Meta-Analysis of Observational Studies in Epidemiology

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Prognostic value of long non-coding RNA plasmacytoma variant translocation1 in human solid tumors

A meta-analysis

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Abstract

Plasmacytoma variant translocation 1 (PVT1) is highly expressed in a variety of cancer tissues and is related to the clinicopathological features and prognosis. However, the prognostic value of PVT1 is still controversial. Therefore, this systematic evaluation and meta-analysis were performed to evaluate the relationship between PVT1 expression and clinicopathological features.

PubMed, EMBASE, Web of science, and Cochrane library databases were searched for literature collection according to inclusion criteria and exclusion criteria. The pooled hazard ratios (HRs) or odds ratios (ORs) were used to evaluate the association between PVT1 expression and overall survival, tumor size, tumor–node–metastasis (TNM) stage, lymph node metastasis, and distant metastasis.

A total of 39 articles including 3974 patients were included in the study. The results showed that the expression of PVT1 was closely related to the overall survival rate of cancers (HR = 1.64, 95% confidence interval [CI]: 1.50–1.78, $P < .000001$). Subgroup analysis showed that the high expression of PVT1 was closely related to the low overall survival rate of patients with clear cell renal cell carcinoma, breast cancer, cervical cancer, colon cancer, epithelial ovarian cancer, gastric cancer, lung cancer, and osteosarcoma. In addition, the high expression of PVT1 was positively correlated with tumor size (OR = 1.50, 95% CI: 1.14–1.96, $P = .004$), TNM stage (OR = 3.39, 95% CI: 2.73–4.20, $P < .00001$), lymph node metastasis (OR = 2.60, 95% CI: 1.76–3.84, $P < .00001$), and distant metastasis (OR = 2.94, 95% CI: 1.90–4.56, $P < .00001$).

PVT1 could serve as a marker for the size, TNM stage, metastasis, and prognosis of different type of cancers.

Abbreviations: ATG7 = autophagy related 7, DFS = disease-free survival, DSS = disease specific survival, FOXM1 = fork head box M1, HR = hazard ratio, lncRNA = long non-coding RNA, miRNA = micro RNA, OR = odds ratio, OS = overall survival, PFS = progression free survival, PVT1 = plasmacytoma variant translocation1, RFS = recurrence free survival, STAT3 = signal transducer and activator of transcription 3, TNM = tumor–node–metastasis, VEGFA = vascular endothelial growth factor A.

Keywords: carcinoma, long non-coding RNA, meta-analysis, plasmacytoma variant translocation 1, prognosis, solid tumor

1. Introduction

Long non-coding RNAs are functionally defined as transcripts >200 bp in length with no protein-coding function. They are expressed by the tens of thousands in many differentiated tissues and cancer tissues. Long non-coding RNA (lncRNA) is an important component of many biological processes, including stem cell biology, development, and differentiation. Abnormal lncRNA expression is believed to be closely related to the occurrence of a variety of human diseases, including various cancers. Therefore, lncRNA is one of the hot spots in cancer research at present.

As a member of the LncRNA family, plasmacytoma variant translocation 1 (PVT1) is a long non-coding RNA with a length of 1.9 KB that can encode a variety of transcripts. It is located in the region 8q24.21 of human chromosome and close to the known oncogene MYC. PVT1 was originally identified as a retrovirus integration site in mouse leukemia virus-induced t-cell lymphoma. In recent years, PVT1 has become the focus of lncRNA research. More and more evidence showed that PVT1 is highly expressed in a variety of tumor tissues, including cervical cancer, multiple myeloma, prostate cancer, lung cancer, nasopharyngeal cancer, etc. PVT1 can inhibit apoptosis of tumor cells, promote cell proliferation by regulating cell cycle,

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and affect tumor invasion and metastasis. It is reported that the high expression of PVT1 increased the expression of autophagy related 7 (Atg7) and Beclin1 (BECN1) by targeting miRNA-186, thereby inducing the protective autophagy of glioma cells and promoting the proliferation, migration and angiogenesis of vascular endothelial cells.[1] In gastric cancer, PVT1 is highly expressed in gastric cancer tissues and interacts with fork head box M1 (FOXM1) to form a positive feedback loop pathway to promote the proliferation and invasion of gastric cancer cells and promote the development of gastric cancer.[2] Studies have also confirmed that PVT1 can interact with signal transducer and activator of transcription 3 (STAT3) signaling pathway and significantly induce angiogenesis in gastric cancer tissues by inducing high vascular endothelial growth factor A (VEGFA) expression.[3] These results indicate that PVT1 plays an important role in the occurrence, development, and recurrence of tumors.

In recent years, some literatures have also reported that PVT1 is related to the clinicopathological features and prognosis of various tumor patients, including lung cancer,[4,5] gastric cancer,[2,6] breast cancer,[7,8] cervical cancer,[9–12] colorectal cancer,[13,14] hepatocellular carcinoma.[15–18] However, most reports are limited by geographical, ethnic, and sample size limitations. Therefore, it is necessary to conduct a comprehensive meta-analysis of the existing data to evaluate the significance of PVT1 as a prognostic marker for the prognosis of various carcinomas.

2. Material and methods

2.1. Search strategy and literature selection

The public databases including PubMed, Web of science, Cochrane library database, and EMBASE database were retrieved independently by 2 researchers (KX and JL). The keywords were set as "((((((cancer) OR tumor) OR carcinoma) OR neoplasm)) AND ((((prognosis) OR survival) OR diagnosis) OR clinicopathological)) AND ((PVT1) OR plasmacytoma variant translocation 1)." The retrieval literature publication date was before November 22, 2018. The study was permitted by the Medical Ethical Committee of Liaocheng People's Hospital.

2.2. Inclusion and exclusion criteria

The inclusion criteria are as follows: the research object is human tumor tissues; the subjects were grouped according to the expression level of PVT1; the study assessed the relationship between PVT1 expression level and prognosis or clinicopathological features of tumors; the study provided enough data to extract hazard ratios (HRs) or odds ratios (ORs); English literature.

The exclusion criteria are as follows: the subjects were cell lines; reviews, editorials, expert opinions, letters, bioinformatics analysis articles, and case reports; duplicate publications; the article does not have enough data available.

2.3. Date extraction and quality assessment

Data extraction was completed independently by the 3 authors and consensus was reached. After the literature was determined according to the previously described criteria, the following information was extracted successively: author, Published year, cancer type, country, tumor size, follow-up period, detection method, cut-off value. the number of patients in each group was divided according to the presence or absence of lymph node metastasis, distant metastasis, tumor size, and tumor–node–metastasis (TNM) stage, as well as the number of patients with high and low PVT1 expression in each group, HRs as well as their 95% CIs. If Kaplan–Meier survival curve is only provided in paper, Engauge Digitizer V4.1 (Mark Mitchell) is used to estimate HR according to the previously reported method.[19] Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of the literatures. NOS scores ranged from 0 to 9, and the higher the score, the higher the quality of the article.

2.4. Statistical analysis

RevMan5.3 (Cochrane community) software was used for meta-analysis to combine HR or OR values. The chi square-based Q test and I^2 statistics were used to evaluate the heterogeneity. If the heterogeneity was obvious (I^2 >50%, P < .05), the random-effects model was used for analysis; if the heterogeneity was absent (I^2 <50%, P > .05), the fix-effects model was used to analyze the results. Begg funnel-plot was used to evaluate the potential publication bias. P < .05 was considered to be statistically significant.

3. Results

3.1. Included literature and their characteristics

A total of 202 literatures were preliminarily retrieved and 23 duplicated literatures were removed. After carefully reading the title, abstract, and full text, 39 literatures were included in this study according to the inclusion criteria and exclusion criteria (Fig. 1).

The 39 literatures were published between 2014 and 2018, including a total of 3974 patients, with the lowest sample size of 26 and the largest of 231, with an average of 102. The samples included in the article came from different regions, including China (3560), Japan (164), the United States (121), and Italy (129). The included studies involved 16 types of cancer, including bladder cancer,[20,21] clear cell renal cell carcinoma,[22–24] breast cancer,[7,8] cervical cancer,[9,11,12] colorectal cancer,[13,14,25] epithelial cancer,[26–28] esophageal squamous cell carcinoma,[29,30] gastric cancer,[2,6,31–34] hepatocellular carcinoma,[15–17] Melanoma,[35] nasopharyngeal carcinoma,[36] lung cancer,[37] Osteosarcoma,[38,39] pancreatic cancer,[40] and prostate cancer.[41] PVT1 expression level was detected by RT-PCR in all but 2 literatures. The clinical outcomes were also recoded including 33 studies for OS, 2 for RFS, 10 for DFS, 3 for PFS, and 1 for DSS. The basic information included in the article is summarized in Table 1.

3.2. The expression of PVT1 was significantly correlated with survival

A total of 35 articles reported the relationship between PVT1 expression level and overall survival in various cancers. Due to the small heterogeneity (I^2 = 19%, P = .17), the fixed-effect model was used for analysis. The result of merged HRs (HR = 1.64, 95% CI: 1.50–1.78, P < .000001) showed that increased PVT1 expression predicted decreased overall survival (Fig. 2). In addition, subgroup analysis was performed according to tumor

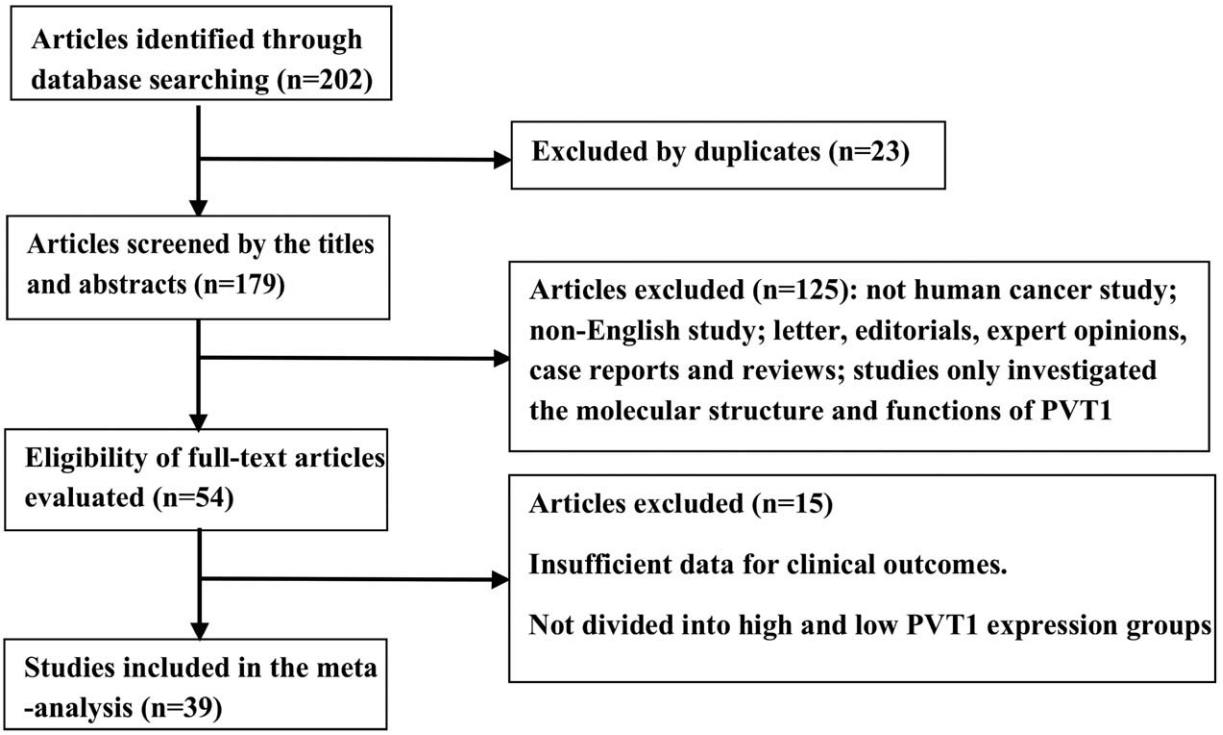

Figure 1. The flow diagram of this meta-analysis.

types, the combined HR value showed that the expression of PVT was negatively correlated with the overall survival rate of patients with clear cell renal cell carcinoma (HR = 1.68, 95% CI: 1.25–2.24, $P = .0005$), breast cancer (HR = 1.96, 95% CI: 1.21–3.18, $P = .007$), cervical cancer (HR = 1.69, 95% CI: 1.27–2.26, $P = .0004$), colon cancer (HR = 2.03, 95% CI: 1.45–2.84, $P < .0001$), epithelial ovarian cancer (HR = 1.28, 95% CI: 1.10–1.48, $P = .002$), gastric cancer (HR = 1.82, 95% CI: 1.46–2.25, $P < .00001$), lung cancer (HR = 2.04, 95% CI: 1.58–2.65, $P < .00001$), osteosarcoma (HR = 2.11, 95% CI: 1.05–4.24, $P = .04$) and others (including: bladder cancer, nasopharyngeal carcinoma, pancreatic cancer, melanoma, prostate cancer) (HR = 2.23, 95% CI: 1.62–3.07, $P < .00001$). However, this negative correlation was not significant in the subgroup analysis of hepatocellular carcinoma (HR = 1.32, 95% CI: 0.92–1.90, $P = .13$).

3.3. The expression of PVT1 was significantly correlated with tumor size

A total of 22 literatures involving 2547 patients reported the expression levels of PVT1 in samples of different tumor sizes. Due to the heterogeneity ($I^2 = 57\%$, $P = .0004$), we used the random-effect model for analysis. The results showed that PVT1 expression was significantly associated with tumor size (OR = 1.50, 95% CI: 1.14–1.96, $P = .004$) (Fig. 3). The subgroup analysis was performed based on the type of cancers, including bladder cancer (n = 2), breast cancer (n = 2), colorectal cancer (n = 2), esophageal and gastric cancer (n = 4), hepatocellular carcinoma (n = 4), and lung cancer (n = 4). The results showed that the expression level of PVT1 was closely related to the tumor size of breast cancer (OR = 2.38, 95% CI: 1.45–3.91, $P = .0006$), hepatocellular carcinoma (OR = 2.04, 95% CI: 1.36–3.06, $P = .0005$), and lung cancer (OR = 1.60, 95% CI: 1.07–2.38, $P = .02$). Interestingly, in esophageal and gastric cancer, the expression of PVT1 seems to be elevated in tumors of small volumes (OR = 0.76, 95% CI: 0.51–1.15, $P = .20$), this requires more data validation.

3.4. The expression of PVT1 was significantly correlated with TNM stage

Twenty-eight studies including 2901 patients reported the relationship between PVT expression level and TNM stage. Due to the small heterogeneity ($I^2 = 38\%$, $P = .02$), we used the fixed-effect model for analysis. The merged OR value showed that the expression level of PVT1 was significantly associated with TNM stage (OR = 3.39, 95% CI: 2.73–4.20, $P < .00001$) (Fig. 4). The subgroup analysis was performed based on the type of cancers, including bladder cancer (n = 2), clear cell renal cell carcinoma (n = 2), breast cancer (n = 2), colorectal cancer (n = 2), esophageal and gastric cancer (n = 7), hepatocellular carcinoma (n = 4), and lung cancer (n = 3). Due to the heterogeneity of bladder cancer subgroup, we used a random model for subgroup analysis, the results showed that the expression level of PVT1 was closely related to the TNM stage of bladder cancer (OR = 2.81, 95% CI: 1.52–5.20, $P = .001$), clear cell renal cell carcinoma (OR = 5.79, 95% CI: 2.81–11.93, $P < .00001$), breast cancer (OR = 2.40, 95% CI: 1.45–3.98, $P = .0007$), colorectal cancer (OR = 5.54, 95% CI: 3.18–9.63, $P < .00001$), esophageal and gastric cancer (OR = 2.90, 95% CI: 2.07–4.05, $P < .00001$), hepatocellular carcinoma (OR = 2.20, 95% CI: 1.46–3.33, $P = .0002$), lung cancer (OR = 3.93, 95% CI: 2.26–6.85, $P < .00001$), and other cancers (OR = 3.98, 95% CI: 2.83–5.60, $P < .00001$).

Table 1

The main characteristics of the included studies in the meta-analysis.

First author	Year	Region	Tumor type	TNM stage	Sample size	Cut-off value	Follow-up, mo	Detection methods	Outcome measure		NOS
Takahashi Y	2014	Japan	Colorectal cancer	0–IV	164	>20%	45.6 (mean)	qRT-PCR	OS		7
Ding J	2014	China	Gastric cancer	I–IV	31	T/N>1	N/A	qRT-PCR	N/A		7
Wang F	2014	China	Hepatocellular carcinoma	I–IV	89	Median	N/A	qRT-PCR	OS	RFS	7
Yang YR	2014	China	Lung cancer	I–III	82	Median	41 (mean)	qRT-PCR	OS		7
Zhuang CL	2015	China	Bladder cancer	0–IV	32	N/A	N/A	qRT-PCR	N/A		7
Kong R	2015	China	Gastric cancer	I–IV	80	Median	N/A	qRT-PCR	OS	DFS	7
Ding CF	2015	China	Hepatocellular carcinoma	I–IV	214	ROC	27.58 (mean)	qRT-PCR	OS	RFS	7
Huang C	2015	China	pancreatic cancer	I–IV	85	Mean	10.2 (mean)	qRT-PCR	OS		7
Zhang SR	2016	China	Cervical cancer	N/A	90	Median	60 (total)	qRT-PCR	OS		5
Iden M	2016	America	Cervical cancer	N/A	121	Median	60 (total)	qRT-PCR	OS		5
Zheng XX	2016	China	Esophageal squamous cell carcinoma	I–IV	77	Median	N/A	qRT-PCR	N/A		7
Yuan C	2016	China	Gastric cancer	I–IV	111	Median	36 (median)	qRT-PCR	OS	DFS	7
Cui D	2016	China	Lung cancer	I–IV	108	Median	32 (median)	qRT-PCR	OS	DFS	7
Wan L	2016	China	Lung cancer	I–IIIa	105	Median	N/A	qRT-PCR	OS	PFS	7
Zhou Q	2016	China	Osteosarcoma	N/A	26	N/A	60 (total)	qRT-PCR	OS		5
Huang CS	2016	China	Lung cancer	N/A	120	Median	90 (total)	qRT-PCR	OS		7
Cui Yu	2017	China	Bladder cancer	I–IV	146	Median	32 (median)	qRT-PCR	OS		7
Bao X	2017	China	Clear cell renal cell carcinoma	I–IV	129	Median	N/A	qRT-PCR	OS	DFS	7
Yang T	2017	China	Clear cell renal cell carcinoma	I–IV	50	Median	N/A	qRT-PCR	OS	DFS	7
Li X	2017	China	Breast cancer	I–IV	158	Median	N/A	qRT-PCR	OS	DFS	5
Wang Y	2017	China	Breast cancer	I–IV	110	N/A	N/A	qRT-PCR	OS		7
Zhang Dongli	2017	China	Cervical cancer	I–III	87	N/A	N/A	qRT-PCR	OS		7
Martini P	2017	Italy	Ovarian cancer	I	129	Median	72 (median)	qRT-PCR	OS	PFS	7
Li PD	2017	China	Esophageal squamous cell carcinoma	I–III	104	T/N>2	61 (median)	qRT-PCR	OS	DFS	7
Xu MD	2017	China	Gastric cancer	I–IV	190	Mean	32.43 (mean)	qRT-PCR	DFS	DSS	7
Huang T	2017	China	Gastric cancer	I–IV	68	Mean	N/A	qRT-PCR	N/A		7
Chen J	2017	China	Gastric cancer	I–IV	187	N/A	26 (median)	qRT-PCR	OS	DFS	7
Gou X	2017	China	Hepatocellular carcinoma	I–IV	92	N/A	N/A	qRT-PCR			5
Lan T	2017	China	Hepatocellular carcinoma	I–IV	48	Median	N/A	In situ hybridization	OS		6
Wu D	2017	China	Lung cancer	I–IV	31	N/A	N/A	qRT-PCR	OS		5
Song J	2017	China	Osteosarcoma	I–III	46	N/A	N/A	qRT-PCR	OS		7
Yang J	2017	China	Prostate cancer	II–IV	152	>25%	N/A	qRT-PCR	OS	DFS	6
Li Weicong	2018	China	clear cell renal cell carcinoma	I–IV	40	T/N>1.5	N/A	qRT-PCR	OS		5
Fan H	2018	China	Colorectal cancer	I–IV	210	Median	N/A	qRT-PCR	OS	DFS	7
Yu X	2018	China	Colorectal cancer	I–IV	60	N/A	N/A	qRT-PCR	OS		7
Chen Ying	2018	China	Ovarian cancer	I–IV	231	Median	N/A	qRT-PCR	OS	PFS	7
Yang Q	2018	China	Ovarian cancer	N/A	42	N/A	N/A	qRT-PCR	OS		5
Wang BJ	2018	China	Melanoma	N/A	35	N/A	N/A	qRT-PCR	OS		5
He Yi	2018	China	Nasopharyngeal carcinoma	I–IV	94	Median	60–120 (total)	In situ hybridization	OS	RFS	7

DFS = disease-free survival, DSS = disease specific survival, OS = overall survival, PFS = progression free survival, RFS = recurrence free survival.

3.5. The expression of PVT1 was closely related to lymph node metastasis

Twenty-two studies including 2329 patients reported the relationship between PVT expression level and lymph node metastasis. Due to the heterogeneity ($I^2 = 73\%$, $P < .00001$), we used the random-effect model for analysis. The results showed that PVT1 expression was significantly associated with lymph node metastasis (OR = 2.60, 95% CI: 1.76–3.84, $P < .00001$) (Fig. 5). The subgroup analysis was performed based on the type of cancers, including bladder cancer (n = 2), breast cancer (n = 2), colorectal cancer (n = 3), esophageal and gastric cancer (n = 5), lung cancer (n = 4). Due to the heterogeneity of bladder cancer and breast cancer subgroup, we used a random model for subgroup analysis, the results showed that the expression level of PVT1 was closely related to the lymph node metastasis of colorectal cancer (OR = 4.48, 95% CI: 2.81–7.16, $P < .00001$), esophageal and gastric cancer (OR = 2.04, 95% CI: 1.33–3.11, $P = .001$), lung cancer (OR = 3.34, 95% CI: 1.89–5.89, $P < .0001$), and other tumors (OR = 2.60, 95% CI: 1.76–3.84, $P < .00001$).

3.6. The expression of PVT1 was significantly correlated with distant metastasis

Nine studies including 996 patients reported the relationship between PVT expression level and distant metastasis. Due to the heterogeneity ($I^2 = 40\%$, $P = .10$), we used the fix-effect model for analysis. The results showed that PVT1 expression was significantly associated with distant metastasis (OR = 2.94, 95% CI: 1.90–4.56, $P < .00001$) (Fig. 6).

3.7. Publication bias

The Begg test and funnel plot were used to assess the publication bias of this meta-analysis. Funnel plot showed uniform

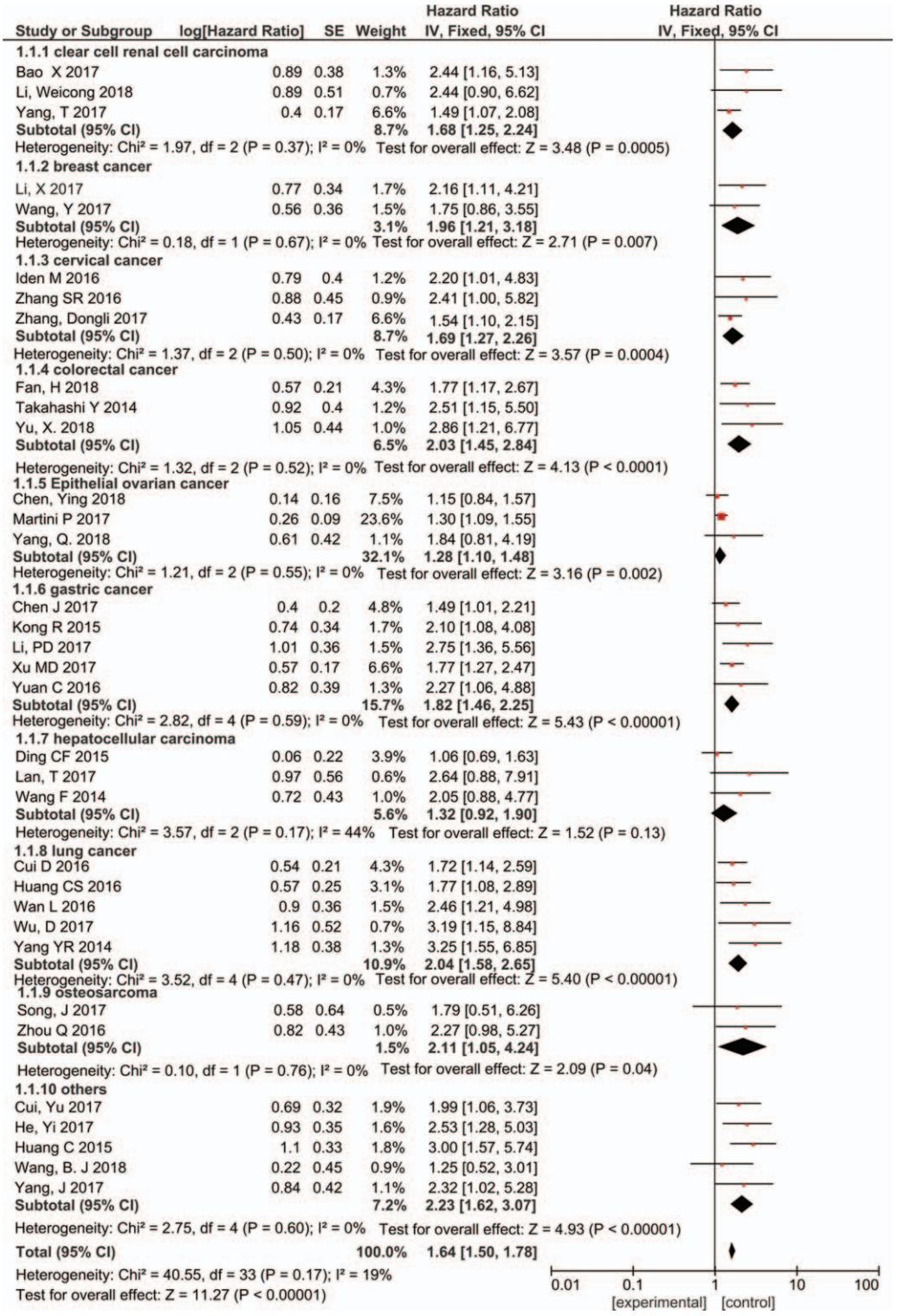

Figure 2. Forest plots of the included studies evaluating the HRs for PVT1 expression for OS by type of cancer. HR = hazard ratio, OS = overall survival, PVT1 = plasmacytoma variant translocation1.

distribution of all studies, and no obvious asymmetry was observed among the studies investigating PVT1 expression on overall survival, tumor size, TNM stage, and distant metastasis (Fig. 7).

4. Discussion

PVT1, which is located at 8q24.21, was found to be upregulated in a diverse range of cancer types. In recent years, some literatures have also reported that PVT1 is related to the

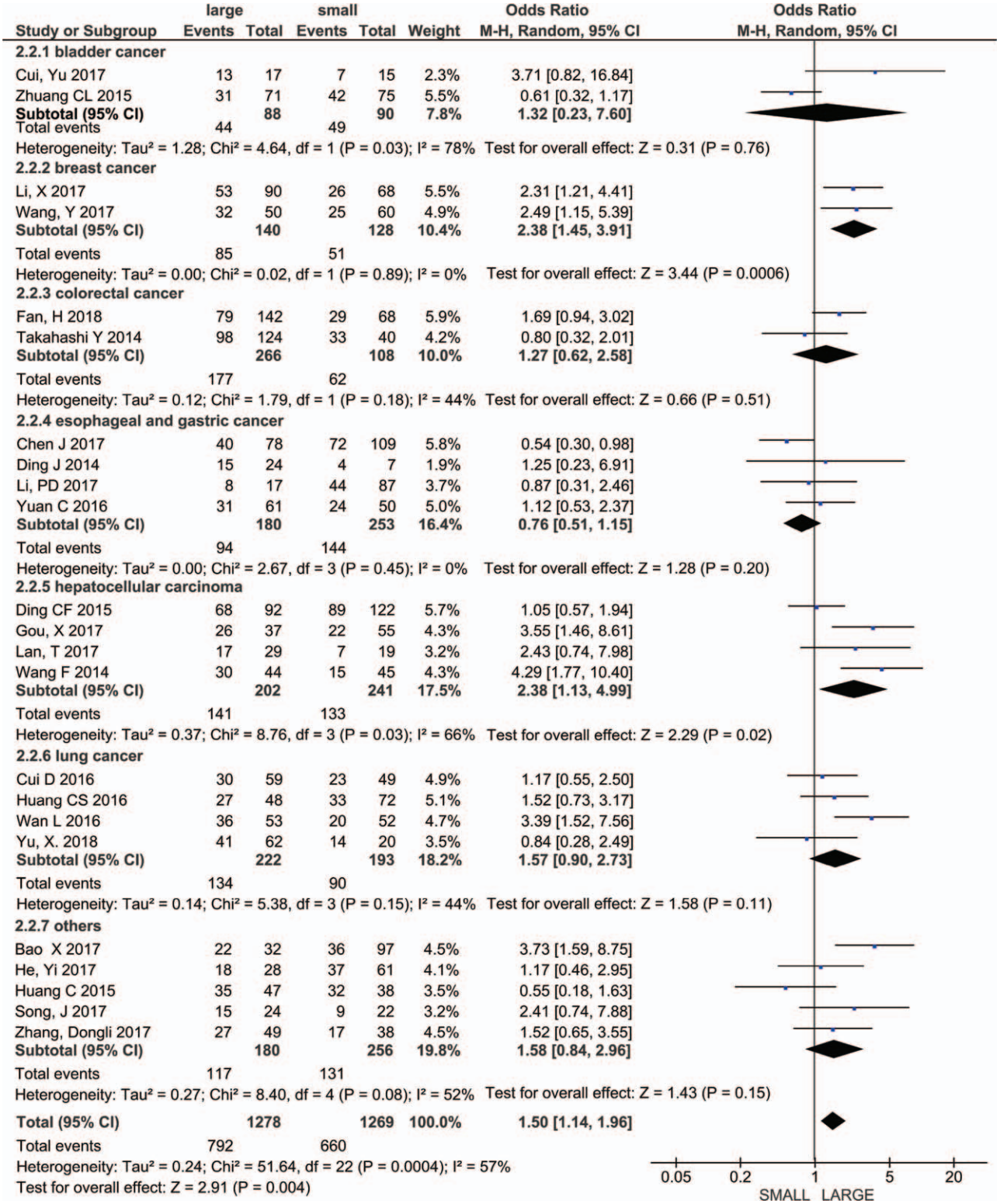

Figure 3. Forest plot for the association between PVT1 expression levels with tumor size. PVT1 = plasmacytoma variant translocation1.

clinicopathological features and prognosis of various tumor patients, including lung cancer,[4,5] gastric cancer,[2,6] breast cancer,[7,8] cervical cancer,[9–12] colorectal cancer,[13,14] hepatocellular carcinoma.[15–18] However, most reports are limited by geographical, ethnic, and sample size limitations. Therefore, it is necessary to conduct a comprehensive meta-analysis of the existing data to evaluate the significance of PVT1 as a prognostic marker for the prognosis of various carcinomas. There have been some meta-analyses on PVT1 and tumor prognosis before,[42,43] but there have been many new literature

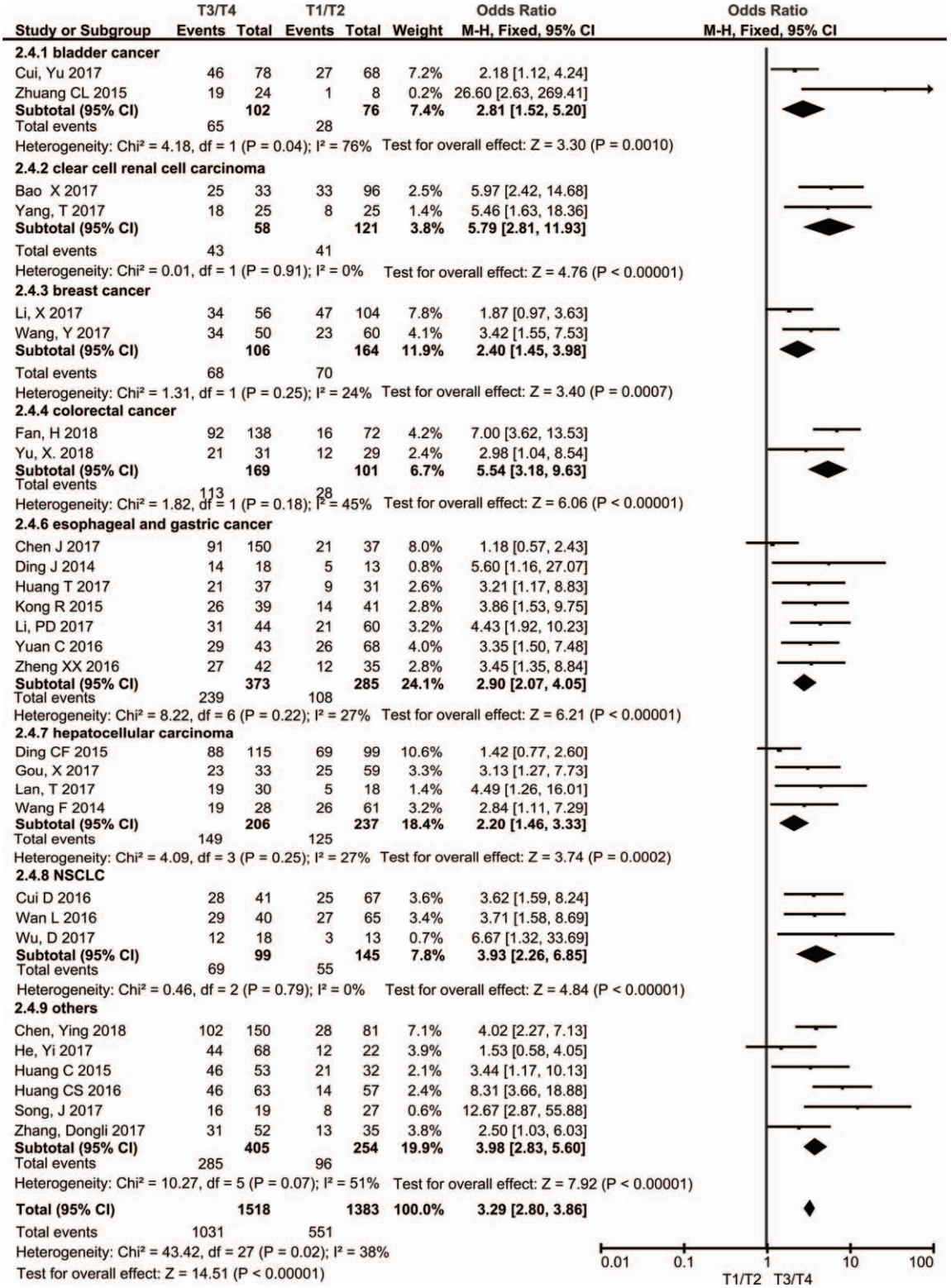

Figure 4. Forest plot for the association between PVT1 expression levels and clinical stage in different cancer patients. PVT1 = plasmacytoma variant translocation1.

reports in recent years. In order to improve the integrity and reliability of meta-analysis, we searched the literature published before November 22, 2018 on PVT1 and tumor prognosis for comprehensive analysis. A total of 39 literatures including 3974 patients were included in this study according to the inclusion and exclusion criteria.

To determine the relationship between PVT1 expression level and survival prognosis of patients, we conducted a comprehen-

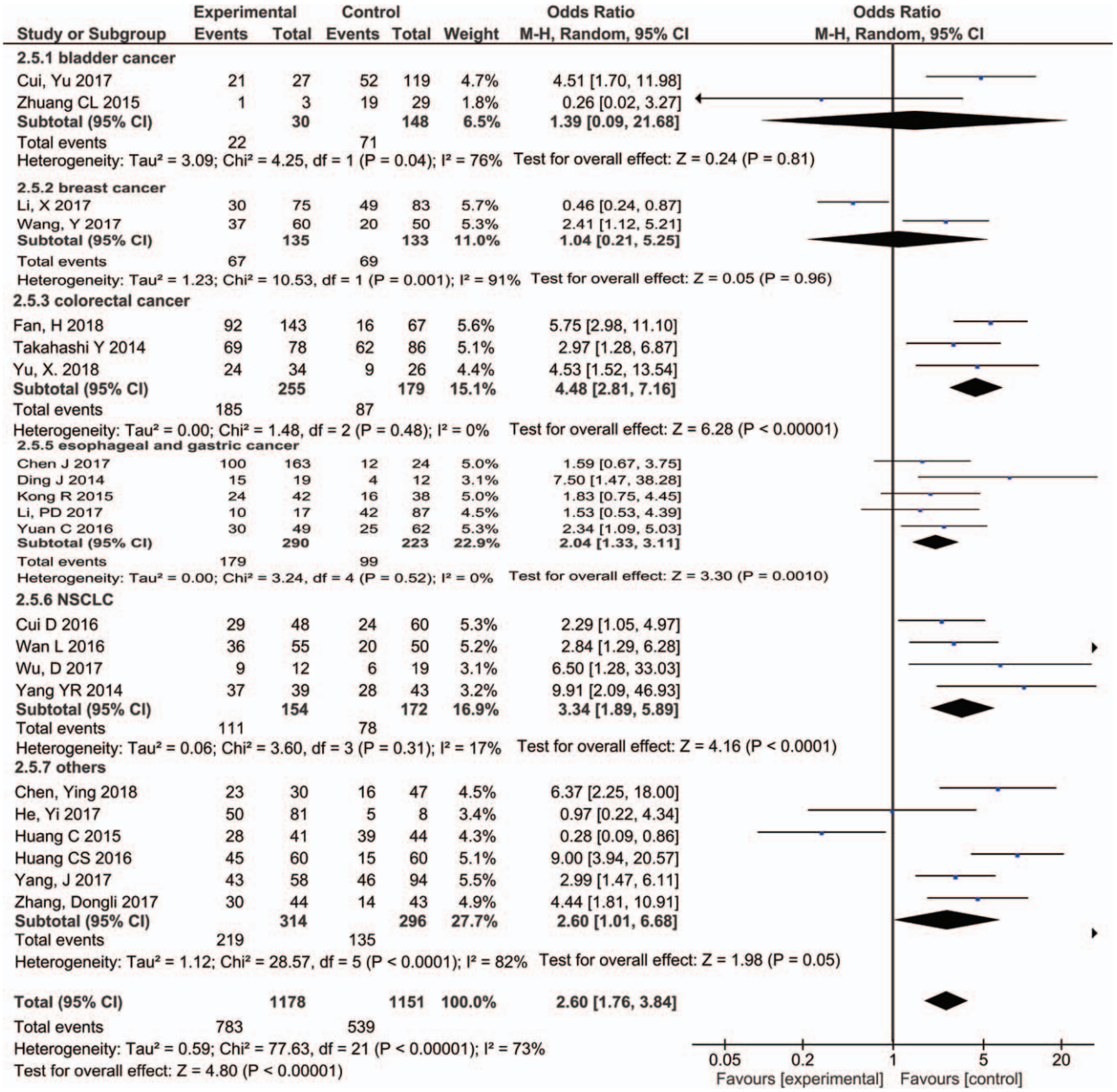

Figure 5. Forest plot for the association between PVT1 expression levels with LNM. LNM = lymph node metastasis, PVT1 = plasmacytoma variant translocation1

sive analysis of 35 literatures including various cancers. The results showed that increased PVT1 expression predicted decreased overall survival (HR = 1.64, 95% CI: 1.50–1.78, $P < .000001$). The subgroup analysis based on different tumor types showed that the high expression of PVT1 was related to the poor overall survival rate of patients with clear cell renal cell carcinoma, breast cancer, cervical cancer, colon cancer, epithelial ovarian cancer, gastric cancer, lung cancer, osteosarcoma and others (including: bladder cancer, nasopharyngeal carcinoma, pancreatic cancer, melanoma, prostate cancer) respectively. However, subgroup analysis of HCC showed that the high expression of PVT1 was not significantly correlated with the survival time of HCC patients. This may be because the number of cases included in Ding et al's[16] study (n = 214) was much higher than that in the other 2 literatures (n = 8948). Although no significant association was found, patients exhibiting high PVT1 expression levels demonstrated a trend for poor prognoses. Therefore, larger sample size data are needed to explore the relationship between PVT1 expression and overall survival of patients with liver cancer.

This study also analyzed the relationship between PVT1 expression and clinicopathological characteristics of different tumors. The results showed that the high expression of PVT1 was related to the tumor size and TNM stage of breast cancer, hepatocellular carcinoma, and lung cancer. Although it was found that the expression of PVT1 was negatively correlated with gastric cancer tumor size, the expression of PVT1 was significantly correlated with TNM stage and lymph node metastasis of gastric cancer. It was reported that PVT1 promotes hepatocellular carcinoma cell proliferation by stabilizing NOP2

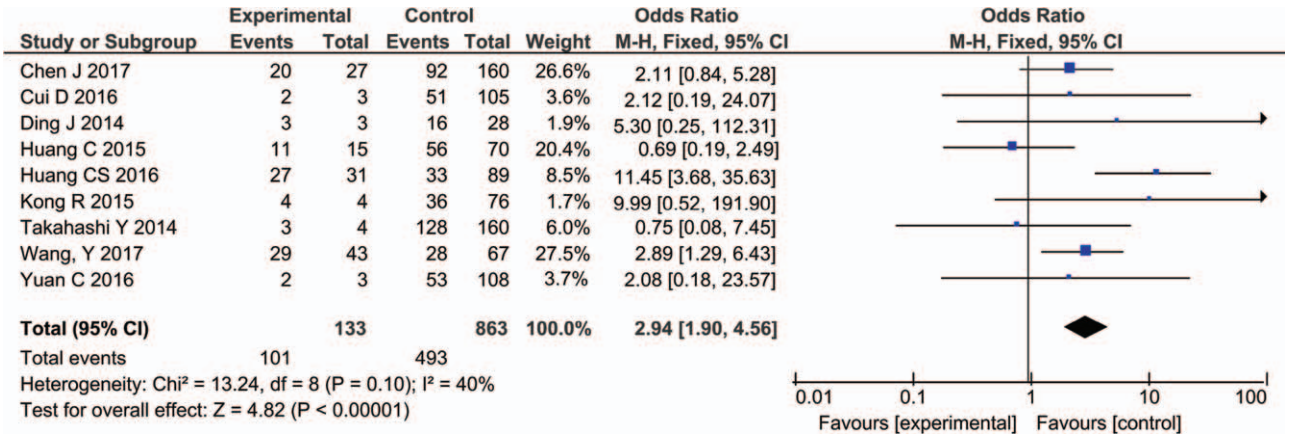

Figure 6. Forest plot for the association between PVT1 expression levels with DM. DM = distant metastasis, PVT1 = plasmacytoma variant translocation1.

protein.[18] It has also been reported that PVT1 inhibits miR-214 expression by interacting with EZH2 enhancer, thereby promoting the proliferation of hepatocellular carcinoma cells.[15] Therefore, pvt1-ezh2-mir-214-nop2 axis may be one of the mechanisms by which PVT1 regulates hepatocellular carcinoma cells. In gastric cancer, PVT1 interacts with FOXm1 to promote the proliferation and invasion of tumor cells.[2] In addition, PVT1 could directly interact with miR-186 and lead to the inhibition of HIF-1a expression, thereby promoting the proliferation of gastric carcinoma cells.[34]

In addition, meta-analysis showed that the increased expression of PVT1 was also significantly correlated with TNM staging

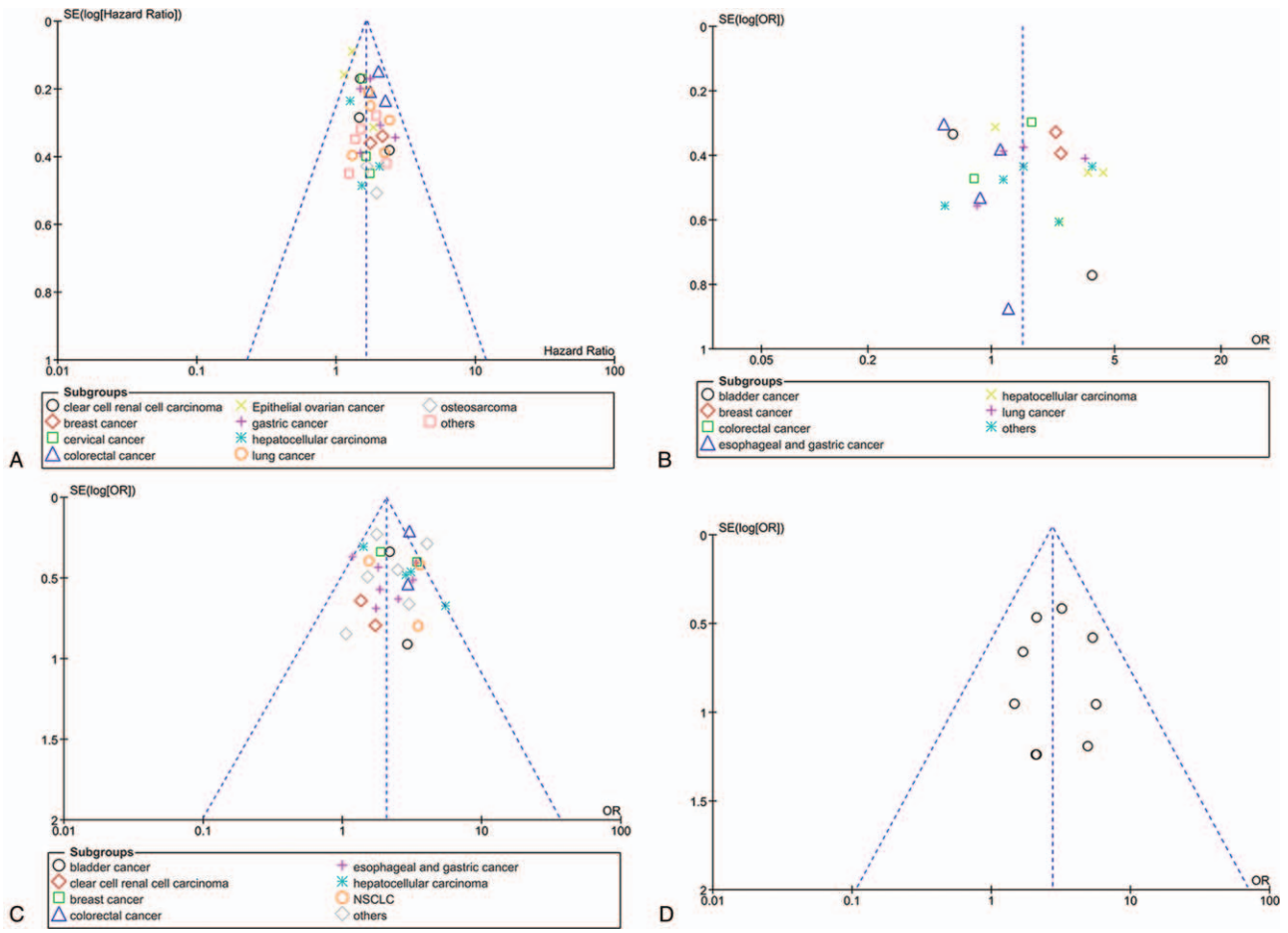

Figure 7. Funnel plot analysis of evaluating publication bias. (A) Begg funnel plot with pseudo 95% CIs for OS; (B) Begg funnel plot with pseudo 95% CIs for tumor size; (C) Begg funnel plot with pseudo 95% CIs for TNM stages; (D) Begg funnel plot with pseudo 95% CIs for distant metastases. CI = confidence interval, OS = overall survival, TNM = tumor–node–metastasis.

of bladder cancer, clear cell renal cell carcinoma, and colorectal cancer, as well as lymph node metastasis of lung cancer and colon cancer. It has been reported that PVT1 may promote metastasis and proliferation of colon cancer via suppressing miR-30d-5p/RUNX2 axis.[25] PVT1 expression was also associated with distant metastasis of different cancers. Furthermore, no significant publication bias was found in our analysis.

Like other meta-analyses, this study also had its limitations. Firstly, there are more reports in Asia and less data in other regions. Secondly, the median value of PVT1 expression is inconsistent among different tumor types and literature reports, which may affect the heterogeneity of meta-analysis. Thirdly, the follow-up period of cancer patients may be inconsistent between different literature reports, which will also have a certain impact on the analysis results. Despite some disadvantages, this meta-analysis still has notable advantages. Firstly, we searched the literature before November 2018, and included 39 literatures including 3974 samples. The sample size was large enough to reduce the errors caused by insufficient sample size. Secondly, subgroup analysis was carried out for different types of tumors to reduce the heterogeneity caused by different types of tumors.

To sum up, although there are some limitations, our meta-analysis showed that high expression of PVT1 was significantly associated with tumor size, TNM stage, lymph node metastasis, distant metastasis, and overall survival time and so on, especially in breast cancer, liver cancer, lung cancer, indicating meaning is more apparent, but in bladder cancer, renal cell carcinoma and nasopharyngeal carcinoma, the indication is relatively weak as the fewer samples.

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