for locating sensitive factor among the included studies. During statistical analysis, exponential transformation has been done. The statistically significant threshold is set to $P < 0.05$.

RESULTS

Study characteristics

The initial search strategies retrieved 244 articles with 72 duplicates. One hundred and seventy-two articles were identified for title and abstract screening, 113 of them were excluded for three reasons. Afterward, 59 of them were taken into full-text evaluation with 31 further excluded. Eventually, 28 articles were included for our meta-analysis.[7-34] Among them, 21 studies[7-27] were about pTERT mutation and others[28-34] were about TERT expression [Figure 1].

This system of selection has been broadened to include 28 articles (2013–2021) according to whether meet the inclusion standards discussed detail above. Each study has a sample size range from 20 to 807 with a total of 5881 participants, which came from 13 countries. By way of illustration, approximately 75% those surveyed focus more attention on pTERT mutational, which is optimized as a whole meta-analysis. The remaining 25% of the literature

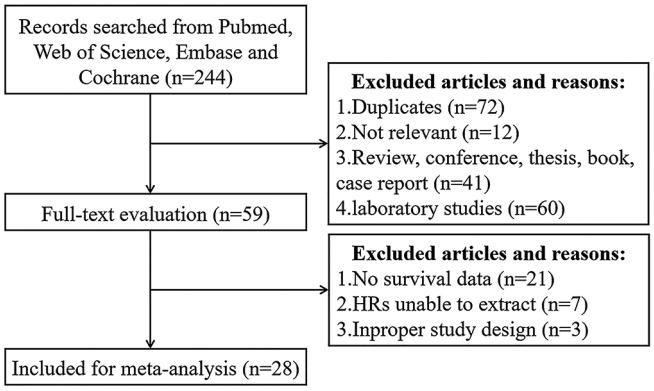

Figure 1: Flow diagram presenting the data selection process and criterions followed in this meta-analysis

is concerned with the expression of TERT, which, as a parameter, can only be managed a subgroup analysis. Particular variables have been extracted including ethnicity, cancer type, sample size, age of patients, cutoff values, etc., Those factors were not all integrated, although we have read every study thoroughly; therefore, we put only those who have certain data into consideration during each subgroup analysis.

To assess whether and how glioma is produced and received, the genotyping was measured by reverse transcription–polymerase chain reaction (RT-PCR), real time-PCR, and PCR-Sanger sequencing. In general, strong evidence suggests a positive correlation between the pTERT mutation (or TERT expression) and OS in glioma. All mentioned characteristics of the study are listed in Tables 1-3.

Influences of pTERT mutation on overall survival and progression-free survival in glioma patients

Figure 2 presents the results of pooled analysis among 21 studies measures of the data of pTERT mutation and OS in glioma participants. In order to confirm the positive correlation between pTERT mutation and OS/PFS of glioma by meta-analysis, the random-effect model is one of the more practical ways to capture the complexities of the phenomenon of bases on the data with obviously heterogeneity (I^2 = 49.9%, P = 0.002). What can be clearly seen in this Figure 2 is the dramatic positive correlation was found between the mutated pTERT and a worse outcome for both OS (combined HR: 1.53, 95% CI: 1.34–1.75, $P < 0.001$, I^2: 49.9%, $p_{heterogeneity}$: 0.002) and PFS (combined HR: 1.55, 95% CI: 1.27–1.88, $P < 0.001$, I^2: 0.0%, $p_{heterogeneity}$: 0.473) in glioma patients.

Subgroup analysis

Given the significant heterogeneity in this meta-analysis of 25% of all the included articles, the reliability of measures of subgroup analyses was assessed to better understand the heterogeneity. The participants were stratified into subgroup 1–6 separately by: IDH genotype, age, diagnosis, pTERT region, ethnicity, and TERT evaluation type.

Further analysis subgroup 1 based on IDH genotype provides the significant positive correlation between pTERT mutations and worse OS in IDH-wildtype gliomas [HR: 1.69, 95% CI: 1.36–2.10, I^2 = 26.1%, $p_{heterogeneity}$: 0.247; Figure 3]. Next, we found a most striking observation that the pTERT mutation became a benefit factor in IDH-mutant patients [HR: 0.73, 95% CI: 0.57–0.93, I^2 = 22.3%, $p_{heterogeneity}$: 0.277; Figure 4], which greatly explain the heterogeneity in pooled analysis. To gain further insights, we next collected additional data in more detail from other subgroups to illustrate two potential indexes. Subgroup 2: The results,

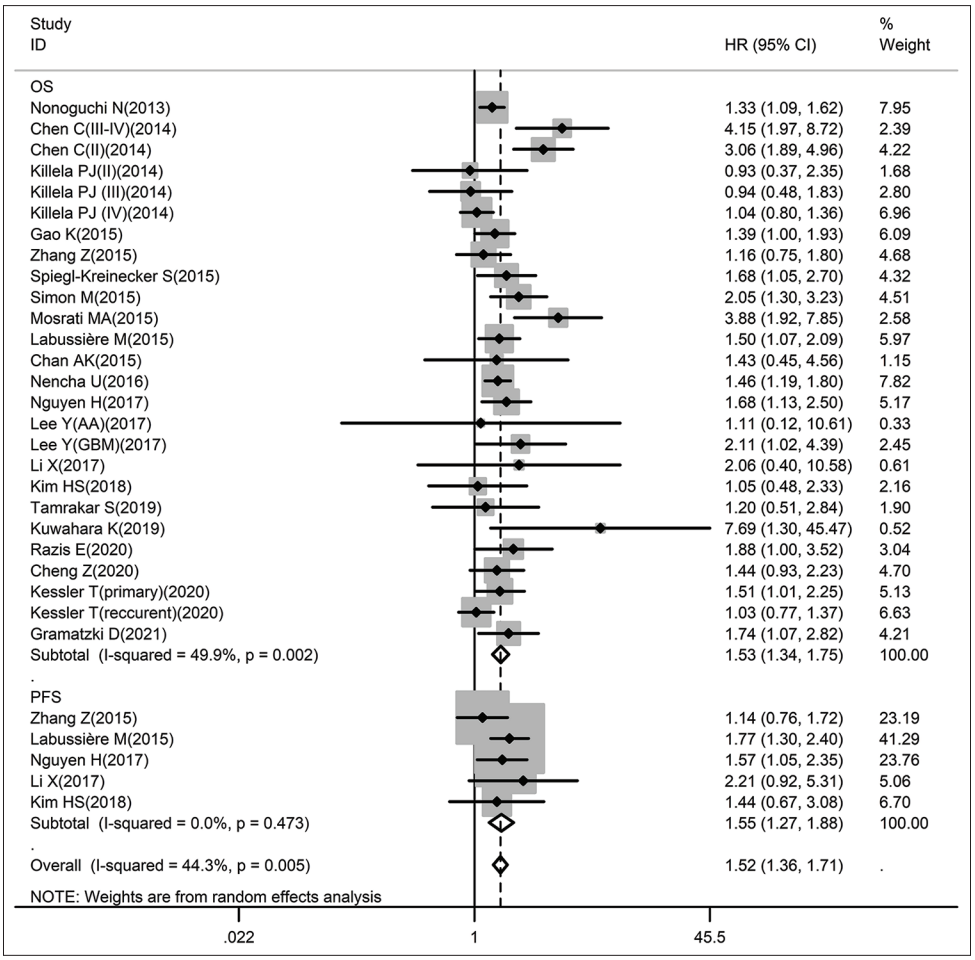

Figure 2: Forest plots for studies on the association between pTERT mutation and OS/PFS in glioma among 28 studies included in the meta-analysis (Some contain multiple HRs). Results are presented as individual and pooled HR (95% CI). OS: Overall survival, PFS: Progression-free survival, HR: Hazard ratio, CI: Confidence interval

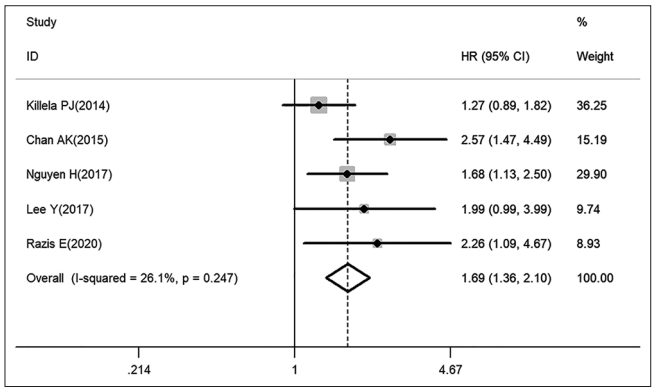

Figure 3: PTERT mutation associated with worse prognosis in IDH-wildtype patients (fixed-effect model). IDH: Iso-citrate dehydrogenase

as shown in Table 4, indicate that a clear disadvantage of pTERT mutation in OS of astrocytoma patients (HR: 2.91, 95% CI: 1.97–4.31, I^2 = 0.00%, $p_{heterogeneity}$: 0.548) than in GBM patients (HR: 1.54, 95% CI: 1.28–1.85, I^2 = 49.8%, $p_{heterogeneity}$: 0.021). Subgroup 3: This result is somewhat counterintuitive that pTERT mutation is slightly more unfavorable in studies that included only adults (HR: 1.62, 95% CI: 1.36–1.92, I^2 = 0.00%, $p_{heterogeneity}$: 0.451) rather than that included both adults and children (HR: 1.42, 95% CI: 0.97–2.07, I^2 = 0.00%, $p_{heterogeneity}$: 0.840) in prognosis. Subgroup 4: Stratification by pTERT mutation region found that both C228T (HR: 1.72, 95% CI: 1.00–2.97, I^2 = 79.6%, $p_{heterogeneity}$: 0.001) and C250T (HR: 1.50, 95% CI: 1.15–1.95, I^2 = 41.4%, $p_{heterogeneity}$: 0.146) mutation are negative predictor for OS in glioma. Subgroup 5: Stratification by ethnicity shows that pTERT as an unfavorable factor in Asian (HR: 1.65, 95% CI: 1.35–1.80, I^2 = 51.7%, $p_{heterogeneity}$: 0.010) and Caucasian (HR: 1.49, 95% CI: 1.28–1.74, I^2 = 56.4%, $p_{heterogeneity}$: 0.014) glioma patient. Subgroup 6: The data demonstrated that for TERT evaluation type, pooled HR was 1.56 (95% CI: 1.35–1.80, I^2 = 57.2%, $p_{heterogeneity}$: 0.001) for pTERT mutation; and 1.11 (95% CI: 1.04–1.18, I^2 = 67.1%, $p_{heterogeneity}$: 0.003) for TERT expression.

In general, through subgroup analysis, we may draw a conclusion that IDH mutation is an unneglectable factor in the association of TERT and prognosis. Moreover, TERT mutation seems to be a worse risk factor in astrocytoma patients. In addition, it is inappropriate to take both children

Table 1: Characteristics of 1-10 studies included in the meta-analysis

Author (year)	Ethnicity	Cancer type	Sample size	Age	Cutoff (hTERT)	Outcome	*R*	95% CI		NOS score
								Lower	Upper	
Gramatzki (2021)	Caucasian	GBM (IV)	298	Adult	Mutant versus wildtype	OS	1.74	1.07	2.82	7
Razis (2020)	Caucasian	Gliomas (III-IV)	77	Adult	Mutant versus wildtype	OS	1.88	1.00	3.51	8
					Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	2.26	1.09	4.66	
Cheng (2020)	Asian	Gliomas (II-IV)	395	All	Mutant versus wildtype	OS	1.44	0.93	2.23	7
Kessler (2020)*	Caucasian	Primary GBM (IV)	455	NA	Mutant (C228T) versus wildtype	OS	1.23	0.77	1.97	7
					Mutant (C250T) versus wildtype	OS	2.56	1.2	5.44	
		Recurrent GBM (IV)			Mutant (C228T) versus wildtype	OS	0.80	0.54	1.20	
					Mutant (C250T) versus wildtype	OS	1.34	0.89	2.01	
Tamrakar (2019)	Asian	Gliomas (II-IV)	97	All	Mutant versus wildtype	OS	1.20	0.50	2.80	7
Kuwahara (2019)	Asian	Astrocytoma (II-III)	36	Adult	Mutant versus wildtype	OS	12.5	2.17	100.00	7
Kim (2018)	Asian	Gliomas (II-IV)	67	Adult	Mutant versus wildtype	OS	1.055	0.495	2.422	8
						PFS	1.436	0.670	3.080	
Nguyen (2017)	Caucasian	Gliomas (II-IV)	303	NA	Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	1.68	1.13	2.50	6
						PFS	1.57	1.05	2.36	
Lee (2017)	Asian	Anaplastic Astrocytoma (III)	67	Adult	Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	1.110	0.116	10.608	8
		GBM (IV)				OS	2.111	1.016	4.389	
Li (2017)*	Asian	Gliomas (II-IV)	47	All	Mutant versus wildtype	OS	2.06	0.40	10.56	6
					Mutant versus wildtype	PFS	2.21	0.92	5.32	

*Data extracted form survival curve. Data of hTERT promoter mutation (*n*=22) and hTERT expression difference (*n*=7) in glioma patients. GBM=Glioblastoma; hTERT=Human telomerase reverse transcriptase; IDH=Iso-citrate dehydrogenase; PFS=Progression-free survival; OS=Overall survival; NA=Not available; CI=Confidence interval; NOS=Newcastle-Ottawa Scale

Table 2: Characteristics of 11-18 studies included in the meta-analysis

Author (year)	Ethnicity	Cancer type	Sample size	Age	Cutoff (hTERT)	Outcome	HR	95% CI		NOS score
								Lower	Upper	
Nencha U (2016)*	Caucasian	GBM (IV)	651	NA	Mutant versus wildtype	OS	1.46	1.19	1.80	7
Gao K (2015)	Asian	Gliomas (I-IV)	389	Adult	Mutant versus wildtype	OS	1.39	1.13	2.17	7
					Mutant (C228T) versus wildtype	OS	7.66	2.21	26.61	
					Mutant (C250T) versus wildtype	OS	2.5	0.57	10.91	
Zhang Z (2015)	Asian	Gliomas (II-III)	295	NA	Mutant versus wildtype	OS	1.158	0.746	1.796	7
						PFS	1.139	0.756	1.716	
					Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.890	0.349	2.267	
Spiegl-Kreinecker S (2015)	Caucasian	GBM (IV)	126	NA	Mutant versus wildtype	OS	1.683	1.048	2.703	8
Simon M (2015)	Caucasian	GBM (IV)	176	Adult	Mutant versus wildtype	OS	2.05	1.30	3.23	7
Mosrati MA (2015)	Caucasian	GBM (IV)	146	NA	Mutant (C228T) versus wildtype	OS	4.04	1.55	10.51	7
					Mutant (C250T) versus wildtype	OS	3.7	1.3	10.51	
Labussière M (2015)	Caucasian	Glioms (II-IV)	807	Adult	Mutant versus wildtype	OS	1.497	1.071	2.092	8
						PFS	1.766	1.299	2.401	9
					Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.57	0.32	1.00	
Chan AK (2015)*	Asian	Gliomas (II-III)	236	NA	Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.46	0.24	0.88	9
					Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	2.70	1.36	5.37	
		Astrocytoma (II-III)			Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	2.42	1.14	5.15	

*Data extracted form survival curve. Data of hTERT promoter mutation (*n*=22) and hTERT expression difference (*n*=7) in glioma patients. GBM=Glioblastoma; hTERT=Human telomerase reverse transcriptase; IDH=Iso-citrate dehydrogenase; PFS=Progression-free survival; OS=Overall survival; NA=Not available; CI=Confidence interval; NOS=Newcastle-Ottawa Scale; HR=Hazard ratio

and adults into accounts, since our results showed no significant differences ($P > 0.05$) in those studies that did not exclude children.

Publication bias and sensitivity analysis

No evidence for notable publication bias for the analysis between pTERT mutation and OS [Pr> |z| = 0.065;

Table 3: Characteristics of 19-28 studies included in the meta-analysis

Author (year)	Ethnicity	Cancer type	Sample size	Age	Cutoff (hTERT)	Outcome	HR	95% CI		NOS score
								Lower	Upper	
Chen C (2014)	Asian	Gliomas (III-IV)	62		Mutant versus wildtype	OS	4.148	1.973	8.721	7
		Astrocytoma (II)				OS	3.058	1.886	4.958	
Killela PJ (2014)*	Caucasian	Gliomas (II)	442	NA	Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.93	0.37	2.37	9
		Gliomas (III)			Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.87	0.42	1.79	
					Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	1.39	0.27	7.16	
		Gliomas (IV)			Mutant/IDH wildtype versus wildtype/IDH wildtype	OS	1.26	0.87	1.82	
					Mutant/IDH mutant versus wildtype/IDH mutant	OS	0.85	0.58	1.25	
Nonoguchi N (2013)	Caucasian	GBM (IV)	187	NA	Mutant (C228T) versus wildtype	OS	1.50	1.07	2.11	8
					Mutant (C250T) versus wildtype	OS	1.17	0.76	1.80	
Gandhi P (2021)	Caucasian	Gliomas (II-IV)	135	NA	Plasma protein expression (1.309 ng/L)	OS	1.230	1.075	1.408	7
Elsers D (2021)	Caucasian	GBM (IV)	53	Adult	IHC expression score	OS	0.691	0.310	1.549	7
Potharaju M (2019)	Caucasian	GBM (IV)	87	Adult	IRS1-6 versus IRS7-12	OS	1.65	0.94	2.89	6
Rute JM (2017)	Caucasian	GBM (IV)	55	Adult	Expression	OS	1.034	1.001	1.067	6
Gandhi P (2017)	Caucasian	Gliomas (II-IV)	72	NA	Intra-tumor expression 2.315%	OS	1.057	1.030	1.080	6
					Plasma protein 1.309 ng/L	OS	1.322	1.160	1.510	
Dorris K (2014)*	Caucasian	Gliomas (IV)	20	Adult	Protein expression	OS	0.90	0.04	19.25	6
Lötsch D (2013)	Caucasian	GBM (IV)	100	All	mRNA expression	OS	1.02	0.61	1.71	7

*Data extracted form survival curve. Data of hTERT promoter mutation (n=22) and hTERT expression difference (n=7) in glioma patients. GBM=Glioblastoma; hTERT=Human telomerase reverse transcriptase; IDH=Iso-citrate dehydrogenase; OS=Overall survival; NA=Not available; CI=Confidence interval; NOS=Newcastle-Ottawa Scale; HR=Hazard ratio; IHC=Immunohistochemistry; IRS=Immunoreactivity score

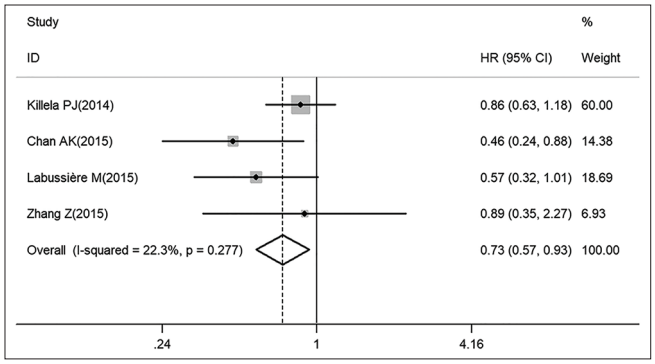

Figure 4: PTERT mutation leads to pleasant prognosis outcomes in IDH-mutant glioma patients (fixed-effect models). IDH: Iso-citrate dehydrogenase

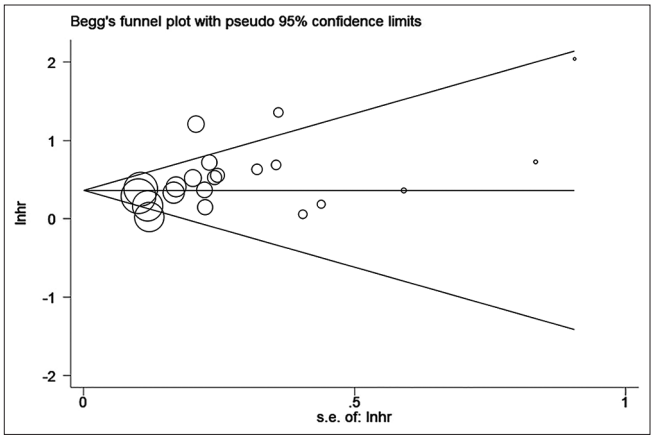

Figure 5: Begg's funnel plot testing publication bias in studies reporting association of OS and pTERT mutation; P = 0.065. OS: Overall survival

Figure 5] or PFS [Pr> |z| = 0.806; Figure 6] was found in Begg's funnel test. Meanwhile, sensitivity analysis suggested that none of the studies affected the combined HR for OS significantly [Figure 7]. Because of the amount of studies on TERT expression was not adequate enough, we did not test its publication bias and sensitivity analysis.

DISCUSSION

As a key factor in tumor oncogenesis, multiple regression analysis revealed that TERT plays an important part in maintaining chromosomes integrity, allowing tumor cell to replicate repeatedly thus regulating the growth of cancer.[35] pTERT promoter mutation is beneficial for its expression, thus may function as a risk factor in tumor. Recently, molecular factors including pTERT, IDH, MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation,[36] Chromosome 1p/19q co-deletion,[37] etc., have found their rising status in disease classification and diagnosis due to the limitation of histological classification. That means TERT is one of the hotspots which we are trying to obtain a full understanding in cancers, especially gliomas. Recent studies on glioma have investigated in TERT, as well as its correlated molecules, which contributes to the rapidly expanding

Table 4: Summary of the subgroup meta-analysis results

Analysis (OS)	*n*	References	Fixed-effect model		Random-effect model		Heterogeneity	
			HR (95% CI)	*P*	HR (95% CI)	*P* (*Z*-test)	I^2 (%)	Ph
Subgroup 1								
IDH-wildtype	5	[8,14,16,23,25]	1.69 (1.36-2.10)	0.000	1.76 (1.42-2. 17)	0.000	22.5	0.271
IDH-mutant	4	[19,23-25]	0.73 (0.57-0.93)	0.012	0.70 (0.52-0.95)	0.023	22.3	0.277
Subgroup 2								
GBM	8	[7,10,16,17,20-22,27]	1.47 (1.31-1.65)	0.000	1.54 (1.28-1.85)	0.000	49.8	0.021
Astrocytoma	4	[12,16,23,26]	2.97 (1.97-4.31)	0.000	2.91 (1.97-4.31)	0.000	0.00	0.548
Subgroup 3								
Adult	8	[7,8,12,13,16,18,21,24]	1.62 (1.36-1.92)	0.000	1.62 (1.36-1.92)	0.000	0.00	0.451
Adult and children	3	[9,11,15]	1.42 (0.97-2.07)	0.072	1.42 (0.97-2.07)	0.072	0.00	0.840
Subgroup 4								
C228T	4	[10,18,22,27]	1.32 (1.06-1.64)	0.012	1.72 (1.00-2.97)	0.052	79.6	0.001
C250T	4	[10,18,22,27]	1.50 (1.15-1.95)	0.003	1.67 (1.13-2.47)	0.010	41.4	0.146
Subgroup 5								
Asian	10	[9,11-13,15,16,18,19,23,26]	1.64 (1.38-1.96)	0.000	1.65 (1.35-1.80)	0.001	51.7	0.010
Caucasian	11	[7,8,10,14,17,20-22,24,25,27]	1.39 (1.27-1.52)	0.000	1.49 (1.28-1.74)	0.000	56.4	0.014
Subgroup 6								
pTERT mutation	21	[7-27]	1.44 (1.33-1.56)	0.000	1.56 (1.35-1.80)	0.000	57.2	0.001
TERT expression	7	[28-34]	1.06 (1.04-1.08)	0.000	1.11 (1.04-1.18)	0.001	67.1	0.003

n=Number of studies; Ph=*P* values of *Q*-test for heterogeneity test. HR=Hazard ratio; CI=Confidence interval; OS=Overall survival; TERT=Telomerase reverse transcriptase; GBM=Glioblastoma; IDH=Iso-citrate dehydrogenase

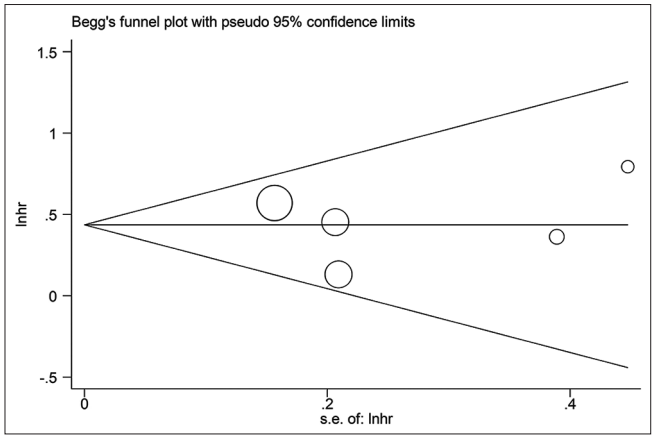

Figure 6: Begg's funnel plot testing publication bias in studies reporting association of PFS and pTERT mutation; *P* = 0.806. PFS: Progression-free survival

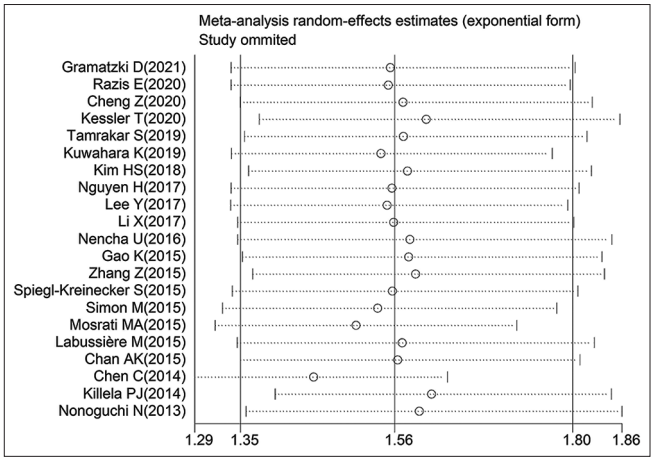

Figure 7: Sensitivity analysis investigating whether certain study remarkably affected the combined HR for OS (with random-effect model). OS: Overall survival, HR: Hazard ratio

field of comprehensive investigation, and found that TERT promoter mutation may have a negative impact on glioma patients' prognosis. Surprisingly, some studies suggested patients with IDH mutation achieve the best survival rate when TERT promoter co-mutated, even better than IDH mutation alone, which was thought to be a protective factor in glioma patients' survival.[38] However, in glioma patients, its inconsistent with previous results of survival make it harder to be applied in diagnosing and targeted drug using. These differences can be explained in part by the proximity of the SNP on TERT and the differences among individuals.[39] Some investigations have also suggested that TERT may have an impact on adjuvant therapies and radiotherapy resistance,[18,19] which makes it more significant and urgent for confirming the role that TERT plays in glioma. That's why there is abundant room for further progress in conducting the meta-analysis as an important issue for present research.

The cohort in our meta-analysis included 28 studies from 2013 to 2021, with 5881 patients in gliomas from 13 different countries involved according to the inclusion criteria. We used the HRs and 95% CIs reported in those studies as many as we could for pooled analysis and subgroup analysis, and those who didn't provide adequate HRs and 95% CIs, we extracted them from Kaplan–Meier curves. Included studies were divided and analyzed separately into studies focused on TERT promoter mutation and TERT expression. Because of the insufficient results in the latter, we did not conduct them in pooled analysis, publication bias test, and sensitivity analysis.

Results suggesting hTERT promoter mutation significantly predicted poorer survival in patients with glioma. Patients with mutated pTERT are more likely to have shorter OS and PFS after surgery or treatment. We also found the correlation between elevated TERT expression and worse OS in glioma. However, there are heterogeneity in our meta-analysis which we believed is caused by many factors such as: most of the study data have not separate pTERT mutation region (C228T and C250T), few of them take IDH mutation into consideration, the patients had quite different age and stages. Luckily, some of the studies have clearer data on those factors mentioned above, so we next conducted subgroup analysis for further examination. Results showed a significant difference between IDH mutation and wild type patients (subgroup 1): patients who have mutated IDH genotype are expected to have longer survival through pTERT mutation, which suggested the opposite since pooled HR showed pTERT mutation as a risk factor. Meanwhile, there are several limitations in this study that need to be mentioned. First, this study is fully retrospective, thus there will inevitably be a subjective bias. Second, the articles we searched were all in the English language, which may result in publication bias. Third, there were not sufficient data about potential interaction among TERT and MGMT, 1p/19q co-deletion, etc., If those data were adequate enough, we may achieve a better result with lower heterogeneity and clearer understanding of how pTERT mutation affects the prognosis of glioma patients.

In general, this meta-analysis demonstrated that hTERT might be the negative prognostic factors for glioma patients. The analysis of hTERT undertaken here has extended our knowledge of the impact of TERT in shortening OS were weaker on expression level than gene level. This could indicate multiple unclear mechanisms in hTERT functioning in prognosis of glioma patients. In future, more well-designed studies with different perspective are needed to confirm the conclusion. One source of weakness in this study was high heterogeneity and less effectivity of the data, which could have affected the measurements of TERT mutation and results in shorter survival time in glioma patients. Therefore, the accuracy and prospection of such predictions might be reduced. Notwithstanding these limitations, this work offers valuable insights into the diagnosis and treatment of glioma in the clinical strategy.

CONCLUSION

Although this study focuses on hTERT in glioma patients' prognosis, one of the more significant findings to emerge from this summary is that the underling mechanism of IDH mutation reverses the poor prognosis outcome along with upregulated hTERT expression. These findings contribute in several ways to our understanding of hTERT and provide a basis for an extremely poor prognosis. Notwithstanding the relatively limited sample, this work offers valuable insights into the mechanism of hTERT expressing pathway and other involved molecules in glioma prognosis.

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Conflicts of interest

There are no conflicts of interest.

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