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Prognostic role of high TET1 expression in patients with solid tumors

A meta-analysis

Qiwei Ke, BD[a], Kai Wang, MD[b], Min Fan, PhD[c], Mengchao Li, BD[a], Guanghua Luo, PhD[d], Daming Wang, PhD[a,*]

Abstract

Background: Recently, increased expression of TET1 has been shown to inhibit tumor development in many studies. Therefore, a meta-analysis was conducted to assess the prognostic role of TET1 in solid tumors.

Methods: PubMed, Embase, and the Web of Science (last updated on June 13, 2019) were searched and 16 eligible studies involving 3100 patients were eventually taken forward into the meta-analysis.

Results: Pooled results indicated that higher TET1 expression in cancer tissues was associated with improved overall survival (OS) [hazard ratio (HR) = 0.736, 95% confidence interval (95% CI) = 0.542–0.998, $P = .049$]. In the subgroup analysis, higher TET1 expression in respiratory tumors (HR = 0.778, 95% CI = 0.639–0.946, $P = .012$) and breast cancer in Asian patients (HR = 0.326, 95% CI = 0.199–0.533, $P < .001$) were significantly associated with better OS. In addition, the association between high TET1 expression and prolonged OS was also statistically significant in the following subgroups; data source from samples (HR = 0.561, 95% CI = 0.384–0.819, $P = .003$), reported in text (HR = 0.539, 95% CI = 0.312–0.931, $P = .027$), TET1 protein (HR = 0.635, 95% CI = 0.409–0.984, $P = .042$), Asians (HR = 0.563, 95% CI = 0.376–0.844, $P = .005$).

Conclusion: This meta-analysis displays that high expression levels of TET1 in tissues is significantly associated with better survival in patients with solid tumors. This finding can be used as evidence to the tone that TET1 may be a useful target for the treatment of patients with solid tumors in the future.

Abbreviations: 2-OGDDs = 2-oxoglutarate-dependent dioxygenases, 5caC = 5-carboxylcytosine, 5fC = 5-formylcytosine, AID = activation-induced cytidine deaminase, BER = base excision repair, CCA = cholangiocarcinoma, CI = confidence intervals, CK2± = casein kinase II subunit alpha, CRC = colorectal cancer, DFS = disease-free survival, DNMTs = DNA methyltransferases, EMT = epithelial-to-mesenchymal transition, EOC = epithelial ovarian carcinoma, GAED = gastric adenocarcinoma with enteroblastic differentiation, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle–Ottawa Quality Assessment Scale, OS = overall survival, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, STIC = serous tubal intraepithelial carcinoma, TET = ten-eleven translocation.

Keywords: meta-analysis, prognosis, solid tumor, TET1

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Raw data for calculation of method validation, tables, and figures are available from the corresponding author upon request.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

DNA methylation is a well-known tumor epigenetic feature, which occurs predominantly on the C-5 atom of cytosine in the context of CpG islands (5-mC). CpG islands are the short regions of CpG dinucleotides in promoter regions of many genes in mammals.[1,2] Abnormal methylation status of promoter regions is associated with transcriptional repression[1,2] and methylation of cancer suppressor genes will lead to the inactivation of themselves and result in the promotion of certain cancers.[3]

TET (ten-eleven translocation) enzymes, which include TET1, TET2, and TET3, is a family member of 2-oxoglutarate-dependent dioxygenases (2-OGDDs). Recent studies have indicated that TET enzymes play a role in DNA demethylation, which proves that existing DNA methylation can be reversed.[4–6] It is well known that loss of 5hmC is a genetic hallmark of many cancers, and the TET enzymes have been shown to be able to catalyze 5mC to 5hmC.[4,5] Silencing of the TET enzymes has been identified as being a key mediator of reduced 5hmC levels.[7,8] Moreover, the TET enzymes have been consistently shown as key mediators in cell differentiation and transformation, most notably in epithelial-to-mesenchymal transition (EMT).[9] DNA demethylation controlled by TETs seems to be a dynamic process that can control the state of cell differentiation.[9] In cancers, silencing of TET enzymes may result in some phenomena, such as pathological cell differentiation and transition, perhaps leading to increased tumor aggressiveness and invasiveness.[9]

Many clinical studies have revealed that the expression of TET1 is closely associated with survival rates in cancer patients with solid tumors, including gastric cancer,[15,18,24] cholangiocarcinoma,[11] hepatocellular cancer,[22] lung cancer,[14,21] breast cancer,[10,12,17,20] endometrial cancer,[16] renal cell cancer,[19] colorectal cancer,[13] and ovarian cancer.[23] Nevertheless, the consistency of the prognostic effect of TET1 remains unclear. So, all published evidence was systematically examined in this meta-analysis to reveal any association between TET1 and the prognosis of patients with different types of solid cancers. Consequently, the diagnosis and treatment of cancer targeting TET1 are hoped to be improved in the future.

2. Materials and methods

2.1. Search strategy

A systematic review of the literature was conducted in accordance with the PRISMA guidelines. PubMed, Embase, and Web of Science databases were searched in order to evaluate the association between expression of TET1 and prognosis in patients with various solid tumor types. Keywords used in the search strategy were "ten eleven translocation 1 OR TET1" (all fields) AND "tumor OR tumour OR neoplasm OR cancer OR carcinoma" (all fields) AND "prognosis OR prognostic OR survival OR outcome" (all fields). The last search was performed on June 13, 2019. The references within the identified literature were screened for further identification of relevant studies. The database search was carried out by 2 authors independently (Q. Ke and K. Wang). This study is a meta-analysis, so there is unnecessary to provide an Ethical Approval.

2.2. Selection criteria

All identified studies were included in this meta-analysis if they adhered to the following criteria. First, TET1 expression was detected in solid tumor tissue, not including hematologic malignancies. Second, the relationship between TET1 expression and survival outcome was represented in overall survival (OS). Third, sufficient data were provided to estimate the hazard ratio (HR) and 95% confidence intervals (95% CIs) according to TET1 expression. Letters, editorials, expert opinions, conference abstracts, reviews, case reports, and animal trials were excluded. Research on nonbinary, variable methods were excluded. The studies lacking key data were also excluded from further analysis. Titles and abstracts of the identified literature were assessed independently by 2 reviewers, before the full text of identified articles was carefully examined for comprehensive evaluation, with literature considered irrelevant being excluded. Regards to the articles with different opinions, 2 observers agreed to decide whether to include the research or not through academic negotiation.

2.3. Data extraction and quality assessment

Two reviewers independently extracted the required information from all eligible studies, and always included the following details: surname of the first author, publication year, patients' country of origin, tumor type, sample size, patients' gender, mean or median age, tumor stage, lymph node metastasis and distant metastasis, cut-off value, follow-up time, median or mean follow-up months, detection method, outcome, and HR and 95% CI of the high TET1 expression group versus the low group for OS if applicable. Multivariate outcomes were preferred to univariate outcomes when both were provided, but if no multivariate results were presented, univariate outcomes were used instead. If an HR was reported in the study, we extracted them directly, otherwise, survival data were extracted from the original study data (Kaplan–Meier curves or required data) using the software Engauge Digitizer 4.1, with the predicted survival data calculated by Tierney method. Finally, before the meta-analysis, the data and identified studies were rechecked to avoid over-analysis among overlapping patients.

2.4. Quality assessment

According to the Newcastle–Ottawa Quality Assessment Scale (NOS), the quality of each study was assessed by 2 reviewers independently.[32] For the score of quality assessment, the lowest score was 0 and the highest score was 9 points, with any study achieving a score of 6 or higher being rated as high quality.

2.5. Statistical analysis

The cut-off values provided by the authors were used to define high expression of TET1. The relationship between the level of TET1 expression and patient prognosis is described in terms of pooled HR and its 95% CI. Heterogeneity was assessed by using Cochran Q test and Higgins I-squared statistics. $I^2 > 50\%$ and/or $P < .1$ means that there is statistically significant heterogeneity. Where this occurred, a random effects model was used. Otherwise, the use of a fixed effects model was allowed. If heterogeneity exists, a subgroup analysis was applied when seeking the source of heterogeneity. Sensitivity analysis was used to assess the stability of the results by omitting each individual study. Publication bias was estimated through the Begg and Egger funnel plots. STATA software version 12.0 (Stata Corporation, College Station, TX) was used in this meta-analysis for merging

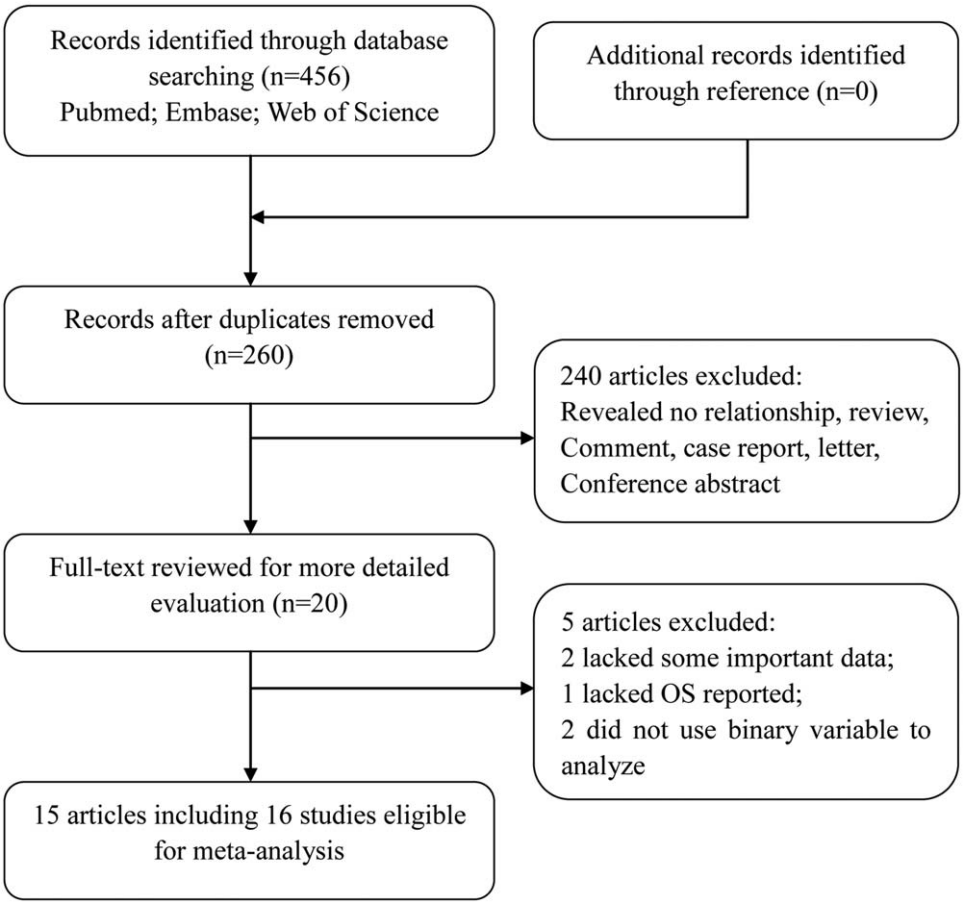

Figure 1. Flow diagram of the study selection process.

HR, and drawing a forest map and funnel plot. A bilateral *P* value of $<.05$ was considered to reach academic significance.

3. Results

3.1. Study characteristics

According to the searching strategy described in the materials and methods, 260 references were initially retrieved. After screening the titles, abstracts, publication types, and full text of each publication, 20 articles, which investigated the correlation between TET1 expression and patient survival in various solid tumors, were selected for the systemic review. Among these, 5 articles were excluded (2 lacked some important data, 1 lacked a reported OS, and 2 did not use a binary variable that could be analyzed). Finally, 15 articles containing 16 studies were adapted into the final meta-analysis (Fig. 1).

The main characteristics of the included studies are summarized in Table 1. A total of 3100 patients from China, Taiwan, Poland, Japan, Korea, and other databases were diagnosed with various cancers, including breast cancer, gastric cancer, colorectal cancer, cholangiocarcinoma, hepatocellular cancer, endometrial cancer, ovarian cancer, lung cancer, and renal cancer. All of studies were designed retrospectively and the year published ranged from 2012 to 2019. Eleven studies were reported in Asian cohorts and only one in a European cohort. OS was reported in all 16 studies, while DFS (disease-free survival) was evaluated in 2 studies. RFS (recurrence-free survival) and PFS (progression-free survival) were reported in only one study each. Therefore, OS reported in all eligible studies was selected as the main research objects for this meta-analysis. HRs, with their 95% CIs, were reported in 5 studies directly. In another 11 studies, the data were extracted from the graphical survival plots. Due to different detection methods, 10 studies were analyzed at the TET1 protein level, and another 6 studies were analyzed based on the TET1 mRNA level. The cut-off values of TET1 expression were also different between these study subsets.

3.2. Quality assessment

On the basis of the NOS, quality assessments were performed on each of the 16 eligible studies included in our meta-analysis. The score of all studies ranged from 5 to 8, with an average score of 6.8. Higher values indicated better methods. Therefore, each of the above studies is included in the subsequent analysis.

3.3. Meta-analysis results

The main results of this meta-analysis are listed in Table 2. Sixteen studies, including 3100 patients, provided suitable data for OS analysis. Due to the fact that studies evaluating OS were of obvious statistical heterogeneity ($I^2=84.1\%$, $P<.001$), the

Table 1

Main characteristics of all studies included in the meta-analysis.

Ref.	Country	Cancer	No. of patients	Age, yr	Gender M/F	Cancer stage	High expression n (%)	Cut-off value	Detected type	HR and 95%CI	Multivariate analysis	Quality score
Yu et al[10]	China	Breast	97	NA	NA	Mixed	49 (50.5%)	H-score>150	Protein	SC	NO	6
Wang et al[11]	China	Cholangio	82	Median 48	NA	TNM I-IV	38 (46.34%)	H-score>6	Protein	Report	YES	7
Good et al[12]	USA*	Breast	160	NA	NA	Mixed	64 (40%)	STDEV>1	Protein	SC	NO	8
Tian et al[13]	China	Colorectal	109	Median 64	65/44	TNM I-IV	54 (49.5%)	Median	Protein	Report	YES	7
Tian et al[13]	China†	Colorectal	372	NA	NA	Mixed	184 (49.5%)	NA	Protein	SC	NO	7
Lai et al[14]	China†	Lung	432	Mean 65.2	200/232	Mixed	216 (50%)	Median	mRNA	SC	NO	6
Deng et al[15]	China	Gastric	76	Median 58	44/32	TNM I-IV	38 (50%)	Median	mRNA	SC	NO	7
Ciesielski et al[16]	Poland	Endometrial	66	NA	0/66	Grade I-III	38 (57.6%)	Median	mRNA	Report	YES	8
Yang et al[17]	China	Breast	162	Median 52	NA	TNM I-III	81 (50%)	Median	mRNA	Report	YES	7
Park et al[18]	Korea	Gastric	80	Mean 57.33	46/34	Mixed	27 (33.75%)	Mean	mRNA	SC	NO	7
Fan et al[19]	China	Renal	54	Mean 36	35/19	Mixed	27 (50%)	Median	Protein	SC	NO	6
Hsu et al[20]	Taiwan	Breast	144	Mean 51.45	NA	TNM is-IV	49 (34%)	NA	Protein	SC	NO	7
Pei et al[21]	China	Lung	461	NA	NA	Mixed	230 (49.9%)	Median	Protein	Report	NO	5
Chen et al[23]	Taiwan‡	Ovarian	646	NA	0/646	Mixed	367 (56.8%)	NA	mRNA	SC	NO	7
Yatagai et al[24]	Japan	Gastric	51	Mean 71.15	42/9	TNM I-IV	22 (43.1%)	IHC>50%	Protein	SC	NO	7
Chen et al[22]	China	Liver	108	NA	NA	Mixed	54 (50%)	Median	Protein	SC	NO	6

IHC = immunohistochemistry, NA = not available, OS = overall survival, SC = survival curve.

* Survival data from Metabric dataset.

† Survival data from TCGA dataset.

‡ Survival data from GEO dataset.

random model was used to pool the HRs and 95% CIs. Overall, compared with the low TET1 expression, high expression of TET1 in cancer tissue was associated with an improved prognosis (HR = 0.736, 95% CI = 0.542–0.998, $P = .049$) (Fig. 2).

To explore the heterogeneity among these studies, subgroup analysis was further performed based on 6 main features, including tumor type, ethnicity, sample source, detection type, analysis type, and method used for obtaining HR, respectively. The first subgroup analysis was evaluated according to tumor type. The positive effect of upregulation of TET1 was demonstrated in patients with respiratory tumors (HR = 0.778, 95% CI = 0.639–0.946, $P = .012$; fixed-effects model), with no heterogeneity ($I^2 = 0.00\%$, $P = .368$) in this data (Table 2, Fig. 3A). In addition, the meta-analysis results showed no

Table 2

The pooled associations between TET1 expression and the prognosis of solid tumors.

Outcome subgroup	Outcome	No. of studies	No. of patients	HR (95% CI)	P	Model	Heterogeneity I^2(%)	Heterogeneity P
All	OS	16	3100	0.736 (0.542–0.998)	.049	Random	84.10%	<.001
Tumor type								
Digestive system	OS	7	878	0.807 (0.434–1.501)	.499	Random	87.80%	<.001
Respiratory system	OS	2	893	0.778 (0.639–0.946)	.012	Fixed	0.00%	.368
Genitourinary system	OS	7	1329	0.606 (0.344–1.068)	.083	Random	84.00%	<.001
Asian breast cancer	OS	3	403	0.326 (0.199–0.533)	<.001	Fixed	7.50%	.339
Ethnicity								
Asian	OS	11	1424	0.563 (0.376–0.844)	.005	Random	77.30%	<.001
European	OS	1	66	0.509 (0.127–0.779)	.038	—	—	—
Data source								
Database*	OS	4	1610	1.305 (0.937–1.817)	.115	Random	79.80%	.002
Sample†	OS	12	1490	0.561 (0.384–0.819)	.003	Random	75.10%	<.001
Analysis type								
Univariate	OS	15	2991	0.740 (0.547–1.000)	.05	Random	83.90%	<.001
Multivariate	OS	4	419	0.467 (0.202–1.079)	.075	Random	74.90%	.008
HR obtained method								
Reported in text	OS	5	880	0.539 (0.312–0.931)	.027	Random	70.50%	.009
Data extrapolated	OS	12	2382	0.799 (0.569–1.122)	.195	Random	84.20%	<.001
Detection type								
Protein	OS	10	1638	0.635 (0.409–0.984)	.042	Random	85.30%	<.001
mRNA	OS	6	1462	0.975 (0.640–1.485)	.905	Random	78.20%	<.001

CI = confidence interval, HR = hazard ratio, OS = overall survival.

* The case data studied in the source literature comes from databases such as The Cancer Genome Atlas (TCGA), Metabric, etc.

† The samples studied in the source literature come from clinical cases in various hospitals and research units.

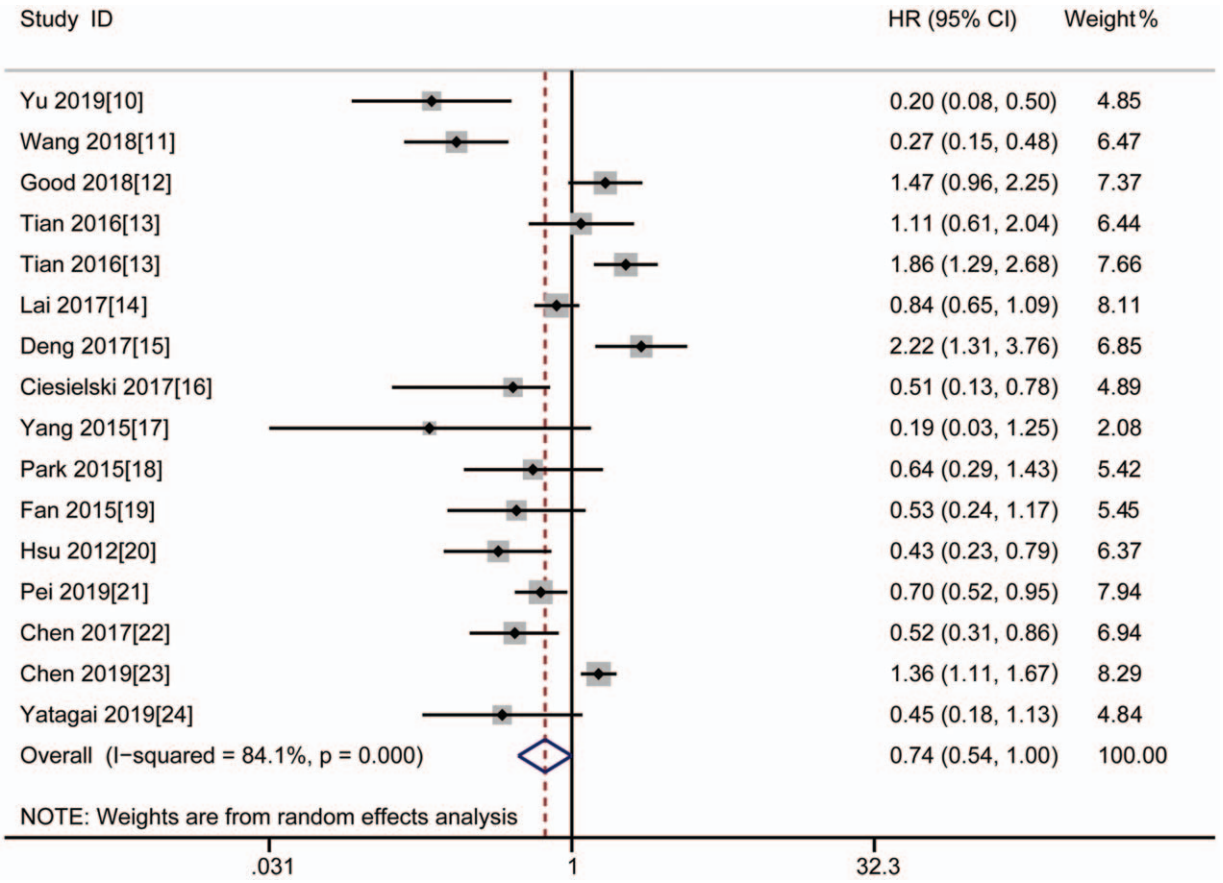

Figure 2. Forest plots of studies evaluating hazard ratios of high TET1 expression for solid tumors. High TET1 expression was associated with improved overall survival in solid tumors.

association between high TET1 expression and better OS in tumors of the genitourinary system (HR = 0.606, 95% CI = 0.344–1.068, $P = .083$; random-effects model) and digestive system neoplasm (HR = 0.807, 95% CI = 0.434–1.501, $P = .499$; random-effects model). The random model was employed because significant statistical heterogeneity was found both in the studies of digestive system cancer ($I^2 = 87.80\%$, $P < .001$) and genitourinary system cancer ($I^2 = 84.00\%$, $P < .001$). Furthermore, 3 studies about OS for breast cancer in Asian cohorts are provided. TET1 overexpression was associated with preferable OS of breast cancer patients in these studies (HR = 0.326, 95% CI = 0.199–0.533, $P < .001$; fixed-effects model), with no heterogeneity ($I^2 = 7.50\%$, $P = .339$) (Table 2, Fig. 3B).

The relationship between upregulation of TET1 and prolonged OS was also considered to have statistical significance in the following subgroups: data source from samples (HR = 0.561, 95% CI = 0.384–0.819, $P = .003$; random-effects model), reported in text (HR = 0.539, 95% CI = 0.312–0.931, $P = .027$; random-effects model), TET1 protein (HR = 0.635, 95% CI = 0.409–0.984, $P = .042$; random-effects model), and Asian cohort (HR = 0.563, 95% CI = 0.376–0.844, $P = .005$; random-effects model). Only 1 study reported that higher TET1 expression was correlated with better OS in European patients (HR = 0.509, 95% CI = 0.127–0.779, $P = .038$). Furthermore, the trend of an improved prognosis was observed among participants with high TET1 expression in the subgroup of univariate analysis (HR = 0.740, 95% CI = 0.547–1.000, $P = .05$; random-effects model). However, in other subgroups, high TET1 expression showed no association with good OS, including data source from database (HR = 1.305, 95% CI = 0.937–1.817, $P = .115$; random-effects model), multivariate analysis (HR = 0.467, 95% CI = 0.202–1.079, $P = .075$; random-effects model), data extrapolated (HR = 0.799, 95% CI = 0.569–1.122, $P = .195$; random-effects model), and TET1 mRNA (HR = 0.975, 95% CI = 0.640–1.485, $P = .905$; random-effects model). Unfortunately, there still exist an obvious significant heterogeneity in all of the above studies ($I^2 > 50\%$).

3.4. Sensitivity analysis

Sensitivity analysis was performed to evaluate the effect of each study on the meta-analysis results of OS. No significant change was found in the results when each single study was ignored sequentially (Fig. 4). This sensitivity analysis confirms the robustness and reliability of the meta-analysis results in this study.

3.5. Publication bias

The potential publication bias was assessed using Begg and Egger tests. The funnel plots figure did not show any unsymmetrical evidence (Fig. 5). The P value of Egger and Begg tests was all

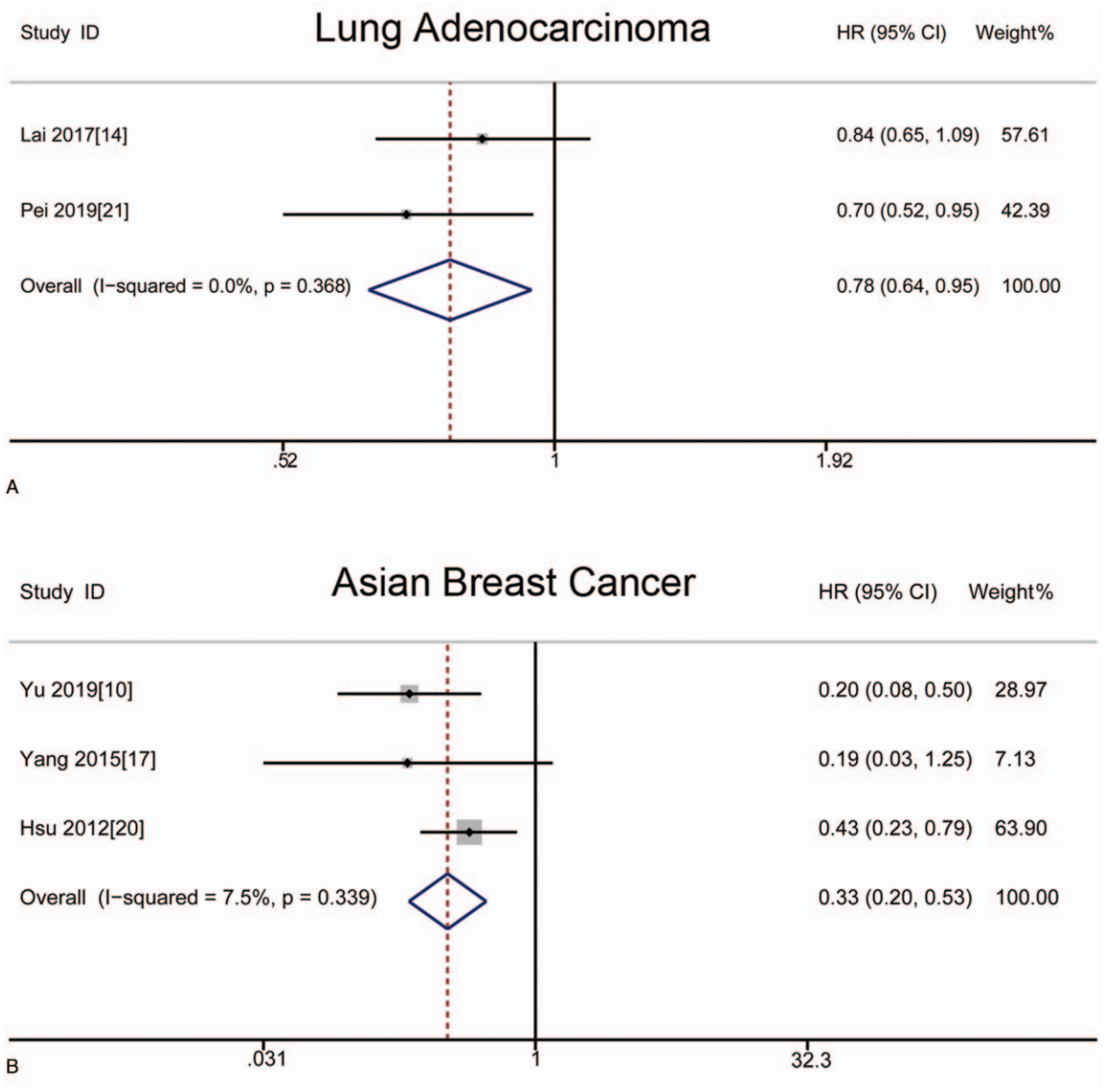

Figure 3. Forest plots of studies evaluating hazard ratios of high TET1 expression for different tumor types. (A) Respiratory tumors. (B) Asian breast cancers.

over .05 (OS, $P=.065$ for the Begg test, $P=.075$ for the Egger test), while all $P<.05$ was considered as significant. Hence, there is no significant publication bias in this meta-analysis.

4. Discussion

Aberrant DNA methylation is an established hallmark of cancer, with the mechanisms and consequences having been extensively investigated. DNA methyltransferases (DNMTs) convert unmethylated cytosine to 5mC, which has an established role in transcriptional regulation through its repressor activity.[25] Methylation of cytosine was historically thought to be permanent. In 2009, Rao et al[4] found that TET1 (ten-eleven translocation 1) protein converts 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), a prerequisite step required for initiation of demethylation. TET1 is a member of the enzyme family, 2-oxoglutarate-dependent dioxygenases (2-OGDDs), which also includes 2 other isoenzymes, TET2 (ten-eleven translocation 2) protein and TET3 (ten-eleven translocation 3). Like other 2-OGDDs, TET1 requires Fe^{2+}, 2-oxoglutarate (2–0G/ax-ketoglutarate), molecular oxygen,[26] and vitamin C to support the reaction,[26,28] with the catalytic activity strongly dependent on Fe^{2+} and 2-OG.[4,27,29] In the case of TETs, hydroxylation of the 5mC substrate in the DNA CpG dinucleotides to 5hmC can be followed by further oxidation of 5hmC to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which is catalyzed by the TETs themselves. This leads to the triggering of base excision repair (BER) and activation-induced cytidine deaminase (AID), leading to active DNA demethylation.[6,27]

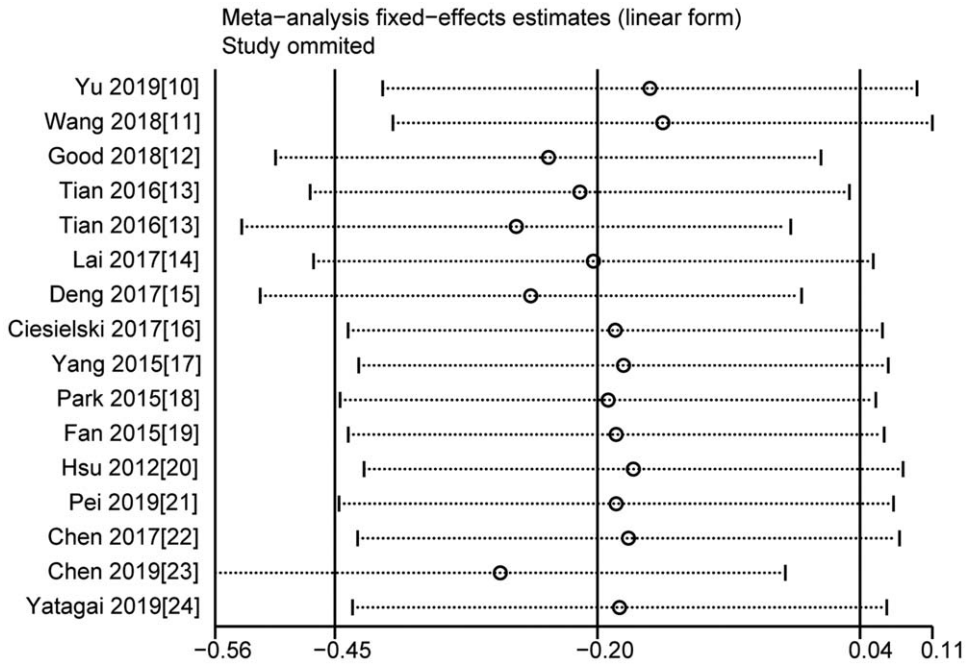

Figure 4. Sensitivity analysis on the relationships between TET1 expression and overall survival in solid cancer patients.

Abnormal expression of TET1 has been observed in many diseases, including cancer. Reduced TET1 expression is associated with increased cell invasion, tumor growth, and cancer metastasis, and has been correlated with poor survival rates. Indeed, differentially expressed TET1 can be used as a marker to improve cancer diagnosis, identify potential therapeutic targets, and improve prognosis in different tumors. To better determine the relationship between TET1 expression and cancer prognosis, a number of studies have been comprehensively undertaken and analyzed, in addition to meta-analysis being conducted to evaluate the potential of TET1 as a novel biomarker for predicting tumor prognosis.

On the basis of our current knowledge, this paper reports the first meta-analysis conducted to understand the association between the level of TET1 expression and the prognosis of patients with solid tumors, systematically and comprehensively. This study describes that high expression of TET1 in cancer tissue is strongly associated with an improved OS in cancer patients (HR = 0.736, 95% CI = 0.542–0.998, $P = .049$; random-effects model). In the subgroup analysis, the association between TET1 overexpression and better OS was statistically significant in respiratory tumor (HR = 0.778, 95% CI = 0.639–0.946, $P = .012$, fixed-effects model) and breast cancer in patients in an Asian population (HR = 0.326, 95% CI = 0.199–0.533, $P = .000$; fixed-effects model). These results demonstrate that there is a positive association between high TET1 expression and an improved prognosis among patients with breast tumors, as well as global respiratory tumors. Further, high TET1 expression was associated with a better prognosis, such as data source from sample (HR = 0.561, 95% CI = 0.384–0.819, $P = .003$; random-effects model), Asian patients (HR = 0.563, 95% CI = 0.376–0.844, $P = .005$; random-effects model), European patients (HR = 0.509, 95% CI = 0.127–0.779, $P = .038$), TET1 protein (HR = 0.635, 95% CI = 0.409–0.984, $P = .042$; random-effects model), and reported in text (HR = 0.539, 95% CI = 0.312–0.931, $P = .027$; random-effects model). Moreover, a trend of an improved OS in the subgroup of univariate analysis (HR = 0.740, 95% CI = 0.547–1.000, $P = .05$; random-effects model) was observed in patients with high TET1 expression.

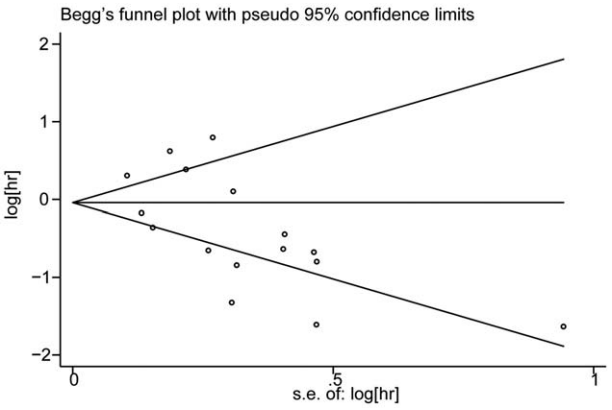

Figure 5. Funnel plots of publication biases on the relationships between TET1 expression and overall survival in solid cancer patient.

The ability of TET1 to inhibit tumor growth, invasion, and metastasis has been reported in several studies. Specifically, in 2014, Neri et al[30] reported TET1 blocked the growth of colon cancer cell in vitro and in vivo. Here, DKK genes, which are inhibitors of the WNT pathway that promote colon cancer growth, were found to be derepressed by TET1 through binding and maintenance of the DKK gene promoter in a hypomethylated state.[30] Akazawa et al[31] demonstrated that gastric adenocarcinoma with enteroblastic differentiation (GAED) is genetically characterized by a frequent TP53 mutation. Further studies

confirmed that aberrant methylation of the TP53 promoter was associated with reduced TET1 and 5-hmc, leading to inactivation of TP53 and subsequent loss of p53 expression in GAED.[24] The survival analysis showed that GAED patients with reduced TET1 and 5-hmc expression had poor OS and RFS.[24] Several studies have demonstrated that breast cancer patients with high levels of TET1 had better survival rates than those with low TET1 expression.[10,17,20] The mechanism of suppressing tumor development and invasion has been partly attributed to TET1-mediated downregulation of methylation in several important genes, including TP53, P53, TIMP.[10,20] TET1 has also been reported to regulate SOCS1 expression in hepatocellular carcinoma (HCC).[22] Negatively regulating TET-family expression decreased 5-hmC levels and subsequent genetic SOCS1 inactivation.[22] As a result, SOCS1 dysfunction triggers MMP9 upregulation, which increases HCC cell growth, invasion, and metastasis.[22] A study from Wang et al[11] demonstrated that TET1 reverses gemcitabine resistance in cholangiocarcinoma (CCA), with overexpression of TET1 leading to increased sensitivity of CCA cells to gemcitabine. Furthermore, multivariate Cox regression analysis showed that TET1 expression was an independent risk factor ($P < .001$) for the clinical results of CCA patients with chemotherapy.[11] In addition, Kaplan–Meier survival and the log-rank test showed that decreased expression of TET1 was associated with poorer prognosis of CCA patients with chemotherapy.[11] Thus, TET1 may be a promising target to overcome chemoresistance in CCA.[11] Ciesielski et al[16] also identified TET1 expression in endometrial cancer as an independent prognostic factor. Here, reduced expression of TET1 was correlated with tumor progression and lower TET1 expression in tumors significantly predicted poorer OS.[16] In summary, the above data show that TET1 acts as an oncosuppressor, playing a positive role in the genetic control of the growth of many tumors.

In contrast to the above, data from other studies have led to high TET1 expression being considered a risk factor in the prognosis of some cancers. For example, studies conducted by Tian et al[13] demonstrated that TET1 could promote cell metastasis and invasion of colorectal cancer (CRC) in vitro. However, this phenomenon was only observed in the extracellular studies and only be adapted to judge the tumor suppressor effects of TET1 in CRC, and failed to provide a clear explanation. In 2018, Good et al[12] analyzed survival data in the METABRIC cohort and found that TNBC patients with high TET1 expression had a significantly worse OS compared with all other TNBC patients ($P = .04$, log-rank test). This study also observed that deletion of TET1 resulted in methylation and subsequent reduced expression of PI3K pathway genes, upregulation of immune response genes, and substantially reduced cellular proliferation,[12] which was in contrast to previous work by Yu et al.[10] These results indicate that TET1-mediated hypomethylation activates oncogenic signaling in triple-negative breast cancer.[12] Nevertheless, this study was limited by the fact only TET1 deletion was studied, and thus, the effect of low expression and high expression of TET1 is lacking. Furthermore, a study from Chen et al[23] showed that TET1 expression correlated with poor survival in advanced-stage epithelial ovarian carcinoma (EOC), as well as cell migration, anchorage-independent growth, cancer stemness, and tumorigenicity. In particular, TET1 was highly expressed in serous tubal intraepithelial carcinoma (STIC), which is currently considered as a type II EOC precursor, and inversely correlated with TP53 mutations.[23] Further, TET1 could activate multiple oncogenic pathways by demethylating the epigenome, including an immunomodulation network having casein kinase II subunit alpha (CK2±) as a hub.[23] These differences may be as a result of the differing cell origins.

There remain elements within this article that require improvement. First, the meta-analysis only included 16 studies and 3100 patients, which led to a relative lack of data in the subgroup analysis. Second, the cut-off values chosen for these studies were different, leading to a lack of uniform standards for TET1 expression. This may affect the effectiveness of TET1 as a predictor of cancer prognosis. Therefore, it is necessary to establish a unified measurement method and select an appropriate cut-off value. In addition, 10 of the 16 studies describe TET1 protein expression, while the remaining 6 studies focused on TET1 mRNA. Protein is known to be the main substance that exert biological functions. Therefore, TET1 protein should be the focus of future research, with an emphasis on defining an appropriate cut-off value. Third, HR and 95% CI in some studies cannot be obtained directly from the original literature. Although these can be calculated by digitizing and extracting data from Kaplan–Meier curves, this inevitably leads to small statistical biases. Considering the limitations of this analysis, further well-designed studies that include assessment of an increased number tumor types with larger sample sizes are needed.

In conclusion, TET1 may be a promising biomarker for solid tumors, which not only contributes to the clinical decision-making process but also serves as an important new therapeutic target. Given the limitations of current analysis, this conclusion should be viewed with caution. In the future, further research is needed to determine the prognostic value of TET1 in cancer patients and to explore more effective treatment strategies.

Author contributions

D.M.W., Q.W.K., and K.W. designed the experiment. D.M.W., Q.W.K., M.C.L., K.W., M.F., and G.H.L. carried out the experiments and calculations. D.M.W., Q.W. K., and K.W. wrote and edited the paper. All authors have read and approved the final manuscript.

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