Original Article

Serine hydroxymethyltransferase 2 predicts unfavorable outcomes in multiple cancer: a systematic review and meta-analysis

Juan Du[1#], Yongkang Huang[2#], Suxian Jing[1#], Yongjian Pei[2], Yajuan Qian[2], Yuanyuan Zeng[1,3,4]

[1]Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Soochow University, Suzhou, China; [2]Department of Respiratory and Critical Care Medicine, the Second Affiliated Hospital of Soochow University, Suzhou, China; [3]Suzhou Key Laboratory for Respiratory Diseases, Suzhou, China; [4]Institute of Respiratory Diseases, Soochow University, Suzhou, China

Contributions: (I) Conception and design: Y Zeng; (II) Administrative support: Y Zeng; (III) Provision of study materials or patients: J Du, Y Huang; (IV) Collection and assembly of data: J Du, Y Huang, S Jing; (V) Data analysis and interpretation: J Du, S Jing; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Yuanyuan Zeng. Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Soochow University, 1 Shizi Road, Suzhou 215006, China. Email: yuanyuanzeng@suda.edu.cn.

Background: Serine hydroxymethyltransferase (SHMT) is critical for one-carbon unit metabolism and is increasingly reported to be associated with tumor patients' outcomes. Thus, we designed and performed this meta-analysis to reveal its prognostic role and relationship with clinicopathological characteristics in human cancer.

Methods: A systematic search of PubMed, Embase, Web of Science and Cochrane Library (CENTRAL) was carried out. Two reviewers independently screened all references for eligibility according to the inclusion criteria. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality and data was extracted for the meta-analysis.

Results: Ten studies, composed of 1,942 patients in total, were included in this meta-analysis. Higher expression of SHMT2 means an unfavorable prognosis [overall survival: hazard ratio (HR) =2.14, 95% confidence interval (CI): 1.53 to 2.99; progression-free survival (PFS)/disease-free survival (DFS)/recurrence-free survival (RFS): HR =1.90, 95% CI: 1.31 to 2.76]. Furthermore, higher SHMT2 expression is associated with larger tumor size [odds ratio (OR) =2.09, 95% CI: 1.58 to 2.77], more lymph node invasions [OR =2.67, 95% CI: 1.78 to 4.00), and higher tumor node metastasis classification (TNM) stage (OR =2.23, 95% CI: 1.55 to 3.21). Higher expression of SHMT2 is also related to higher histopathological grade (OR =3.46, 95% CI: 1.46 to 8.27) and distant metastasis (OR =1.25, 95% CI: 0.32 to 4.90), however, with significant heterogeneity (I^2=61%, P=0.08 for distant metastasis; I^2=82%, P<0.001 for histopathological grade). The prognostic clinical role of SHMT1 in clinical patients has not been directly investigated yet.

Discussion: SHMT2 may serve as a promising prognostic biomarker in various cancer, especially in the alimentary system. Further large-scale studies are warranted to verify the possible effect.

Keywords: Serine hydroxymethyltransferase (SHMT); human cancers; clinicopathological features; predictive biomarker

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Introduction

One carbon unit is a carbon group containing a carbon atom including methyl, methylene, methylene, hydroxymethyl, formyl, and aminomethyl, produced in the catabolism of serine, glycine, tryptophan, or histidine. Once generated, it binds with tetrahydrofolate (THF) to form the stable form, for instance, N^5, N^{10}-methylene-THF (mTHF) or N^5-aminomethyl-THF (amTHF), and subsequently engages in nucleotide and methionine synthesis. Serine hydroxymethyltransferase (SHMT) is an enzyme that catalyzes the interconversion reaction of serine to mTHF and glycine, and the latter product of this process, glycine, can likewise be converted into mTHF in the further enzymatic reaction. Therefore, SHMT plays a pivotal role and is even deemed as the core in generating one-carbon units by some researchers (1,2). There are two isoforms of SHMT, namely SHMT1 located in the cytoplasm and SHMT2 that is mainly expressed in mitochondrion (3), to catalyze the same reaction.

Cancer has been a health challenge worldwide. According to the 2020 report from the International Agency for Research on Cancer (IARC) (4), a total of 19.3 million new cases of various types of cancer were diagnosed in the past year. Approximately one in five people would develop cancer in their lifetime. Moreover, 10 million people, about one in eight men or one in eleven women, died from the advanced cancer in the past year, resulting in incalculable family economic loss and social burden. Therefore, it is of paramount importance to early diagnose and explore new therapy. Cancer cells are featured for aberrant proliferation and entail abundant substances, including one carbon unit. As a key enzyme promoting the generation of one carbon unit, cumulative researches have proved the pro-tumor role of SHMT in multiple cancers, making it possible that SHMT can serve as a tumor biomarker and potential target of anticancer agents. We here investigated the prognostic role of SHMT in human cancers and its relationship with clinicopathological characteristics, which had not been previously recapitulated and quantitatively evaluated.

This meta-analysis was designed, performed, and reported following recommendations of PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2485/rc) and Cochrane Handbook guidelines (5).

Methods

Literature searching strategy

We searched for potential studies in PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and web of science before June 2021, using the keywords and their synonyms. Search terms were modified according to each index term in database, such as Medical Subject Heading (MeSH) in PubMed and Emtree in Embase. We focused on clinical studies on humans when searching on Embase, but set no restrictions on other databases. Detailed search terms are shown in Appendix 1.

Inclusion and exclusion criteria

Studies in our review had to meet all of the following criteria: (I) objects were human patients diagnosed as any tumor pathologically; (II) the study reported the association of SHMT expression with survival outcome and/or clinicopathological characteristics.

The exclusion criteria were: (I) duplicate studies; (II) studies with the same data or overlapping data by the same authors; (III) studies without any one of the predetermined outcomes; (IV) studies without access to the full-text.

Quality assessment

The quality of all selected studies was assessed and scored independently by two reviewers according to the Newcastle–Ottawa Quality Assessment Scale (6) in the following regards: selection, comparability, and outcome. Disagreements on the scores would be resolved by consensus or cross-checking with a third author. The final hierarchy of a study was determined by the sum of the score of each item. The corresponding score of 0–3, 4–6, 7–9 was accepted as low quality, medium quality, and high quality, respectively.

Data extraction

Two researchers independently extracted the following data from each study: characters of the study (first author, publication year, number of participants, cancer type, study period), characters of the participants (gender, age, country, expression level ratio, cut-off value, follow-up),

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and outcomes. If both multivariate analysis and univariate results were reported, hazard ratio (HR) and corresponding 95% confidence interval (CI) of multivariate analysis were preferred. If neither was available, HRs with 95% CIs were extrapolated based on Kaplan-Meier curves using the spreadsheet provided by Tierney *et al.* (7). During the data extraction, any disagreements between the two authors were resolved by consensus or cross-checking with a third author. Additional information was collected through communication with the principal investigator by email if necessary.

Statistical analysis

Statistical analysis was performed by an independent researcher adept in statistics using RevMan (Version 5.4.0; The Nordic Cochrane Centre, The Cochrane Collaboration) and Stata (Version 16.0; The StataCorp LLC). Continuous variables were reported as mean and standard derivation (SD), while dichotomous variables were shown as frequency or proportion. The results were displayed in forest plots. An initial test for clinical, methodological, and statistical heterogeneities was conducted, and we used the chi-square test with $P<0.1$ and $I^2>50\%$ to indicate statistical significance. A random-effects model was applied in the presence of significant heterogeneity and Galbraith radial plot analysis would be performed on the purpose to determine the underlying cause. Otherwise, the fixed-effects model was chosen. HR or odds ratio (OR) with 95% CI was calculated according to the data type.

Results

Study selection

Two hundred sixty-three studies were identified from the primary research, and 114 were omitted for duplication by manual comparing the authors, publication years, and titles. Whereas the remaining were screened by abstract, and 83 articles not relevant to this topic, 25 studies that reported none of the interested outcomes, and 23 reviews or comments, were subsequently excluded. Then, 18 articles were viewed through the whole text for eligibility, of which 7 studies with inadequate or explicit data and one without excess were voted out. Finally, 10 studies were included in the meta-analysis (8-17). The flowchart of the study is shown in *Figure 1*.

Characteristics and quality of the enrolled studies

The included studies all focused on SHMT2 and were carried out in China (n=7), Japan (n=2) and Germany (n=1). All chosen studies were published between 2016 and 2019, and involved mainly the alimentary system malignancy including liver carcinoma (n=3), gastric cancer (n=2), colorectal cancer (n=2), esophageal cancer (n=1), pancreatic ductal adenocarcinoma (n=1), and breast cancer (n=2), and human glioma (n=1). All studies utilized immunohistochemistry (IHC) to evaluate the expression level of SHMT2 except the study of Bernhardt *et al.* (14) that performed the reverse phase protein arrays. Most researchers reported the HR of overall survival (OS) and progression-free survival (PFS)/disease-free survival (DFS)/recurrence-free survival (RFS) with their 95% CI directly while 3 offered the Kaplan-Meier curve and P-value. Characteristics of studies and participants are shown in *Tables 1* and *2*, respectively.

The quality of the included studies was scored and classified. Nine of the included studies (90%) received no less than 7, which stratified into high-quality studies group, while the left (16) was scored 6 and deemed as the moderate quality study. Detailed Newcastle-Ottawa quality assessment scales of each study are summarized and shown in *Table 3*.

Analysis of the survival associated with SHMT2 expression

Nine studies (8-15,17), involving 1,814 participants in total, reported the association between SHMT2 expression and overall survival. These studies were subjected to OS analysis, and the pooled HR indicates higher SHMT2 correlated with decreased OS (HR =2.14, 95% CI: 1.53 to 2.99), however, with a significant heterogeneity ($I^2=81.4\%$, $P<0.001$). Subgrouped by the system, the result showed that higher expression of SHMT2 invariably means poorer OS in all involved systems (HR =1.74, 95% CI: 1.50 to 2.03, for the alimentary system; HR =9.89, 95% CI: 6.12 to 15.98 for glioma cancer; HR =1.53, 95% CI: 1.10 to 2.12 for breast cancer) with a decent homogeneity ($I^2=0\%$, $P=0.678$ for the alimentary system). The Forest plot of overall survival is shown in *Figure 2*.

Seven studies (10,12-17), composed of 1,568 participants, included in the PFS/RFS/DFS synthesis also uncover an unfavorable role of SHMT2 (HR =1.90, 95% CI: 1.31 to 2.76, $I^2=80.9\%$, $P<0.001$), when subgrouped by the system, the trend remains consistent (HR =1.63, 95% CI: 1.35 to

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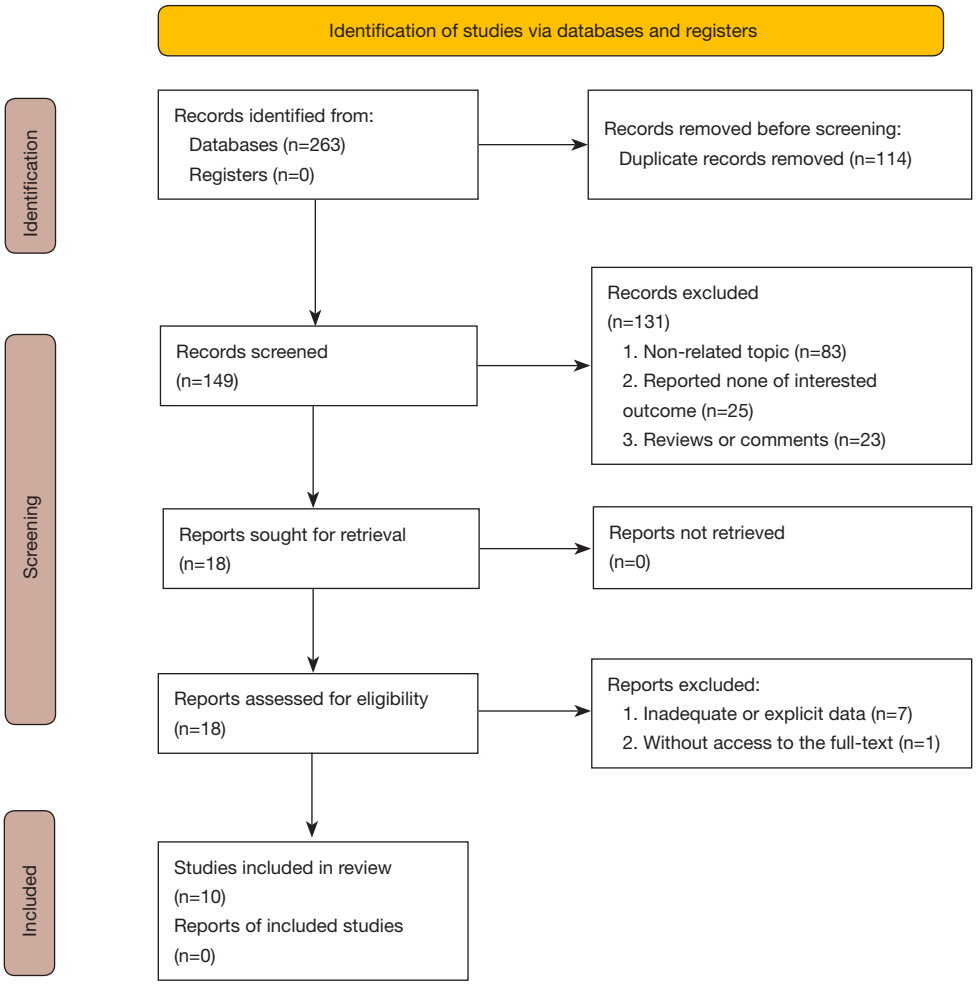

Figure 1 Study flow.

1.97 for the alimentary system; HR =7.4, 95% CI: 4.69 to 11.68 for glioma cancer; HR =1.58, 95% CI: 1.21 to 2.07 for breast cancer). The Forest plot of PFS/RFS/DFS is shown in *Figure 3*.

Analysis of the clinicopathological characteristics associated with SHMT2 expression

We also tried to analyze the association between clinicopathological characteristics and SHMT2 expression. The results are encapsulated in *Table 4*, which reveal that higher expression of SHMT2 was correlated to bigger tumor size (OR =2.09, 95% CI: 1.58 to 2.77), more lymph node invasion (OR =2.67, 95% CI: 1.78 to 4.00), and eventually higher TNM grade (OR =2.23, 95% CI: 1.55 to 3.21). There was also a tendency that showed the unfavorable correlation between expression and distant metastasis (OR =1.25, 95% CI: 0.32 to 4.90) and histopathological grade (OR =3.46, 95% CI: 1.46 to 8.27), but with non-negligible heterogeneity (I^2=61%, P=0.08 for distant metastasis; I^2=82%, P<0.001 for histopathological grade). Relevant forest plots are shown in Figures S1-S4.

Heterogeneity analysis and sensitivity analysis

The Chi-square test was utilized for heterogeneity analysis. Regrettably, it revealed significant heterogeneity exists for the eligible researchers evaluating OS (I^2=81.4%, P<0.001), A following Galbraith radial plot (*Figure 2*) was generated and indicated heterogeneity was probably caused by the

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Table 1 Characteristics of the studies

Author	Publication year	Samples	SHMT type	SHMT detection	Cut-off value of SHMT expression	Follow-up (month)	Study period	Country	Source of HR
Shi *et al.*	2019	130	SHMT2	IHC	Staining scores with intensity and proportion (>3)	46.6	2008–2016	China	Reported
Ji *et al.*	2019	144	SHMT2	IHC	Staining scores with intensity and proportion	36	2006–2017	China	Reported
Liu *et al.*_GC	2019	58	SHMT2	IHC	Staining scores with intensity and proportion (>4)	Until May 2018	2010–2013	China	Reported
Liu *et al.*_EC		65	SHMT2	IHC	Staining scores with intensity and proportion (>4)	Until May 2018	2010–2013		
Liu *et al.*_CC		60	SHMT2	IHC	Staining scores with intensity and proportion (>4)	Until May 2018	2010–2013		
Ning *et al.*	2018	100	SHMT2	IHC	Staining scores including intensity and proportion (>4/12)	37	2005–2015	China	Reported
Noguchi *et al.*	2018	103	SHMT2	IHC	Staining scores with proportion (≥2/2)	60.9	2007–2013	Japan	Reported
Wang *et al.*	2017	150	SHMT2	IHC	Staining scores with intensity (≥2/2)	36	2012–2013	China	Survival curve
Bernhardt *et al.*	2017	801	SHMT2	Reverse phase protein arrays	Median expression level	–	2009–2011	Germany	Reported
Miyo *et al.*	2017	117	SHMT2	IHC	The samples showing an average staining were used as a positive control	58.8	2006–2009	Japan	Survival curve
Zhang *et al.*	2016	128	SHMT2	IHC	Staining scores with intensity and proportion	Until 30 September 2010	2002–2006	China	Reported
Wu *et al.*	2016	86	SHMT2	IHC	Staining scores with intensity (≥3/4)	–	–	China	Survival curve

GC, gastric cancer; EC, esophageal cancer; CC, colorectal cancer; SHMT, serine hydroxymethyltransferase; IHC, immunohistochemistry; HR, hazard ratio.

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Table 2 Characteristics of the participants

Author	Expression (high/low)	Gender (male/total)	Age (years, mean ± SD)	Age (percentage of the older)	Cancer type	Control group	Survival outcome	Survival analysis
Shi *et al.*	69/61	81/130	–	66.2%	Gastric cancer	High *vs.* low	OS	Multivariate analysis
Ji *et al.*	80/64	89/144	–	60.4%	Hepatocellular carcinoma	High *vs.* low	OS	Multivariate analysis
Liu *et al.*_GC	43/15	29/58	–	58.6%	Gastric cancer	High *vs.* low	OS and RFS	Univariate and multivariate analysis
Liu *et al.*_EC	45/20	35/65	–	49.2%	Esophageal cancer	High *vs.* low		
Liu *et al.*_CC	43/17	27/60	–	53.3%	Colorectal cancer	High *vs.* low		
Ning *et al.*	52/48	69/100	–	48.0%	Intrahepatic cholangiocarcinoma	High *vs.* low	OS	Univariate and multivariate analysis
Noguchi *et al.*	63/40	64/103	67.2±9.6	–	Pancreatic ductal adenocarcinoma	High *vs.* low	OS and DFS	Univariate and multivariate analysis
Wang *et al.*	68/82	76/150	48±11	–	Human glioma	High *vs.* low	OS and PFS	Univariate analysis
Bernhardt *et al.*	400/401	NR	62.3±13.7	–	Breast cancer	High *vs.* low	OS and RFS	Univariate and multivariate analysis
Miyo *et al.*	89/88	71/117	–	51.3%	Colorectal cancer	High *vs.* low	OS and RFS	Univariate and multivariate analysis
Zhang *et al.*	95/33	NR	–	50.0%	Breast cancer	High *vs.* low	OS and PFS	Univariate and multivariate analysis
Wu *et al.*	51/35	64/86	–	66.3%	Hepatocellular carcinoma	High *vs.* low	OS and PFS	Univariate analysis

GC, gastric cancer; EC, esophageal cancer; CC, colorectal cancer; SD, standard derivation; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival; NR, not reported.

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Table 3 Newcastle-Ottawa quality assessment scales of each study

Author	Year	Selection (☆☆☆☆)				Comparability (☆☆)	Outcome (☆☆☆)			Total
		1	2	3	4	5	6	7	8	
Shi *et al.*	2019	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ji *et al.*	2019	☆	☆	☆	☆	☆	☆	☆	☆	8
Liu *et al.*	2019	☆	☆	☆	☆	☆	☆	–	☆	7
Ning *et al.*	2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Noguchi *et al.*	2018	☆	☆	☆	☆	☆	☆	☆	☆	8
Wang *et al.*	2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Bernhardt *et al.*	2017	☆	☆	☆	☆	☆	☆	–	–	6
Miyo *et al.*	2017	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhang *et al.*	2016	☆	☆	☆	☆	☆	☆	–	–	6
Wu *et al.*	2016	☆	☆	☆	☆	☆	☆	–	☆	7

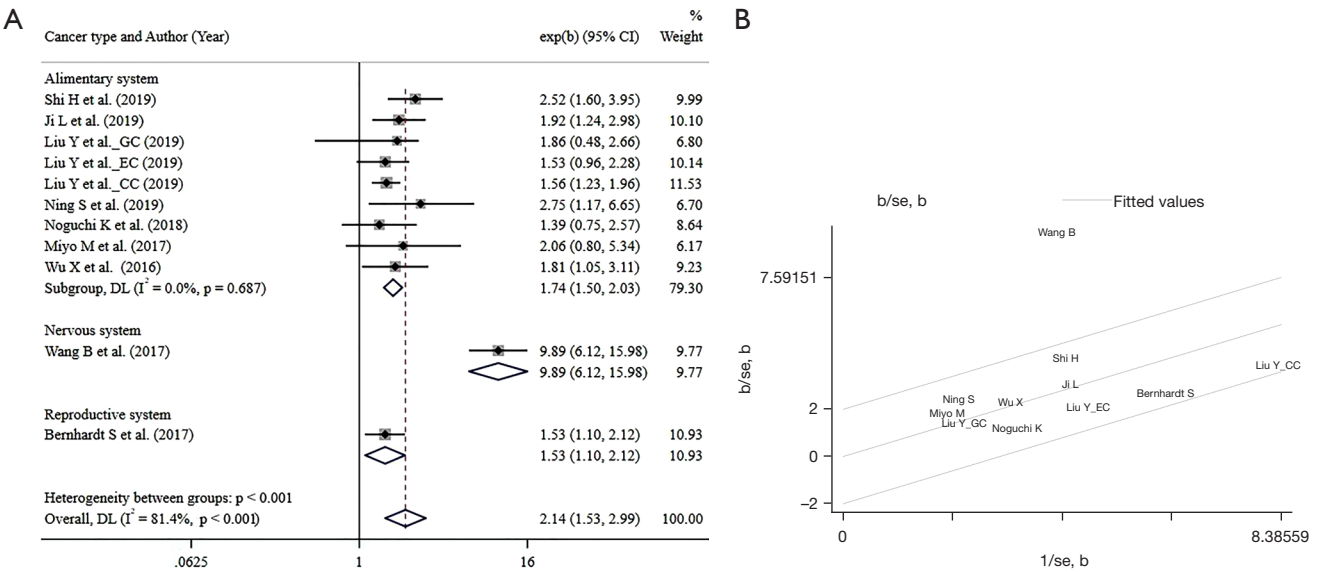

Figure 2 The Forest plots and Galbraith radial plot of overall survival analysis: (A) the Forest plots of overall survival analysis; (B) Galbraith radial plot of overall survival analysis. GC, gastric cancer; EC, esophageal cancer; CC, colorectal cancer; CI, confidence interval; DL, DerSimoniar and Laird method; se, standard error.

study of Wang *et al.* (13). As expected, heterogeneity diminished when the mentioned study was removed, and the result remained consistent (HR =1.70, 95% CI: 1.49 to 1.96, heterogeneity: I^2=0, P=0.725). Besides, similarity reoccured when we evaluated PFS/RFS/DFS in the eligible studies. There was a significant heterogeneity (I^2=80.9%, P<0.001), which was also imputed to the study of Wang *et al.* (13) in the Galbraith radial plot (*Figure 3*). Heterogeneity vanished along with the removal of the study of Wang *et al.* (HR =1.61, 95% CI: 1.38 to 1.88, heterogeneity: I^2=0, P=0.826). There was no significant heterogeneity in the subgroup analysis of OS and PFS/RFS/DFS.

Sensitivity analysis was conducted by omitting the included studies one by one. Expectedly, As shown in *Figure 4*, no study would influence the pooled HRs and 95% CI except the study of Wang *et al.* (13), indicating the

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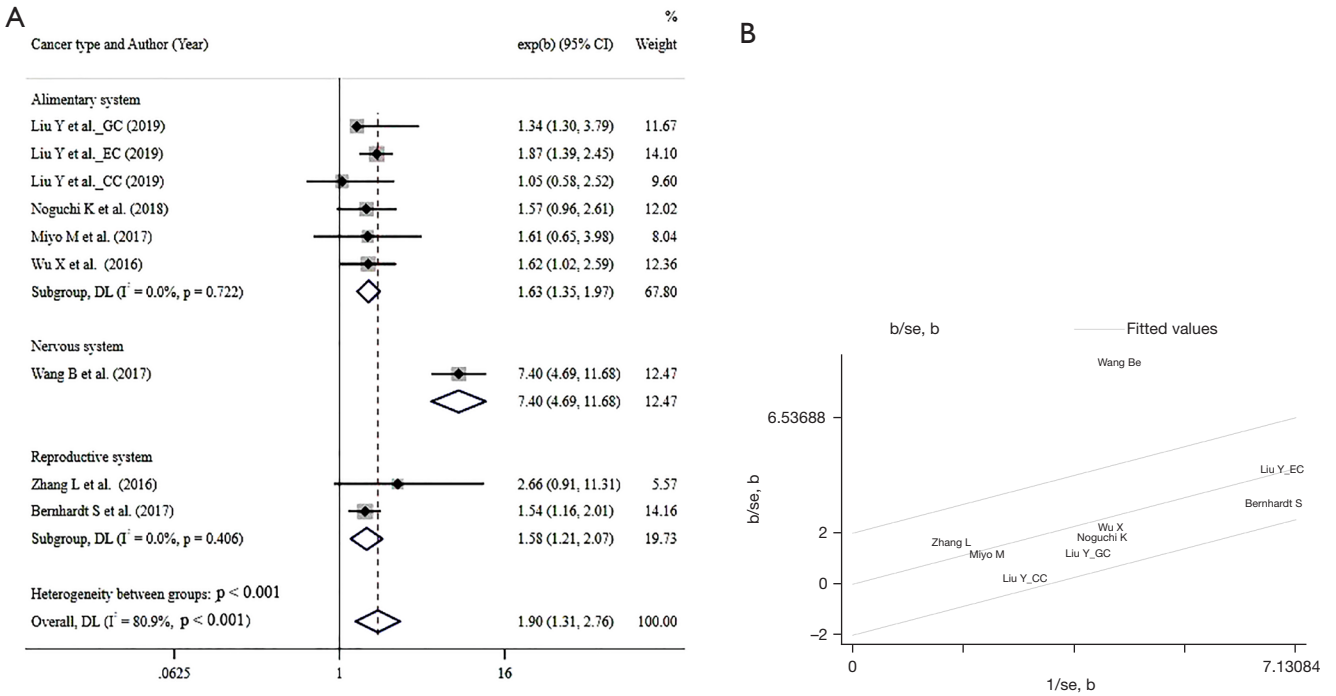

Figure 3 The Forest plots and Galbraith radial plot of PFS/RFS/DFS analysis: (A) the Forest plots of PFS/RFS/DFS analysis; (B) Galbraith radial plot of PFS/RFS/DFS analysis. GC, gastric cancer; EC, esophageal cancer; CC, colorectal cancer; CI, confidence interval; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival; DL, DerSimoniar and Laird method; se, standard error.

result possess decent stability both in OS (*Figure 4A*) and PFS/RFS/DFS (*Figure 4B*) analysis.

Discussion

Tumor researches have been in full blossom in recent years and thusly facilitates individualized treatment, which was closely related to the personal genetic pattern. SHMT was first discovered in the 1980s and accepted as a trivial enzyme for catalyzing the so-called futile cycle of serine to glycine. Then it has begun to exhibit various functions in life processes, including energy metabolism, cell growth, and proliferation. Currently, ongoing studies tried to unveil its role in carcinogenesis and cancer development. In this study, we focused on the prognostic role and association with clinicopathological characteristics in human cancer.

In this study, all the included researches examined the expression of SHMT2 in protein level for subsequent analysis. This is important because coding messenger ribonucleic acid (mRNA) expression may not always completely reflect the level of relevant protein. For example, it was reported Spearman's rank correlation coefficient between mRNA and protein translations was less than 0.4 in non-small cell lung cancer, indicating that their expression levels are not highly correlated (18).

We found that patients with higher expression of SHMT2 had a poorer prognosis in any studies included. Classified by the system, the pooled results showed an unfavorable correlation between high SHMT2 expression and patients' outcomes with decent stability. In line with that, the expression of SHMT2 was naturally supposed to be an adverse factor for patients' outcomes in the overall combination of different systems, but with significant heterogeneity caused by the study of Wang *et al.* (13). This could suggest that SHMT2 in different organ derivations may have somewhat varying prognostic values. Notwithstanding, it can't be ignored that the curves in Wang *et al.*'s study separated in an early stage and the HR extrapolated from univariate Kaplan-Meier curves, irrespective of effects of other co-factors, was also beyond other studies (HR =9.89 in Wang *et al.*'s study while HR of others was about 2).

In this study, we also found that higher SHMT2 expression symbolized larger tumor size and more lymph

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Table 4 summary of the association between clinicopathological characteristics

Characteristic	Number of studies	Number of patients	Pooled OR [95% CI]	P value	Model	Heterogeneity	
						I^2 (%)	P value
Tumor size							
Alimentary system	5	639	1.84 [1.32, 2.58]	<0.001	Fixed	33	0.17
Reproductive system	1	123	2.78 [1.18, 6.57]	0.020	–	–	–
Nervous system	1	150	2.95 [1.51, 5.78]	0.002	–	–	–
Merged result	7	912	2.09 [1.58, 2.77]	<0.001	Fixed	28	0.19
Lymphatic invasion							
Alimentary system	5	641	2.54 [1.68, 3.84]	<0.001	Fixed	0	0.64
Reproductive system	1	128	5.53 [0.70, 43.81]	0.110	–	–	–
Merged result	6	769	2.67 [1.78, 4.00]	<0.001	Fixed	0	0.59
Distant metastasis							
Alimentary system	3	295	1.25 [0.32, 4.90]	0.08	Random	61	0.08
TNM grade							
Alimentary system	4	559	2.23 [1.55, 3.21]	<0.001	Fixed	0	0.82
Histopathological grade							
Alimentary system	5	550	2.35 [1.00, 5.51]	0.001	Random	75	0.001
Reproductive system	1	150	27.73 [9.18, 83.78]	0.003	–	–	–
Nervous system	1	111	4.22 [1.62, 10.98]	<0.001	–	–	–
Merged result	7	811	3.46 [1.46, 8.23]	0.005	Random	82	<0.001

OR, odds ratio; TNM, tumor node metastasis classification.

node invasions, which eventually led to a higher TNM stage, revealing that SHMT2 may promote the proliferation and invasion ability of tumor cells. The relationship of the expression level of SHMT2 with histopathological grade was not consistent among the 7 eligible works of literature. 2 studies (11,17) reported higher SHMT2 expression tended to signify lower histopathological grade although the difference did not reach statistical significance. On the contrary, the remaining studies suggest these two matters were negatively related. The merged results of all studies manifested that higher expression increased the risk of higher histopathological grade, however, with significant heterogeneity. In terms of distant metastasis, the final synthetic results also showed heterogeneity which might be caused by the limited studies and small sample.

Concerning the underlying mechanism why SHMT is endowed with the predictive role in cancer patients, the potential reason could be as follows. On the one hand, SHMT is a key enzyme for the production of one carbon unit and is crucial for DNA and methionine synthesis as mentioned previously. On the other hand, SHMT was also implicated in redox homeostasis in the tumor microenvironment and immunology regulation. In the study of Ye *et al.* (19), SHMT2 was correlated to hypoxia-inducible factor-1α (HIF-1α) in myc-amplified neuroblastoma patient samples and contributed to the survival in an ischemia environment. And it has also been proven that SHMT2 activity weakens pyruvate kinase and consequently lowers oxygen demand and helps to turn into the beneficial metabolic state for survival in poorly vascularized tumor regions (20). Moreover, SHMT1 over-expression can repress the killing effect of natural killer (NK) cells to lung adenocarcinoma cells (21). Accumulative studies have revealed that knockdown of SHMT2 could hinder the proliferation and invasion in tumor cells or animal xenograft models, such as colon cancer cells (22,23), hepatocellular carcinoma (17), breast cancer (24) and so

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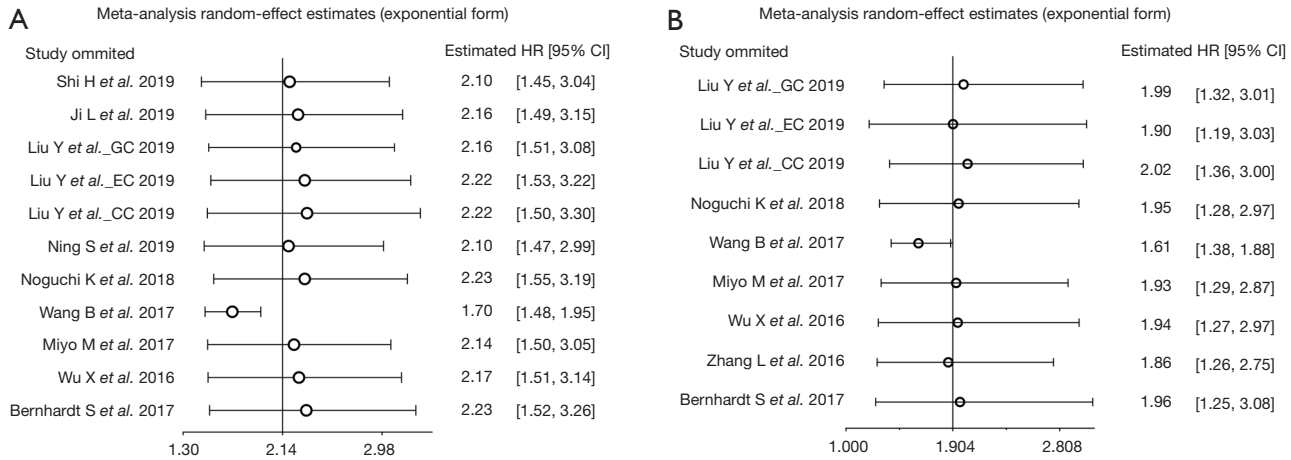

Figure 4 Sensitivity analysis: (A) sensitivity analysis of studies according to OS; (B) sensitivity analysis of studies according to PFS/RFS/DFS. GC, gastric cancer; EC, esophageal cancer; CC, colorectal cancer; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival.

on. While aberrant over-expression of SHMT2 not only reinforces cell proliferation *in vitro* but potentiates tumor growth *in vivo* (25).

Considering the incredible importance of SHMT for tumor cells in the growth and reprogramming process, researchers have taken cognizance of the potential of SHMT as a novel drug development target. And several inhibitors have been designed and demonstrated the encouraging anti-tumor efficacy *in vitro* and xenografts. For example, AGF347, an SHMT2 inhibitor, manifests a significant antitumor efficacy *in vivo* and both early-stage and upstage MIA PaCa-2 pancreatic tumor xenografts. And 2.12, inhibitor for both the SHMT isoforms, could induce apoptosis in lung cancer cell lines. Additionally, He *et al.* (26) developed the alanine-scanning-interaction-entropy method that could help calculate protein-ligand binding free energy, identify hot spots and explain the structure-activity relationship beneficial for researchers to design more effective SHMT inhibitors. We are looking forward to furthering studies.

Overall, our study revealed that SHMT could be used as a prognostic factor in clinical practice. Nevertheless, there were a few shortcomings in our study. To begin with, the majority of included studies (9/10) were carried out in Asia and focused on the alimentary system (7/10). Thus, there might be some bias when applying to the rest population. Moreover, some predetermined outcomes were insufficiently reported due to various reasons, and the resultant limited population could mitigate the credibility of the corresponding result, and even caused heterogeneity. Lastly, we did not perform publication bias test for the inadequate number of eligible studies, as it was recommended that the funnel plot was only suitable with no less than 10 studies (5).

Conclusions

SHMT2 may serve as a promising biomarker in various cancer, especially in the alimentary system. Also, it can be a target for drug development. Further large-scale studies are warranted to confirm the possible effect.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.

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com/article/view/10.21037/tcr-21-2485/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

A. Detailed search terms

(A1) Search terms in PubMed

#1
"Glycine Hydroxymethyltransferase"[Mesh] OR "SHMT protein"
#2
"Prognosis" [Mesh] OR "prognoses" OR "survival" OR "prognostic factors"
#3
"Neoplasms"[Mesh] OR "tumour" OR "cancer" OR ""neoplasm"
#4
#1 AND #2 AND #3

(A2) Search terms in Embase

#1
'glycine hydroxymethyltransferase'/exp
#2
'shmt protein'
#3
'shmt'
#4
'serine hydroxymethyltransferase'
#5
'shmt-1'
#6
'shmt-2'
#7
'prognosis'/exp
#8
'survival'
#9
'prognostic factors'
#10
'neoplasm'/exp
#11
'tumour'
#12
'cancer'
#13
'neoplasms'
#14
#1 OR #2 OR #3 OR #4 OR #5 OR #6
#15
#7 OR #8 OR #9
#16
#10 OR #11 OR #12 OR #13
#17
#14 AND #15 AND #16

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(A3) Search terms in Web of Science

#1
TS = ("Prognosis" OR "survival" OR "prognostic factors")
#2
AK = ("Prognosis" OR "survival" OR "prognostic factors")
#3
TS = ("Glycine Hydroxymethyltransferase" OR "SHMT protein" OR "SHMT" OR "serine hydroxymethyltransferase" OR "SHMT-1" OR "SHMT-2")
#4
AK = ("Glycine Hydroxymethyltransferase" OR "SHMT protein" OR "SHMT" OR "serine hydroxymethyltransferase" OR "SHMT-1" OR "SHMT-2")
#5
TS = ("Neoplasms" OR "tumour" OR "cancer" OR "neoplasm" OR "tumor")
#6
AK = ("Neoplasms" OR "tumour" OR "cancer" OR "neoplasm" OR "tumor")
#7
#2 OR #1
#8
#4 OR #3
#9
#6 OR #5
#10
#9 AND #8 AND #7

(A4) Search terms in Cochrane Central Register of Controlled Trials (CENTRAL)

#1
(Glycine Hydroxymethyltransferase):ti,ab,kw (Word variations have been searched)
#2
SHMT protein
#3
Prognosis
#4
survival
#5
prognostic factors
#6
Neoplasms
#7
cancer
#8
tumour
#9
#1 OR #2
#10
#3 OR #4 OR #5
#11
#7 OR #9 OR #9
#12
#9 AND #10 AND #11

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B. Relevant forest plots of the clinicopathological characteristics associated with SHMT2 expression

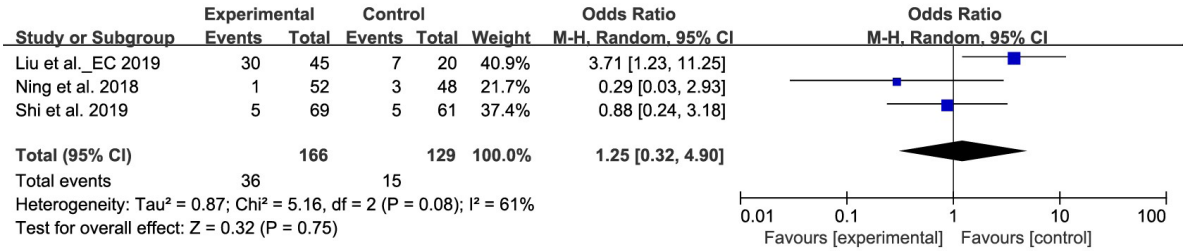

Figure S1 The forest plots of distant metastasis.

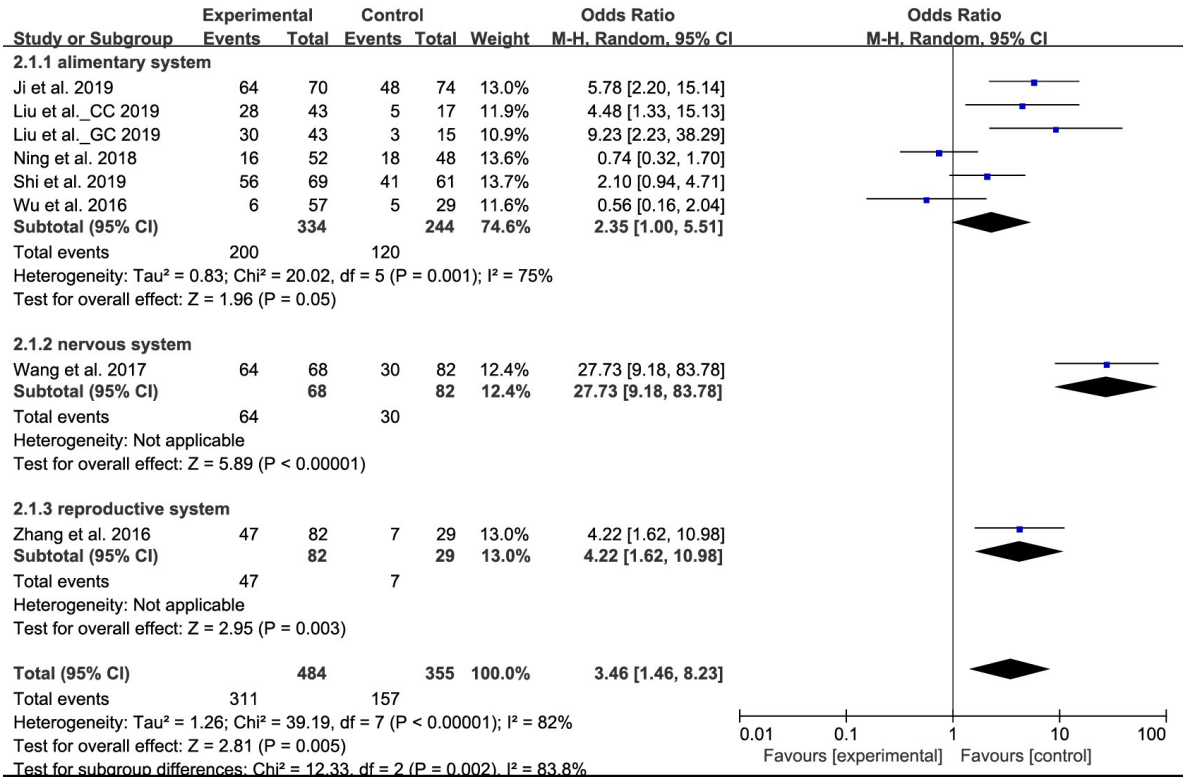

Figure S2 The forest plots of histopathological grade.

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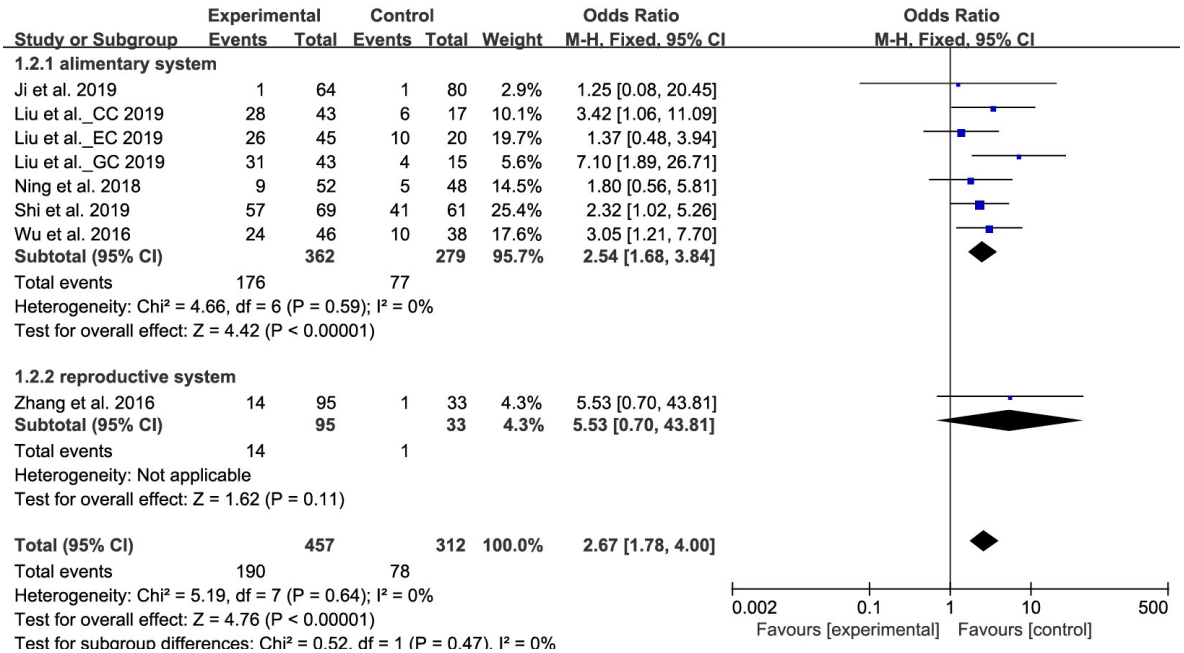

Figure S3 The forest plots of lymphatic invasion.

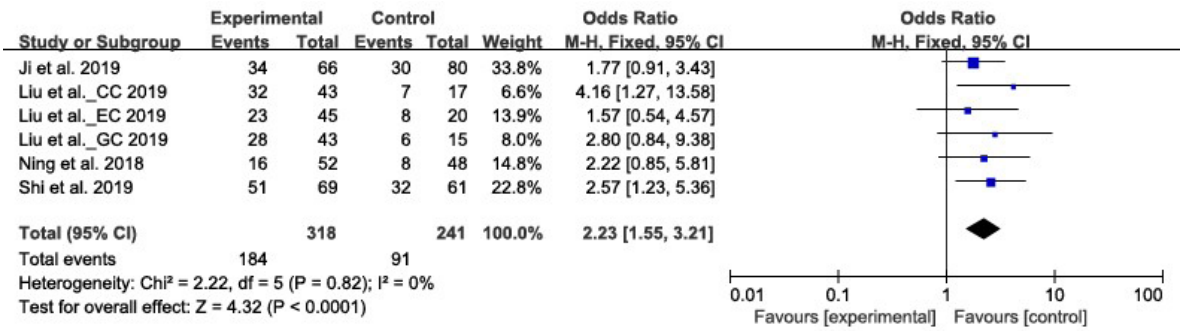

Figure S4 The forest plots of TNM grade.

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