

# 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 metaanalysis 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, IncRNA = 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

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# 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,

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.<sup>[1]</sup> 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.<sup>[2]</sup> 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.<sup>[3]</sup> 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,<sup>[4,5]</sup> gastric cancer,<sup>[2,6]</sup> breast cancer,<sup>[7,8]</sup> cervical cancer,<sup>[9–12]</sup> colorectal cancer,<sup>[13,14]</sup> hepatocellular carcinoma.<sup>[15–18]</sup> 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-nodemetastasis (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.<sup>[19]</sup> 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 metaanalysis to combine HR or OR values. The chi square-based Qtest and  $I^2$  statistics were used to evaluate the heterogeneity. If the heterogeneity was obvious ( $I^2 > 50\%$ , P < .05), the randomeffects 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,<sup>[20,21]</sup> clear cell renal cell carcinoma,<sup>[22–24]</sup> breast cancer,<sup>[7,8]</sup> cervical cancer,<sup>[9,11,12]</sup> colorectal cancer,<sup>[13,14,25]</sup> epithelial cancer,<sup>[26,31–34]</sup> hepatocellular carcinoma,<sup>[15–17]</sup> Melanoma,<sup>[35]</sup> nasopharyngeal carcinoma,<sup>[36]</sup> lung cancer,<sup>[37]</sup> Osteosarcoma,<sup>[38,39]</sup> pancreatic cancer,<sup>[40]</sup> and prostate cancer.<sup>[41]</sup> 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 randomeffect 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 fixedeffect 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=1)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.

				TNM	Sample	Cut-off	Follow-up,	Detection	Out	come	
First author	Year	Region	Tumor type	stage	size	value	mo	methods	mea	asure	NOS
Takahashi Y	2014	Japan	Colorectal cancer	0–IV	164	>20%	45.6 (mean)	gRT-PCR	0S		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	-	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	0S	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	0S		5
lden M	2016	America	Cervical cancer		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	0S	DFS	7
Wan L	2016	China	Lung cancer	I–IIIa	105	Median	N/A	qRT-PCR	0S	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	1	129	Median	72 (median)	qRT-PCR	OS	PFS	7
Li PD	2017	China	Esophageal squamous cell carcinoma	-	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	-	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	⊢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

				Hazard Ratio	Hazard	Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% C	I IV, Fixed	, 95% CI
1.1.1 clear cell renal	cell carcinoma					
Bao X 2017	0.89	0.38	1.3%	2.44 [1.16, 5.13]		
Li, Weicong 2018	0.89	0.51	0.7%	2.44 [0.90, 6.62]	+	
Yang, T 2017	0.4	0.17	6.6%	1.49 [1.07, 2.08]		-
Subtotal (95% CI)			8.7%	1.68 [1.25, 2.24]		•
Heterogeneity: Chi <sup>2</sup> = '	1.97, df = 2 (P = 0.37	); $ ^2 = ($	0% Test f	for overall effect: Z =	= 3.48 (P = 0.0005)	92.
1.1.2 breast cancer					1794294001 CICLID4309	
Li, X 2017	0.77	0.34	1.7%	2.16 [1.11, 4.21]		
Wang, Y 2017	0.56	0.36	1.5%	1.75 [0.86, 3.55]	+	
Subtotal (95% CI)			3.1%	1.96 [1.21, 3.18]	Cartary Real and Cartary	•
Heterogeneity: Chi <sup>2</sup> = 0	0.18, df = 1 (P = 0.67)	); $ ^2 = ($	0% Test fo	or overall effect: Z =	= 2.71 (P = 0.007)	
1.1.3 cervical cancer	0.70		1.001			
Iden M 2016	0.79	0.4	1.2%	2.20 [1.01, 4.83]		•
Zhang SR 2016	0.88	0.45	0.9%	2.41 [1.00, 5.82]		
Zhang, Dongli 2017	0.43	0.17	6.6%	1.54 [1.10, 2.15]		T.
Subtotal (95% CI)	1 27 H - 2 /D - 0 FO	. 12 - 0	8.7%	1.69 [1.27, 2.26]	2 57 (5 - 0 000 ()	•
1 1 4 colorectal cance	1.37, di = 2 (P = 0.50)	;  - = (	1est 1	or overall effect: Z =	= 3.57 (P = 0.0004)	
Fan. H 2018	0.57	0.21	4 3%	1 77 [1 17 2 67]		
Takahashi Y 2014	0.92	0.4	1.2%	2.51 [1.15 5.50]		
Yu X 2018	1.05	0.44	1.0%	2 86 [1 21 6 77]		
Subtotal (95% CI)	1.05	0.44	6.5%	2.03 [1.45, 2.84]	2	•
Hotorogonoity: Chi2 -	1 32 df = 2 /D = 0.52	12 - 1	1% Test f	or overall effect: 7 -	= 4.13 (P < 0.0001)	0.00763
1.1.5 Epithelial ovaria	1.52, ul = 2 (P = 0.52) n cancer	, r= (	J/o Test l	or overall effect. Z =	4.10 (r = 0.0001)	
Chen, Ying 2018	0.14	0.16	7.5%	1.15 [0.84, 1.57]	+	
Martini P 2017	0.26	0.09	23.6%	1.30 [1.09, 1.55]	-	
Yang, Q. 2018	0.61	0.42	1.1%	1.84 [0.81, 4,19]	+	
Subtotal (95% CI)			32.1%	1.28 [1.10, 1.48]		
Heterogeneity: Chi <sup>2</sup> = 1	.21, df = 2 (P = 0.55)	; $ ^2 = 0$	% Test	for overall effect: Z :	= 3.16 (P = 0.002)	
1.1.6 gastric cancer	COMPANIES POR				Sectored Construction	
Chen J 2017	0.4	0.2	4.8%	1.49 [1.01, 2.21]	T	
Kong R 2015	0.74	0.34	1.7%	2.10 [1.08, 4.08]	ſ	An an
Li, PD 2017	1.01	0.36	1.5%	2.75 [1.36, 5.56]		
Xu MD 2017	0.57	0.17	6.6%	1.77 [1.27, 2.47]		-
Yuan C 2016	0.82	0.39	1.3%	2.27 [1.06, 4.88]	t t	
Subtotal (95% CI)	00 df = 4 (D = 0 50)	12 - 0	15.7%	1.82 [1.46, 2.25]	5 10 /5 - 0 00001	•
Heterogeneity: Chi <sup>+</sup> = 2	(.82, df = 4 (P = 0.59))	;  * = 0	% lest	for overall effect: Z	= 5.43 (P < 0.00001)	
Ding CE 2015	arcinoma	0.22	2 00/	1 06 10 60 1 621	· ·	_
Lon T 2017	0.00	0.22	0.6%	2.64 [0.99, 7.01]	1	
Lan, 1 2017	0.97	0.50	1.0%	2.04 [0.00, 7.91]		
Subtotal (05% CI)	0.72	0.45	5.6%	2.05 [0.00, 4.77]		
Heterogeneity: Chi <sup>2</sup> = '	357 df = 2 (P = 0.17)	· 12 = 4	14% Tos	t for overall effect: 7	7 = 1.52 (P = 0.13)	
1.1.8 lung cancer	5.57, 01 - 2 (1 - 0.17	, ,	1470 165	tion overall effect. 2	L = 1.52 (F = 0.15)	
Cui D 2016	0.54	0.21	4.3%	1.72 [1.14, 2.59]	-	
Huang CS 2016	0.57	0.25	3.1%	1.77 [1.08, 2.89]	-	
Wan L 2016	0.9	0.36	1.5%	2.46 [1.21, 4.98]		
Wu, D 2017	1.16	0.52	0.7%	3,19 [1,15, 8,84]		
Yang YR 2014	1.18	0.38	1.3%	3.25 [1.55 6.85]		
Subtotal (95% CI)	1.10	0.00	10.9%	2.04 [1.58, 2.65]	2010-000-000-000-000-00	•
Heterogeneity: Chi <sup>2</sup> = 3	3.52, df = 4 (P = 0.47)	;  2 = (	% Test f	or overall effect: Z =	= 5.40 (P < 0.00001)	2020
1.1.9 osteosarcoma	0.50	0.04	0.50	1 70 10 54 0 001		
Song, J 2017	0.58	0.64	0.5%	1.79 [0.51, 6.26]		
Zhou Q 2016	0.82	0.43	1.0%	2.27 [0.98, 5.27]		
Subtotal (95% CI)			1.5%	2.11 [1.05, 4.24]	0.00 (5. 0.00)	
Heterogeneity: Chi <sup>2</sup> =	0.10, df = 1 (P = 0.76)	); $ ^2 = 1$	0% Test	for overall effect: Z	= 2.09 (P = 0.04)	
1.1.10 others	0.00	0.00	4 004	1 00 14 00 0 701		
Cul, Yu 2017	0.69	0.32	1.9%	1.99 [1.06, 3.73]		
He, Yi 2017	0.93	0.35	1.6%	2.53 [1.28, 5.03]		
Huang C 2015	1.1	0.33	1.8%	3.00 [1.57, 5.74]		
Wang, B. J 2018	0.22	0.45	0.9%	1.25 [0.52, 3.01]		
Yang, J 2017	0.84	0.42	1.1%	2.32 [1.02, 5.28]	L L	
Subtotal (95% CI)			7.2%	2.23 [1.62, 3.07]		•
Heterogeneity: Chi <sup>2</sup> = 2	2.75, df = 4 (P = 0.60)	); $ ^2 = ($	0% Test	for overall effect: Z	= 4.93 (P < 0.00001)	
Total (95% CI)			100.0%	1.64 [1.50, 1.78]	Les market and the second s	•
Heterogeneity: Chi2 =	40.55  df = 33 (P = 0)	17) 12	= 19%		1 I I	1 1
Test for overall effect:	7 = 11.27 / P < 0.000	01)	1010		0.01 0.1 1	10 100
toot for overall enect.					[experimental]	[control]

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

	large	sma	ll .		Odds Ratio	Odds Ratio
Study or Subgroup	Events T	otal Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.2.1 bladder cancer						
Cui, Yu 2017	13	17 7	15	2.3%	3.71 [0.82, 16.84]	
Zhuang CL 2015	31	71 42	75	5.5%	0.61 [0.32, 1.17]	
Subtotal (95% CI)	1.11	88	90	7.8%	1.32 [0.23, 7.60]	
Total events	44	49			<b>-</b>	0.04 (5
Heterogeneity: Tau <sup>2</sup> = 1 2.2.2 breast cancer	.28; Chi <sup>2</sup> =	4.64, df = 1 (	P = 0.03	3); l <sup>2</sup> = 78%	Test for overall effect: 2	L = 0.31 (P = 0.76)
Li, X 2017	53	90 26	68	5.5%	2.31 [1.21, 4.41]	
Wang, Y 2017	32	50 25	60	4.9%	2.49 [1.15, 5.39]	
Subtotal (95% CI)		140	128	10.4%	2.38 [1.45, 3.91]	
Total events	85	51				
Heterogeneity: Tau <sup>2</sup> = 0	.00; Chi <sup>2</sup> =	0.02, df = 1 (	P = 0.89	9); l <sup>2</sup> = 0%	Test for overall effect: 2	Z = 3.44 (P = 0.0006)
2.2.3 colorectal cance	r					
Fan, H 2018	79	142 29	68	5.9%	1.69 [0.94, 3.02]	
Takahashi Y 2014	98	124 33	40	4.2%	0.80 [0.32, 2.01]	
Subtotal (95% CI)		266	108	10.0%	1.27 [0.62, 2.58]	-
Total events	177	62				
Heterogeneity: Tau <sup>2</sup> = 0	).12; Chi <sup>2</sup> =	1.79, df = 1 (	P = 0.18	3); l <sup>2</sup> = 44%	Test for overall effect: 2	Z = 0.66 (P = 0.51)
2.2.4 esophageal and	gastric car	ncer				
Chen J 2017	40	78 72	109	5.8%	0.54 [0.30, 0.98]	
Ding J 2014	15	24 4	7	1.9%	1.25 [0.23, 6.91]	
Li. PD 2017	8	17 44	87	3.7%	0.87 [0.31, 2.46]	
Yuan C 2016	31	61 24	50	5.0%	1.12 [0.53, 2.37]	
Subtotal (95% CI)		180	253	16.4%	0.76 [0.51, 1.15]	•
Total events	94	144			the state of the state of the state of the	
Heterogeneity: $Tau^2 = 0$	00: Chi <sup>2</sup> =	2.67  df = 3.0	P = 0.45	5): $I^2 = 0\%$	Test for overall effect: Z	r = 1.28 (P = 0.20)
2.2.5 hepatocellular ca	arcinoma	2.07, 0. 0	0.10			
Ding CE 2015	68	92 89	122	5 7%	1 05 [0 57 1 94]	
Gou, X 2017	26	37 22	55	4.3%	3 55 [1 46, 8,61]	
Lan T 2017	17	29 7	19	3.2%	2 43 [0 74 7 98]	
Wang F 2014	30	44 15	45	4 3%	4 29 [1 77 10 40]	
Subtotal (95% CI)	00	202	241	17.5%	2.38 [1.13, 4.99]	-
Total events	141	133				1.000
Heterogeneity: $Tau^2 = 0$	37. Chi2 =	8.76 df = 3.0	P = 0.03	3) $1^2 = 66\%$	Test for overall effect:	7 = 2.29 (P = 0.02)
2 2 6 lung cancer		0.70, 01 - 0 (	- 0.00	, i = 0070		L = 2.20 (1 = 0.02)
Cui D 2016	20	50 22	10	4 00/	1 17 10 55 2 501	
Gui D 2010	27	19 23	49	4.9 /0	1.17 [0.33, 2.30]	
Man L 2016	21	40 33	12	0.1%	1.52 [0.75, 5.17]	
Wan L 2010	30	53 20	52	4.1%	3.39 [1.52, 7.50]	and the second se
ru, X. 2018 Subtotal (95% CI)	41	02 14	103	3.5%	0.84 [0.28, 2.49]	
Tatal averate	104		135	10.2 /0	1.57 [0.50, 2.75]	
I otal events	134	5 20 45 - 2 (	D = 0.40	= 12 - 440/	Toot for everall offects	7 = 1.59 (D = 0.11)
Heterogeneity: Tau <sup>2</sup> = 0	14; Chr =	5.38, df = 3 (	P = 0.13	5); I <sup>2</sup> = 44%	Test for overall effect.	L = 1.58 (P = 0.11)
2.2.7 others	1000	201 322	0250	1,1283	12/22/07/22/24/22/2	
Bao X 2017	22	32 36	97	4.5%	3.73 [1.59, 8.75]	
He, Yi 2017	18	28 37	61	4.1%	1.17 [0.46, 2.95]	
Huang C 2015	35	47 32	38	3.5%	0.55 [0.18, 1.63]	
Song, J 2017	15	24 9	22	3.2%	2.41 [0.74, 7.88]	
Zhang, Dongli 2017	27	49 17	38	4.5%	1.52 [0.65, 3.55]	
Subtotal (95% CI)		180	256	19.8%	1.58 [0.84, 2.96]	
Total events	117	131			1 <u>2 1 1 2 1 2 1 2 1 2 1 2 2 2 2 2 2 2 2</u>	N Service Courses
Heterogeneity: Tau <sup>2</sup> = 0	.27; Chi <sup>2</sup> =	8.40, df = 4 (	P = 0.08	3); l <sup>2</sup> = 52%	Test for overall effect: 2	Z = 1.43 (P = 0.15)
Total (95% CI)	1	278	1269	100.0%	1.50 [1.14, 1.96]	•
Total events	702	660	1100		inter turni, usel	
Heterogeneity: Tau <sup>2</sup> = 0	24. Chi2 -	51 64 df = 2	2(P = 0)	0004) 12 -	57%	-1 -1 -1 -1 -1-
Test for overall offect: 7	= 2 01 /P	= 0.004	- (1 - 0		01/0	0.05 0.2 1 5 20
LEALIN OVER IL ELECT Z	- 2.51 (P	- 0.004)				SMALL LADCE

Figure 3. Forest plot for the association between PVI1 expression levels with tumor size. PVI1=plasmacytoma variant translocation1.

clinicopathological features and prognosis of various tumor patients, including lung cancer,<sup>[4,5]</sup> gastric cancer,<sup>[2,6]</sup> breast cancer,<sup>[7,8]</sup> cervical cancer,<sup>[9-12]</sup> colorectal cancer,<sup>[13,14]</sup> hepatocellular carcinoma.<sup>[15–18]</sup> 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,<sup>[42,43]</sup> but there have been many new literature

	T3/T4	1	T1/T2	2		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2.4.1 bladder cancer							
Cui, Yu 2017	46	78	27	68	7.2%	2.18 [1.12, 4.24]	
Zhuang CL 2015	19	24	1	8	0.2%	26.60 [2.63, 269.41]	
Subtotal (95% CI)		102	14	76	7.4%	2.81 [1.52, 5.20]	-
Total events	65		28	2006-0	an senten tett		
Heterogeneity: Chi <sup>2</sup> = 4	4.18, df = 1	1 (P = (	$(0.04);  ^2 =$	76%	Test for ov	verall effect: Z = 3.30 (P = 0.0010)	
2.4.2 clear cell renal of	cell carcin	ioma					
Bao X 2017	25	33	33	96	2.5%	5.97 [2.42, 14.68]	
Yang, T 2017	18	25	8	25	1.4%	5.46 [1.63, 18.36]	
Subtotal (95% CI)		58		121	3.8%	5.79 [2.81, 11.93]	-
Total events	43		41				
Heterogeneity: Chi <sup>2</sup> = 0	0.01, df = 1	1 (P = 0)	0.91); l <sup>2</sup> =	0%	Test for or	verall effect: Z = 4.76 (P < 0.00001	1)
2.4.3 breast cancer							
Li, X 2017	34	56	47	104	7.8%	1.87 [0.97, 3.63]	
Wang, Y 2017	34	50	23	60	4.1%	3.42 [1.55, 7.53]	
Subtotal (95% CI)		106		164	11.9%	2.40 [1.45, 3.98]	•
Total events	68		70				
Heterogeneity: Chi <sup>2</sup> = 1	1.31, df = 1	1 (P = (	).25); l <sup>2</sup> =	24%	Test for ov	verall effect: Z = 3.40 (P = 0.0007)	K
2.4.4 colorectal cance	er		a.c.				
Fan, H 2018	92	138	16	72	4.2%	7.00 [3.62, 13.53]	
Yu, X. 2018	21	31	12	29	2.4%	2.98 [1.04, 8.54]	
Subtotal (95% CI)		169		101	6.7%	5.54 [3.18, 9.63]	•
I otal events	113		28		Tank		0
Heterogeneity: Chi <sup>2</sup> = 1	1.82, df = 1	1 (P = (	J.18); l <sup>2</sup> =	45%	lest for o	verall effect: Z = 6.06 (P < 0.00001	0
2.4.6 esophageal and	gastric c	ancer					
Chen J 2017	91	150	21	37	8.0%	1.18 [0.57, 2.43]	
Ding J 2014	14	18	5	13	0.8%	5.60 [1.16, 27.07]	
Huang T 2017	21	37	9	31	2.6%	3.21 [1.17, 8.83]	
Kong R 2015	26	39	14	41	2.8%	3.86 [1.53, 9.75]	
Li, PD 2017	31	44	21	60	3.2%	4.43 [1.92, 10.23]	
Yuan C 2016	29	43	26	68	4.0%	3.35 [1.50, 7.48]	
Zheng XX 2016	27	42	12	35	2.8%	3.45 [1.35, 8.84]	
Subtotal (95% CI)	230	373	108	285	24.1%	2.90 [2.07, 4.05]	-
Heterogeneity: Chi <sup>2</sup> = 8	3.22, df = 6	B(P = 0)	).22); l <sup>2</sup> =	27%	Test for ov	verall effect: Z = 6.21 (P < 0.00001	)
2.4.7 hepatocellular c	arcinoma					AND AND A DOUGLASS AND	50 C
Ding CF 2015	88	115	69	99	10.6%	1.42 [0.77, 2.60]	+
Gou, X 2017	23	33	25	59	3.3%	3.13 [1.27, 7.73]	
Lan, T 2017	19	30	5	18	1.4%	4.49 [1.26, 16.01]	
Wang F 2014	19	28	26	61	3.2%	2.84 [1.11, 7.29]	
Total events	140	206	125	237	18.4%	2.20 [1.46, 3.33]	-
Heterogeneity: Chi <sup>2</sup> = 4	.09. df = 3	B (P = 0	).25): 1 <sup>2</sup> =	27%	Test for ov	erall effect: Z = 3.74 (P = 0.0002)	
2.4.8 NSCLC		- (r - t			501101 01	5.1.1 5.100. 2 - 5.14 (1 - 5.0002)	
Cui D 2016	28	41	25	67	3.6%	3 62 [1 59 8 24]	
Wan L 2016	29	40	27	65	3.4%	3.71 [1.58, 8.69]	
Wu D 2017	12	18	3	13	0.7%	6 67 [1 32 33 69]	
Subtotal (95% CI)	14	99		145	7.8%	3.93 [2.26, 6.85]	•
Total events	69		55	100		De la construction de la	-
Heterogeneity: Chi <sup>2</sup> = (	0.46, df = :	2 (P =	0.79); l <sup>2</sup> =	0%	Test for o	verall effect: Z = 4.84 (P < 0.0000	1)
2.4.9 others							
Chen, Ying 2018	102	150	28	81	7.1%	4.02 [2.27, 7.13]	
He, Yi 2017	44	68	12	22	3.9%	1.53 [0.58, 4.05]	
Huang C 2015	46	53	21	32	2.1%	3.44 [1.17, 10.13]	
Huang CS 2016	46	63	14	57	2.4%	8.31 [3.66, 18.88]	
Song, J 2017	16	19	8	27	0.6%	12.67 [2.87, 55.88]	
Zhang, Dongli 2017	31	52	13	35	3.8%	2.50 [1.03, 6.03]	
Subtotal (95% CI)	100	405		254	19.9%	3.98 [2.83, 5.60]	•
I otal events	285		96				
Heterogeneity: Chi <sup>2</sup> = 1	10.27, df =	5 (P =	0.07); 12 =	= 51%	Test for	overall effect: Z = 7.92 (P < 0.000	01)
Total (95% CI)		1518		1383	100.0%	3.29 [2.80, 3.86]	•
Total events	1031		551				
Heterogeneity: Chi <sup>2</sup> = 4	13.42, df =	27 (P	= 0.02); 12	= 38%	0	L.	
Test for overall effect:	Z = 14.51	(P < 0.	00001)			0.01	U.1 1 10 1

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-

Chudu or Cubarcus	Experim	Tetel	Events	Tatal	Mainht	M H Bandom 05% CI		H Bandom 05% Cl
Study or Subgroup	Events	Total	Events	Iotal	weight	m-H, Random, 95% CI	M	-n, Kandom, 95% Cl
2.5.1 bladder cancer	-	1000						
Cui, Yu 2017	21	27	52	119	4.7%	4.51 [1.70, 11.98]		
Zhuang CL 2015	1	3	19	29	1.8%	0.26 [0.02, 3.27]	• • •	
Subtotal (95% CI)		30		148	6.5%	1.39 [0.09, 21.68]		
Total events	22		71			T. 1/	0.04 (0 0.04)	
Heterogeneity: Tau <sup>2</sup> =	3.09; Chi <sup>2</sup>	= 4.25, 0	df = 1 (P =	= 0.04)	$1^2 = 76\%$	Test for overall effect: 2	= 0.24 (P = 0.81)	
2.5.2 breast cancer								
Li, X 2017	30	75	49	83	5.7%	0.46 [0.24, 0.87]	-	
Wang, Y 2017	37	60	20	50	5.3%	2.41 [1.12, 5.21]	1.000	
Subtotal (95% CI)		135		133	11.0%	1.04 [0.21, 5.25]		
Total events	67	- 40 50	69	- 0.00	41. 12 - 04	V Toot for overall offect	7 - 0.05 /P - 0.06	N .
Heterogeneity: 1 au- =	1.23; Chr	= 10.53,	ar = 1 (F	= 0.00	(1); 1- = 91	% Test for overall effect.	2 - 0.05 (F - 0.96)	
2.5.3 colorectal cance	r							
Fan, H 2018	92	143	16	67	5.6%	5.75 [2.98, 11.10]		
akahashi Y 2014	69	78	62	86	5.1%	2.97 [1.28, 6.87]		
(u, X. 2018	24	34	9	26	4.4%	4.53 [1.52, 13.54]		1 million and a second
Subtotal (95% CI)		255		179	15.1%	4.48 [2.81, 7.16]		-
Total events	185		87					
Heterogeneity: Tau <sup>2</sup> = (	).00; Chi <sup>2</sup> =	= 1.48, d	f = 2 (P =	0.48);	$ ^2 = 0\%$	Test for overall effect: Z =	= 6.28 (P < 0.00001	1)
2.5.5 esophageal and	gastric ca	ancer						2010-
Chen J 2017	100	163	12	24	5.0%	1.59 [0.67, 3.75]		
Kong R 2015	24	42	16	38	5.0%	1.83 [0.75, 4.45]		
Li, PD 2017	10	17	42	87	4.5%	1.53 [0.53, 4.39]		
Yuan C 2016	30	49	25	62	5.3%	2.34 [1.09, 5.03]		
Subtotal (95% CI)	170	290	00	223	22.9%	2.04 [1.33, 3.11]		
Heterogeneity: Tau <sup>2</sup> =	0.00: Chi <sup>2</sup>	= 3.24.	df = 4 (P =	= 0.52)	$1^2 = 0\%$	Test for overall effect: Z =	3.30 (P = 0.0010)	
2.5.6 NSCLC		1000100	And the second					
Cui D 2016	20	40	24	60	E 20/	2 20 14 05 4 071		
	29	40	24	50	5.3%	2.29 [1.05, 4.97]		and the second
Wan L 2016	30	55	20	50	5.2%	2.84 [1.29, 6.28]		
Wu, D 2017	9	12	6	19	3.1%	6.50 [1.28, 33.03]		
Yang YR 2014	37	39	28	43	3.2%	9.91 [2.09, 46.93]		
Subtotal (95% CI)		154	70	172	16.9%	3.34 [1.89, 5.89]		
I otal events	111	0.00	/8 - 2 (D	0.041	12 - 470/	Test for everall effect: 7	- 1 16 /P < 0 0001	nv.
Heterogeneity: Tau- =	0.06; Chi-	= 3.60, 0	$\mathbf{I} = \mathbf{J} \left( \mathbf{P} \right)$	= 0.31)	1- = 17%	Test for overall effect. Z	- 4.10 (F < 0.0001	0
2.5.7 Others	1000							61 TH 11
Chen, Ying 2018	23	30	16	47	4.5%	6.37 [2.25, 18.00]		
He, Yi 2017	50	81	5	8	3.4%	0.97 [0.22, 4.34]	1.00	
Huang C 2015	28	41	39	44	4.3%	0.28 [0.09, 0.86]		
Huang CS 2016	45	60	15	60	5.1%	9.00 [3.94, 20.57]		
Yang, J 2017	43	58	46	94	5.5%	2.99 [1.47, 6.11]		
Zhang, Dongli 2017	30	44	14	43	4.9%	4.44 [1.81, 10.91]		
Subtotal (95% CI)	12.225	314		296	27.7%	2.60 [1.01, 6.68]		
Total events	219		135			THE NEW ACCURATION AND		
Heterogeneity: Tau <sup>2</sup> =	1.12; Chi2 :	= 28.57,	df = 5 (P	< 0.00	01); l <sup>2</sup> = 8	2% Test for overall effect	: Z = 1.98 (P = 0.05	5)
		1170		1151	100.0%	2 60 14 76 2 941		
	-	11/0		1131	100.0%	2.00 [1.70, 3.04]		
otal events	783		539				77 20	N
Heterogeneity: Tau <sup>2</sup> = (	J.59; Chi <sup>2</sup> =	= 77.63,	df = 21 (	< 0.0	0001); l <sup>2</sup> =	- 13%	0.05 0.2	1 5 20
lest for overall effect:	Z = 4.80 (P	< 0.000	001)				Equoure fornori	imentall Equatro Coentroll

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<sup>[16]</sup> 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

	Experimental Events Total		Contr	o		Odds Ratio		Odd	s Ratio	
Study or Subgroup			<b>Events Total</b>		Weight M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl			
Chen J 2017	20	27	92	160	26.6%	2.11 [0.84, 5.28]				
Cui D 2016	2	3	51	105	3.6%	2.12 [0.19, 24.07]				
Ding J 2014	3	3	16	28	1.9%	5.30 [0.25, 112.31]			*	
Huang C 2015	11	15	56	70	20.4%	0.69 [0.19, 2.49]			<u> </u>	
Huang CS 2016	27	31	33	89	8.5%	11.45 [3.68, 35.63]				-7
Kong R 2015	4	4	36	76	1.7%	9.99 [0.52, 191.90]		_		
Takahashi Y 2014	3	4	128	160	6.0%	0.75 [0.08, 7.45]				
Wang, Y 2017	29	43	28	67	27.5%	2.89 [1.29, 6.43]				
Yuan C 2016	2	3	53	108	3.7%	2.08 [0.18, 23.57]			-	
Total (95% CI)		133		863	100.0%	2.94 [1.90, 4.56]			•	
Total events	101		493							
Heterogeneity: Chi <sup>2</sup> = 13.24, df = 8 (P = 0.10); l <sup>2</sup> = 40%										100
Test for overall effect:	Z = 4.82 (F	< 0.000	001)				0.01	0.1	1 10	100
n na anticipation de la contraction de la contractica de la contractica de la contractica de la contractica de La contractica de la c			100000				Favo	urs [experimental]	Favours [control]	

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

protein.<sup>[18]</sup> It has also been reported that PVT1 inhibits miR-214 expression by interacting with EZH2 enhancer, thereby promoting the proliferation of hepatocellular carcinoma cells.<sup>[15]</sup> 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.<sup>[2]</sup> 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.<sup>[34]</sup>

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.<sup>[25]</sup> 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 sum up, although there are some limitations, our metaanalysis 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.

### **Author contributions**

Conceptualization: Bin Zhang.

- Data curation: Bin Zhang.
- Formal analysis: Bin Zhang.
- Funding acquisition: Dong Wang.
- Investigation: Dong Wang.
- Methodology: Dong Wang.
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- Validation: Bo Zou, Dao-ying Yuan.
- Visualization: Bo Zou, Dao-ying Yuan, Zhen Meng.

Writing – original draft: Zhen Meng.

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