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Meta-analysis of the prognostic value of long non-coding RNA PVT1 for cancer patients

Chao Ma, MD[a], Xing-Guo Nie, MD[a], Yan-Li Wang, MD[b], Da-Peng Wu, MD[a,*], Qiu-dong Liang, MD[a,*]

Abstract

Background: Plasmacytoma variant translocation 1 (PVT1) is reported to be dysregulated in various cancers. Therefore, this meta-analysis was performed to clarify its utility as a prognosis marker in malignant tumors.

Methods: Electronic databases, including PubMed, OVID, Cochrane Library, and Web of Science databases, were retrieved from inception to December 16, 2017. Typically, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated, so as to explore the relationship between PVT1 expression and patient survival. In addition, odds ratios (OR) were calculated to assess the association of PVT1 expression with pathological parameters.

Results: A total of 23 studies involving 2350 patients were included in this meta-analysis. The pooled HR suggested that high PVT1 expression levels were correlated with poor overall survival (OS, HR = 1.99, 95% CI: 1.73–2.28), disease-free survival (DFS, HR = 1.76, 95% CI: 1.45–2.14), and recurrence-free survival (RFS, HR = 1.74, 95% CI: 1.26–2.39) in cancer patients without obvious heterogeneity. Moreover, high PVT1 expression levels were also correlated with larger tumor size (OR = 1.47, 95% CI: 1.02–2.11), poor differentiation grade (OR = 1.79, 95% CI: 1.39–2.30), advanced tumor stage (pooled OR = 3.28, 95% CI: 2.46–4.38), lymph node metastasis (OR = 2.67, 95% CI: 1.66–4.29) and distant metastasis (OR = 4.00, 95% CI: 1.39–11.50) in cancer patients.

Conclusions: Findings of this meta-analysis suggest that a high PVT1 expression level may serve as a novel biomarker of poor prognosis in cancers.

Abbreviations: ANT = adjacent noncancerous tissue, BC = bladder cancer, CI = confidence interval, CRC = colorectal cancer, CVC = cervical cancer, DFS = disease-free survival, DM = distant metastasis, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, LNM = lymph node metastasis, NSCLC = non-small cell lung cancer, OR = odds ratio, OS = overall survival, OSC = osteosarcoma, PC = pancreatic cancer, PHG = poor histological grade, PVT1 = Plasmacytoma variant translocation 1, RFS = recurrence-free survival, SCLC = small cell lung cancer, TS = high tumor stage.

Keywords: meta-analysis, metastasis, neoplasms, prognosis, PVT1

1. Introduction

According to statistics, the U.S. has witnessed approximately 1.7 million new cancer cases and 600,000 cancer-related deaths in 2017.[1] Unfortunately, the 5-year survival rates for most cancers remain dismal, and many scientists are looking for new biomarkers to improve the diagnosis and prognosis in cancers. Therefore, great efforts have been made to develop new prognostic markers to facilitate their clinical application in cancers.

Long noncoding RNAs (lncRNAs) are the transcribed RNA molecules greater than 200 nucleotides in length, which lack an open reading frame.[2] LncRNAs have many important functions in diseases, including the epigenetic, transcriptional and posttranscriptional effects.[3] Moreover, dysregulation of lncRNAs has been discovered in various cancer types.[4–7] Some lncRNAs play vital roles in cancer progression, as well as the proliferation, invasion, and metastasis of cancer cells.[8,9] Consequently, lncRNAs are regarded as promising markers for cancer prognosis.[10]

Plasmacytoma variant translocation 1 (PVT1) is originally identified as a retroviral integration site in murine leukemia virus (MLV)-induced T lymphomas.[11] PVT1 gene, which is located adjacent to the MYC locus on chromosomal region 8q24, is reported to be associated with various tumor processes, and affect the overall survival (OS), distant metastasis (DM), lymph node metastasis (LNM), and tumor stage.[12–14] Thus, PVT1 expression may be related with the prognosis and metastasis in human cancers. However, most studies reported so far are limited in terms of their discrete outcomes and small sample size. Therefore, this updated meta-analysis was carried out to determine the prognostic value of PVT1 in cancer patients.

2. Materials and methods

2.1. Literature collection

According to the standard guidelines of meta-analysis,[15,16] the following electronic databases, including PubMed, OVID,

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[a] Department of Orthopedics, [b] Department of Operating room, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang 453000, Henan province, People's Republic of China.

[*] Correspondence: Qiu-dong Liang, Department of Orthopedics, The First Affiliated Hospital of Xinxiang Medical University, No. 88 Weihui health Road, Xinxiang, Henan, 453100, China (e-mail: liangqd2015@sina.com); Da-Peng Wu, Department of Orthopedics, The First Affiliated Hospital of Xinxiang Medical University, No. 88 Weihui health Road, Xinxiang, Henan, 453100, China (e-mail: wudapeng2016@163.com).

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and Web of Science for relevant articles, were systemically retrieved by 2 authors independently, to collect studies regarding PVT1 as a prognostic marker for survival of cancer patients. The latest retrieval was updated on December 16, 2017. Specifically, literature retrieval was performed by means of both text word and MeSH strategy using the terms "PVT1", "PVT1", "lncRNA" or "noncoding RNA" or "long intergenic noncoding RNA", "carcinoma" or "neoplasm" or "tumor" or "cancer", "prognostic" or "prognosis", "outcome" or "survival or "recurrence". Notably, the strategy was correspondingly adjusted in different databases. In the retrieval process, a manual retrieval was also carried out using the reference lists from relevant articles to recruit eligible studies. All analyses were performed based on previously published studies. Thus, no ethic approval and informed consent were required in this study.

2.2. Study selection

All the included studies were evaluated and data were extracted by two researchers independently. The study inclusion criteria were as follows:

1. studies in which the role of PVT1 in the development of human cancer was investigated;
2. studies that described the related clinicopathological parameters;
3. studies that measured the PVT1 expression levels in human tumor tissues; and
4. studies in which patients were grouped according to the PVT1 expression levels.

The study exclusion criteria were as follows:

1. reviews, letters, editorials, case reports, and expert opinions;
2. non-English language and non-human studies;

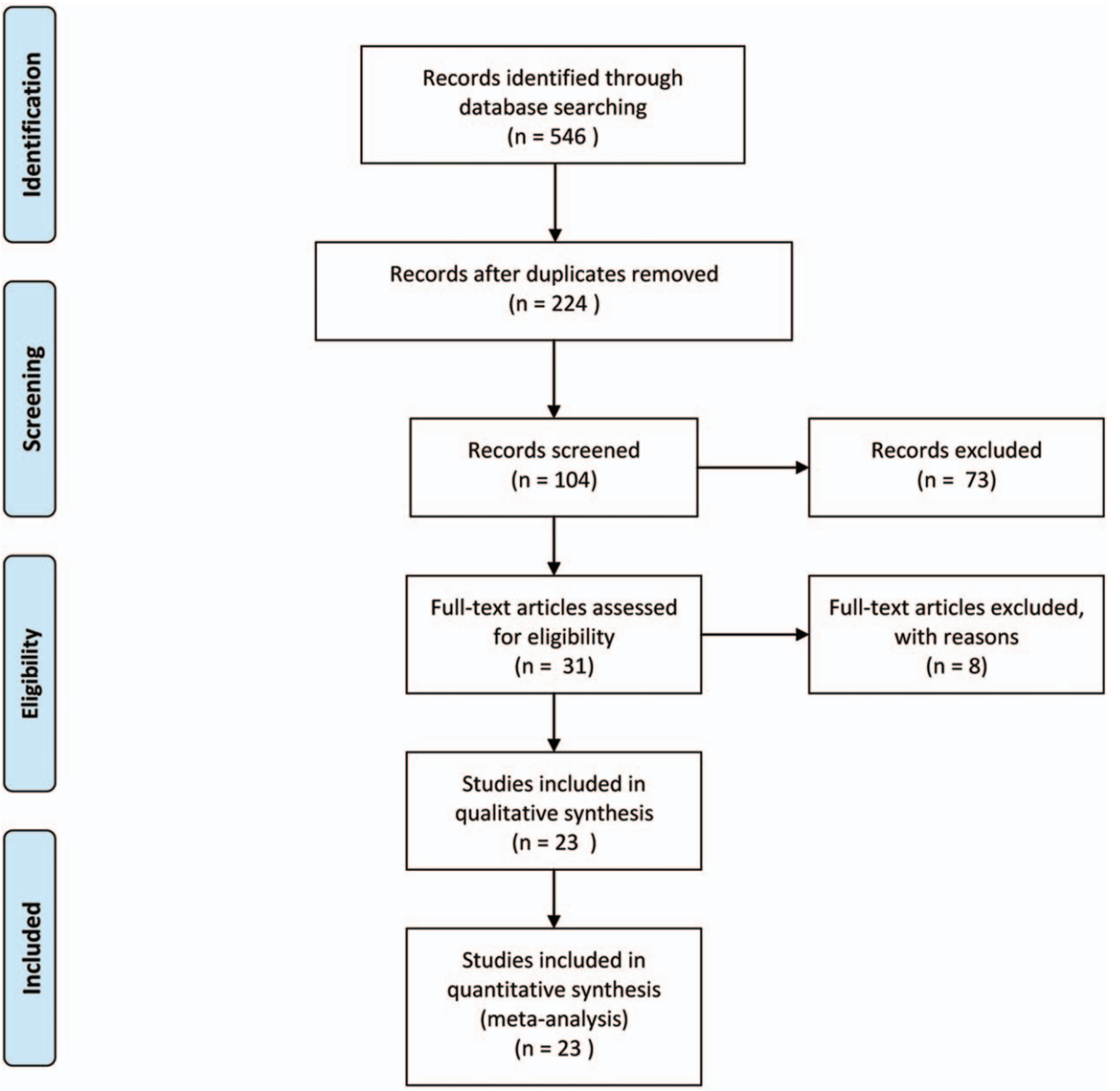

Figure 1. Flowchart showing the steps of study selection in this meta-analysis.

Table 1

The basic information and data of all included studies in the meta-analysis.

					PVT1 expression									
					High			Low						
Study	Year	Region	Tumor type	Sample size	Total	PHG	HTS	Total	PHG	HTS	Cut-off value	HR (95% CI) High / Low OS	Reference gene	Method
Chen[19]	2017	China	GC	187	112	28	91	75	19	59	YD	1.455 (1.005–2.105)	–	PCR
Cui[20]	2016	China	NSCLC	108	53	16	28	55	16	13	Median	1.72 (1.14–3.25)	GAPDH	PCR
Cui[21]	2017	China	BC	146	73	54	46	73	40	32	Mean	2.00 (1.06–3.79)	GAPDH	PCR
Ding[22]	2014	China	GC	31	19	–	14	12	–	4	ANT	–	B-actin	PCR
Ding[23]	2015	China	HCC	214	157	82	88	57	22	27	Mean	1.15 (0.44–3.03)	GAPDH	PCR
Huang[24]	2015	China	PC	85	67	62	46	18	16	7	–	3.013 (1.574–6.673)	GAPDH	PCR
Huang[25]	2016	China	SCLC	120	60	–	46	60	–	17	Median	1.782 (1.078–2.945)	GAPDH	PCR
Huang[26]	2017	China	GC	68	30	15	21	38	12	16	Mean	–	GAPDH	PCR
Kong[27]	2015	China	GC	80	40	28	26	40	20	13	Median	2.092 (1.068–4.096)	GAPDH	PCR
Lan[28]	2017	China	HCC	48	24	5	19	24	4	11	Median	1.76 (1.041–2.977)	GAPDH	PCR
Li[29]	2016	China	CRC	30	15	–	5	15	–	6	–	4.38 (1.804–10.634)	GAPDH	PCR
Li[30]	2017	China	ESCC	104	52	19	31	52	8	13	Median	2.75 (1.35–5.59)	GAPDH	PCR
Song[31]	2017	China	OSC	46	24	–	16	22	–	3	Mean	2.37 (1.219–4.609)	GAPDH	PCR
Takahashi[11]	2014	Japan	CRC	164	131	10	74	33	2	9	20%	2.532 (1.152–10.747)	GAPDH	PCR
Wan[32]	2016	China	NSCLC	105	56	–	29	49	–	11	Median	2.464 (1.214–4.999)	GAPDH	PCR
Wang[33]	2014	China	HCC	89	45	–	19	44	–	9	Median	1.98 (1.15–4.17)	B-actin	PCR
Xu[34]	2017	China	GC	190	96	–	–	94	–	–	Mean	1.64 (1.15–2.39)	B-actin	PCR
Yang[35]	2014	China	NSCLC	82	65	39	–	17	3	–	Median	3.273 (2.184–6.937)	RUN6B	PCR
Yuan[36]	2016	China	GC	111	55	17	29	56	16	14	Median	2.280 (1.054–4.930)	GAPDH	PCR
Zhang[37]	2017	China	CVC	87	44	–	31	43	–	21	–	2.27 (1.24–4.15)	GAPDH	PCR
Zhao[38]	2017	China	PC	34	18	–	16	16	–	5	Median	–	B-actin	PCR
Zheng[39]	2016	China	ESCC	77	39	–	27	38	–	15	Median	–	GAPDH	PCR
Zhuang[40]	2015	China	BC	32	20	12	19	12	2	5	–	–	GAPDH	PCR

Note: The dashes represent no data.

ANT = adjacent noncancerous tissue, BC = bladder cancer, CRC = colorectal cancer, CVC = cervical cancer, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, NSCLC = non-small cell lung cancer, OS = overall survival, OSC = osteosarcoma, PC = pancreatic cancer, PHG = poor histological grade, SCLC = small cell lung cancer, TS = high tumor stage, YD = Youdeng's index.

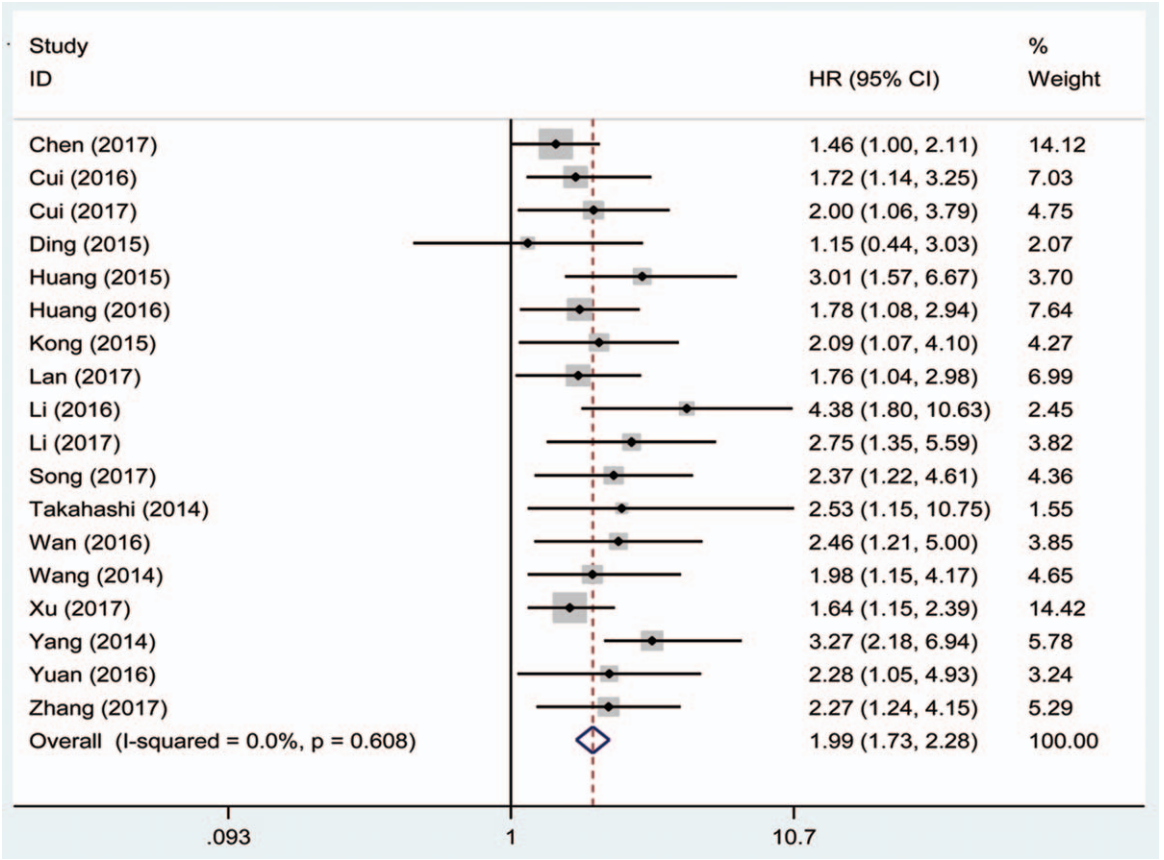

Figure 2. Forest plot reflecting the association between OS and PVT1 expression level in cancer. OS = overall survival.

3. studies without available data; and
4. laboratory studies mentioning the molecular structure and functions of PVT1 alone.

2.3. Date extraction

Data from the original articles were extracted and examined by 2 reviewers independently. Any disagreements in the literature assessment were resolved through consensus with a third reviewer. The following data were extracted: surname of the first author, publication year, country, tumor type, sample size, the cut-off value of PVT1 expression, the number of patients with poor histological grade and high tumor stage, adjusted HR and 95% CI of elevated PVT1 for OS, the reference gene of PVT1, and detection method of PVT1.

2.4. Statistical methods

The statistical analyses were performed using the Stata version 12.0 software. The heterogeneities among different studies were measured by Q and I^2 tests, respectively. Typically, a probability value of $I^2 \geq 50\%$ and $P < .1$ indicated the presence of significant heterogeneity.[17] Moreover, a random effects model or fixed effects model was employed depending on the results of the heterogeneity analysis. To be specific, the random-effects model was adopted in the presence of significant heterogeneity among studies. In addition, the potential publication bias was assessed by Begg's funnel plot. The pooled hazard ratios (HRs) and odds ratios (ORs) were extracted from the published data. For HRs that could be obtained directly from the publications, the crude ones were adopted; while for HR and 95% that were not directly reported in the studies, the survival data were extracted from Kaplan–Meier curve to estimate HR. Moreover, the log HR and standard error (SE) were used to summarize the OS outcome.[18] Importantly, the ORs and their 95% CIs were combined to assess the association of PVT1 expression with clinicopathological parameters, including tumor size, differentiation grade, tumor stage, LNM, and DM.

3. Results

3.1. Study characteristics

The detailed screening process is shown in Figure 1. According to the study inclusion and exclusion criteria, a total of 23 studies involving 2350 patients were included in this meta-analysis.[11,19–40] Additionally, the characteristics of these 23 included studies are summarized in Table 1. As could be seen, the sample size of these 23 studies ranged from 30 to 214, with a mean of 102.2. Meanwhile, these studies, which were published from 2014 to

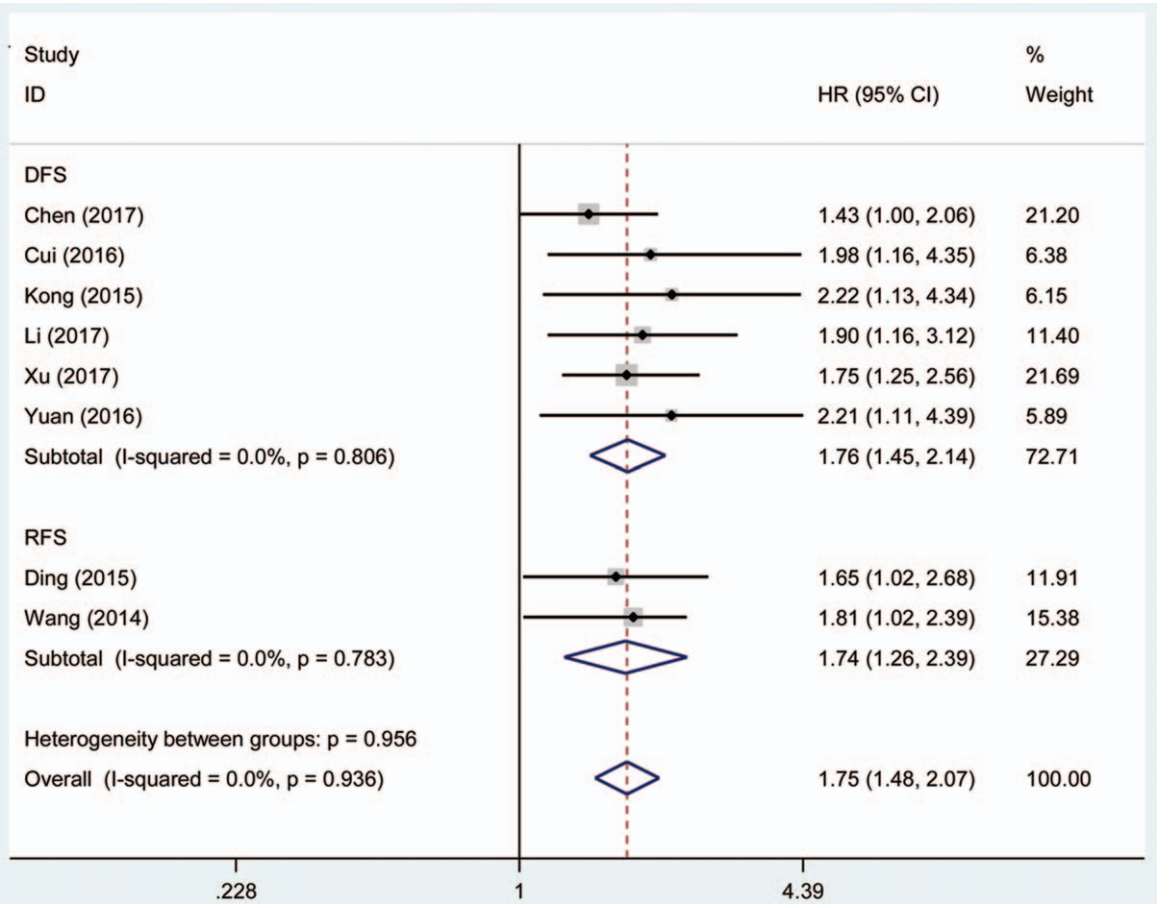

Figure 3. Forest plot reflecting the association between DFS, RFS and PVT1 expression level in cancer. DFS = disease-free survival, RFS = recurrence-free survival.

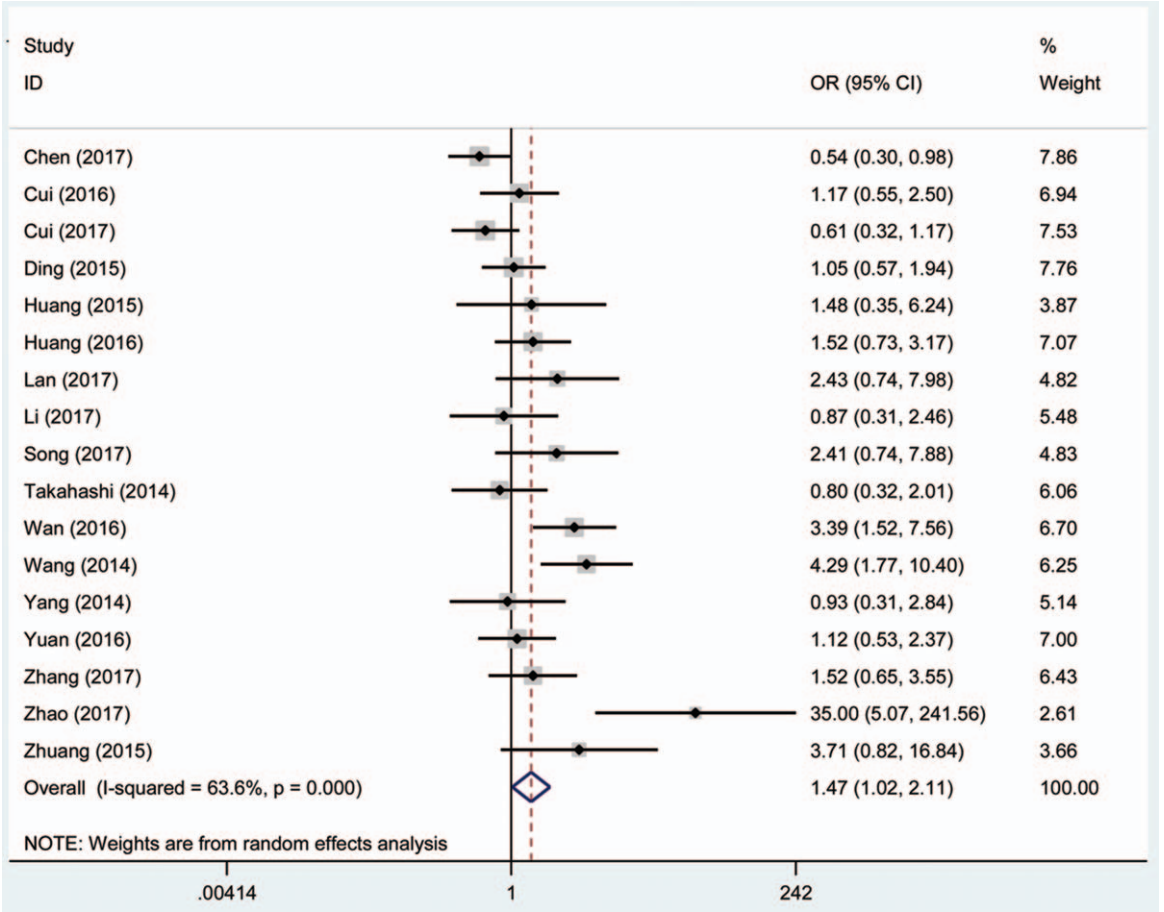

Figure 4. Forest plot reflecting the association between tumor size and PVT1 expression level in cancer.

2017, were from different countries, including 22 in China and 1 in Japan. Among the included studies, six focused on gastric cancer,[19,22,26,27,34,36] three on non-small cell lung cancer (NSCLC),[20,32,35] 3 on hepatocellular carcinoma (HCC),[23,28,33] 2 on bladder cancer,[21,40] 2 on pancreatic cancer,[24,38] 2 on colorectal cancer (CRC),[11,29] 2 on esophageal squamous cell carcinoma,[30,39] and respectively 1 on small cell lung cancer,[25] osteosarcoma,[31] and cervical cancer.[37] Besides, PVT1 expression was measured in cancerous specimens. All diagnoses of LNM, DM and differentiation grade were pathologically confirmed.

3.2. High PVT1 expression was correlated with shorter OS

Cumulative meta-analysis was performed to assess the function of PVT1 in the OS for cancer patients. Eighteen of the included studies covering 2108 patients had reported the relationship between OS and PVT1 expression. Typically, a significant association was observed between PVT1 expression and OS in cancer patients (pooled HR = 1.99, 95% CI: 1.73–2.28; Fig. 2). In addition, no significant heterogeneity was discovered among the eligible studies ($I^2 = 0\%$, $P_Q = 0.608$). Such results demonstrated that cancer patients with high PVT1 expression might be associated with a shorter OS. It could be discovered from the analysis results that PVT1 expression was an independent factor of OS among cancer patients.

3.3. High PVT1 expression was correlated with shorter DFS and RFS

Cumulative meta-analysis was also carried out to determine the role of PVT1 in disease-free survival (DFS) of 780 cancer patients and in recurrence-free survival (RFS) of 303 cancer patients from the eligible studies (Fig. 3). Statistical analyses revealed that PVT1 expression was associated with DFS (pooled HR = 1.76, 95% CI: 1.45–2.14), and RFS (pooled HR = 1.74, 95% CI: 1.26–2.39) of cancer patients. In addition, no significant heterogeneity was identified among the eligible studies. Therefore, our data indicated that PVT1 expression was an independent factor of DFS and RFS among cancer patients, and that high PVT1 expression was associated with shorter DFS and RFS.

3.4. High PVT1 expression was remarkably correlated with tumor size

Seventeen studies had reported the number of patients with larger tumor size based on different PVT1 expression levels. Typically, significant heterogeneity was observed among these 17 studies ($I^2 = 0\%$, $P_Q = 0.936$, Fig. 4), so the random effects model was used in the meta-analysis. The results suggested that there was a marked association between PVT1 expression level and larger tumor size (OR = 1.47, 95% CI: 1.02–2.11). Besides, difference in the tumor size between the high and low expression groups was statistically significant. Such findings revealed that cancer

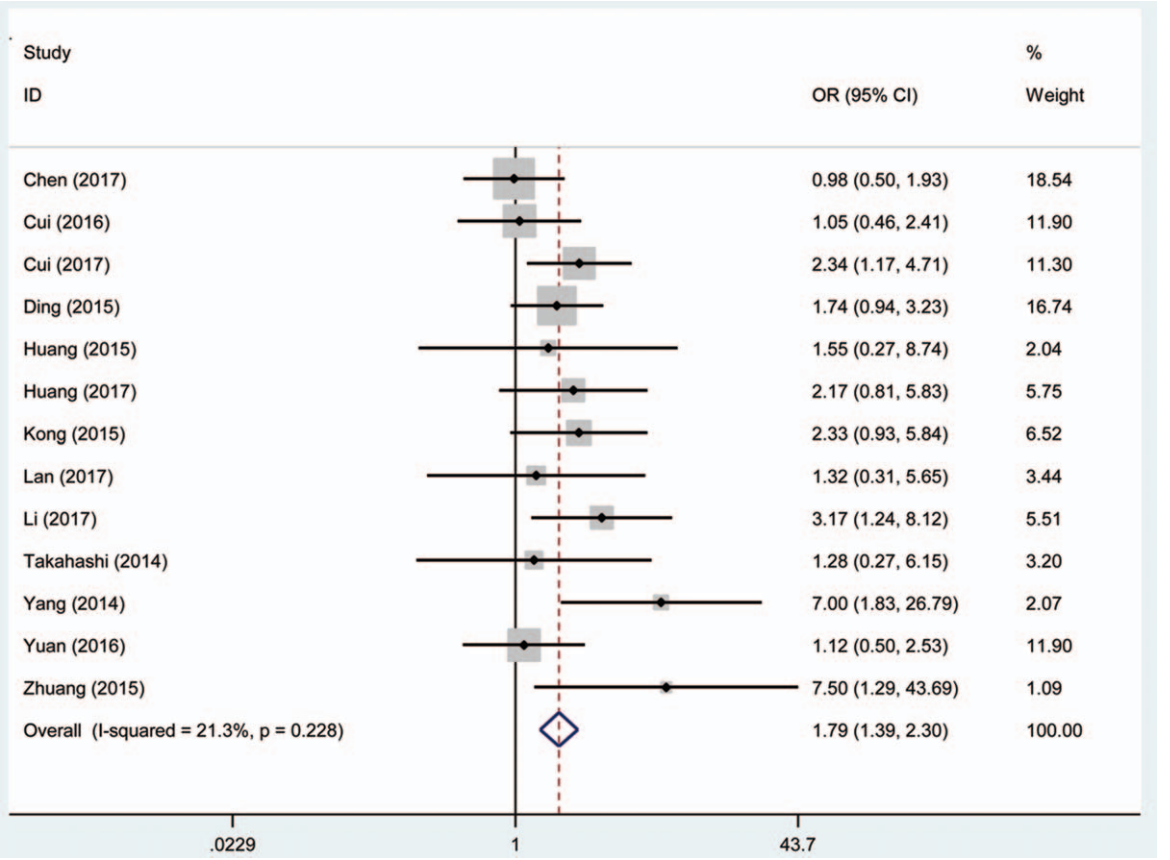

Figure 5. Forest plot reflecting the correlation between differentiation grade and PVT1 expression level in cancer.

patients with high PVT1 expression might be correlated with larger tumor size.

3.5. High PVT1 expression was markedly related to poor differentiation grade

A total of 1429 cancer patients from thirteen eligible studies were collected and analyzed. The fix effects model was adopted since there was limited heterogeneity ($I^2 = 21.3\%$, $P_Q = 0.228$). The OR, which was expressed as high PVT1 expression group versus low PVT1 expression group, was 1.79 (95% CI: 1.39–2.30, Fig. 5). Difference in the incidence of poor differentiation grade between these 2 groups was statistically significant. The results suggested that high PVT1 expression was dramatically related to the poor differentiation grade for cancer patients.

3.6. High PVT1 expression was evidently correlated with advanced tumor stage

A total of 1966 patients from twenty-one studies were included to detect the relationship between PVT1 expression level and tumor stage in this meta-analysis. As could be figured out, an evident relationship was found between high PVT1 expression and advanced tumor stage in cancer patients (pooled OR = 3.28, 95% CI: 2.46–4.38, Fig. 6) with obvious heterogeneity ($I^2 = 44.6\%$, $P_Q = 0.010$). Subgroup analysis was conducted based on the cancer type due to the presence of heterogeneity, which revealed significant associations between PVT1 expression and advanced tumor stage in gastric cancer (GC, OR = 2.72, 95% CI: 1.57–4.70), non-small cell lung cancer (NCLC, OR = 3.66, 95% CI: 2.03–6.62), hepatocellular carcinoma (HCC, OR = 2.33, 95% CI: 1.14–4.33) and other cancer types (OR = 4.02, 95% CI: 2.53–6.39). Taken together, the above results indicated that, the high PVT1 expression group was associated with advanced tumor stage compared with that in the low PVT1 expression group.

3.7. High PVT1 expression was notably correlated with LNM

A total of 1388 cancer patients from thirteen eligible studies were collected and analyzed. The random effects model was adopted for the significant heterogeneity ($I^2 = 66.5\%$, $P_Q = 0.000$). The OR, which was expressed as high PVT1 expression group versus low PVT1 expression group, was 2.67 (95% CI: 1.66–4.29, Fig. 7). Subgroup analysis indicated that PVT1 expression was an independent factor for LNM in GC (OR = 2.15, 95% CI: 1.36–3.41) and NSCLC (OR = 3.12, 95% CI: 1.64–5.95) patients without heterogeneity. According to the results, difference in the LNM incidence between the 2 groups was statistically significant, and that high PVT1 expression was remarkably correlated with LNM for cancer patients.

3.8. High PVT1 expression was evidently associated with DM

The correlations between PVT1 expression and DM are presented in Figure 8. Three studies with 835 patients had declared the association between PVT1 expression and the

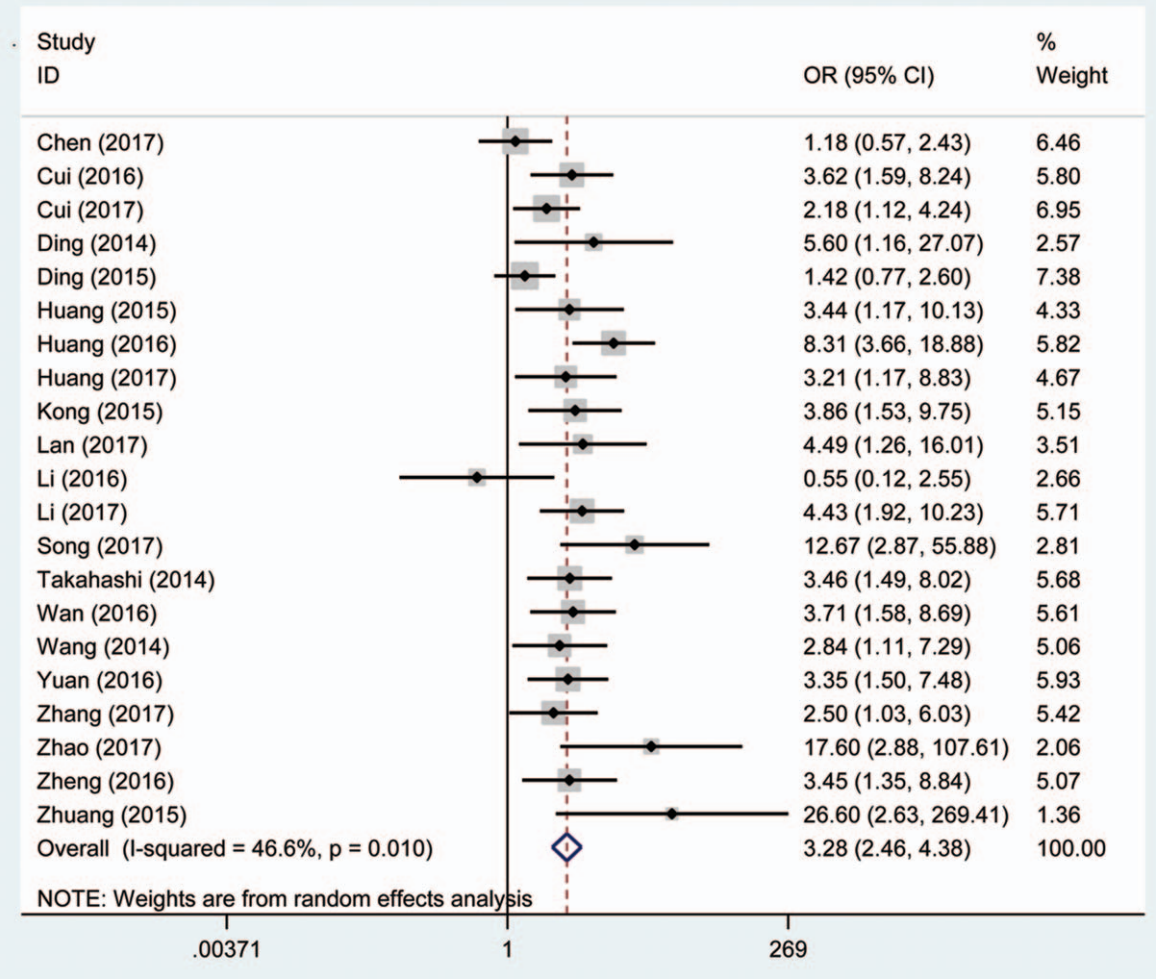

Figure 6. Forest plot reflecting the correlation between tumor stage and PVT1 expression level in cancer. PVT1 = Plasmacytoma variant translocation 1.

number of cancer patients with DM. Significant heterogeneity was detected among these studies, and thus the random-effects model was applied ($I^2 = 58.2\%$, $P_Q = 0.019$). The analysis showed that a pooled OR was 4.00 (95% CI: 1.39–11.50, high versus low PVT1 expression; Fig. 8). Meanwhile, meta-regression analysis and subgroup analysis (GC or other cancer) were also performed to explore the potential sources of heterogeneity. In the subgroup analysis, significant association was found between PVT1 expression and DM in GC (OR = 2.51, 95% CI: 1.13–5.56) without heterogeneity. As a result, the number of patients with DM was evidently increased in the high PVT1 expression group. These results revealed that patients with high PVT1 expression were markedly associated with DM, especially for the GC patients.

3.9. Publication bias

Subsequently, the potential publication bias was evaluated using a Begg's funnel plot. The diagram of the Begg's funnel plot (Fig. 9) did not reveal any evidence of obvious asymmetry for LNM. Similarly, there was no evidence for significant publication bias in terms of DM (Fig. 10).

4. Discussion

Great improvements have been made in cancer detection and treatment; however, the 5-year survival rate remains relatively low for most cancers. Typically, most cancers eventually develop metastasis, including LNM and DM, which is an important indicator of prognosis.[41,42] Moreover, LNM and DM are of important significance for tumor-node-metastasis (TNM) staging, and hotspot-molecular biomarkers play critical roles in cancer prediction and treatment.[43,44] However, the precise mechanism underlying metastasis remains uncertain. Therefore, it is of significant necessity to find the new molecular markers predictive of tumor metastasis. Some lncRNAs have the potential to serve as biomarkers for diagnosing and monitoring tumors due to their specific expression during tumor occurrence and development.[45]

Previous studies show that PVT1 is a critical oncogene in a variety of human cancers, including CRC, osteosarcoma, HCC, pancreatic cancer, and GC.[11,19–40] Recent advances have confirmed that high PVT1 expression is associated with advanced tumor stage and poor survival in GC and NSCLC.[27,32] In addition, Chen et al[46] found that overexpression of PVT1 could promote the proliferation, cell cycle progression, and the migration of melanoma cells. Moreover, Gao et al[47] found that after transfected with PVT1 siRNA, the proliferation, migration, and invasion of cervical cancer cells were greatly decreased. These studies suggest that PVT1 can potentially serve as an important prognostic factor in cancer patients. In this meta-analysis, the clinicopathologic significance and prognostic value

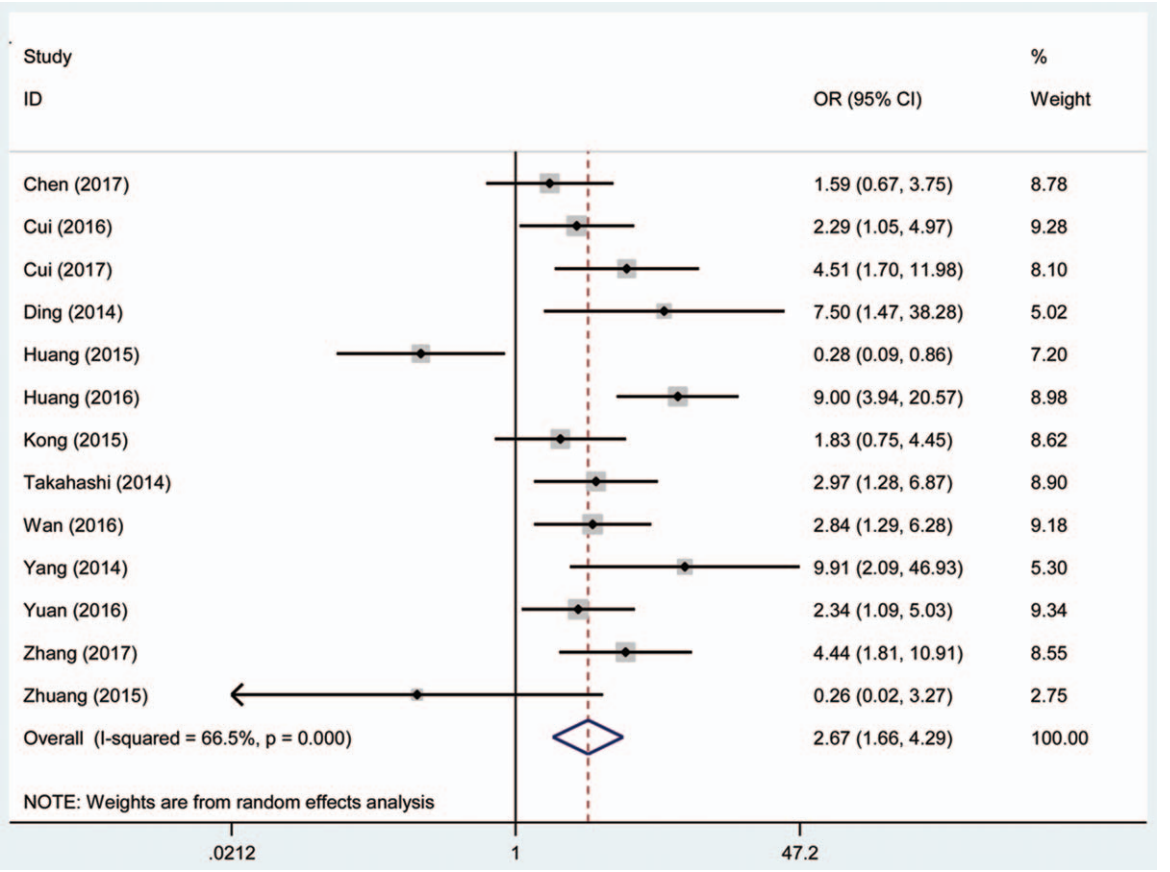

Figure 7. Forest plot reflecting the correlation between LNM and PVT1 expression level in cancer. LNM = lymph node metastasis, PVT1 = Plasmacytoma variant translocation 1.

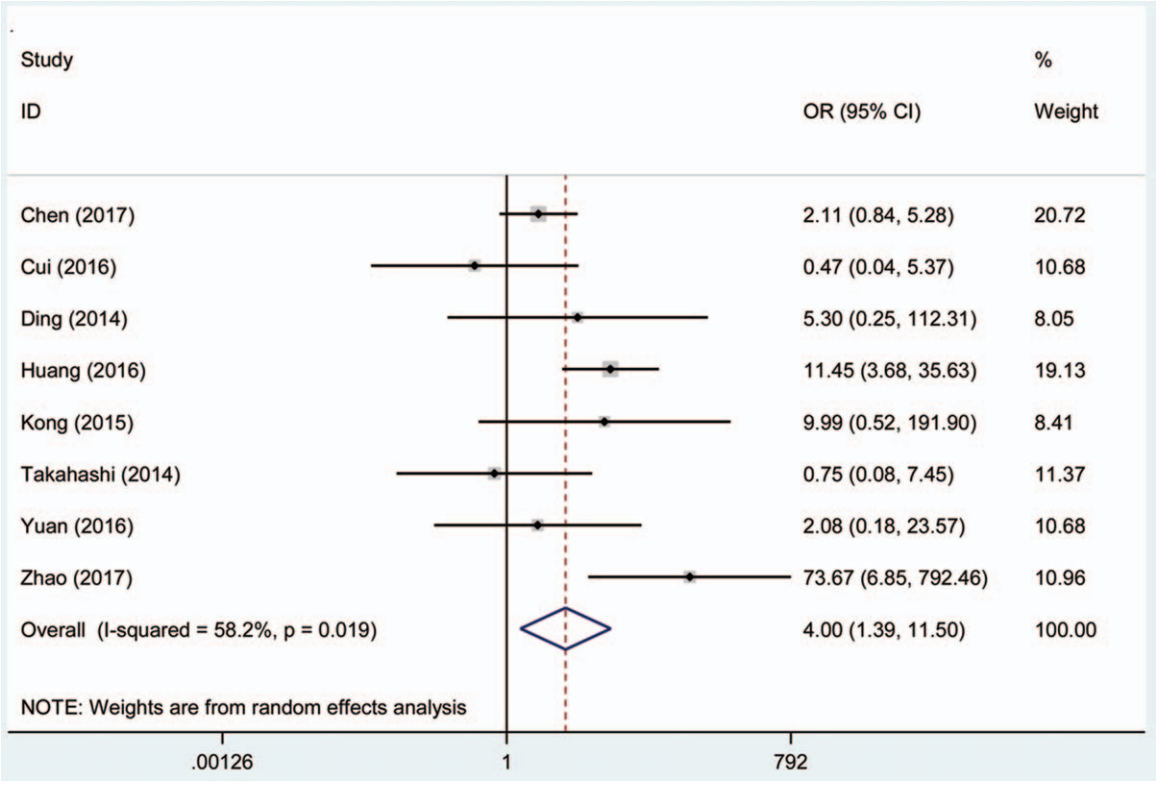

Figure 8. Forest plot reflecting the relationship between DM and PVT1 expression level in cancer. DM = distant metastasis, PVT1 = Plasmacytoma variant translocation 1.

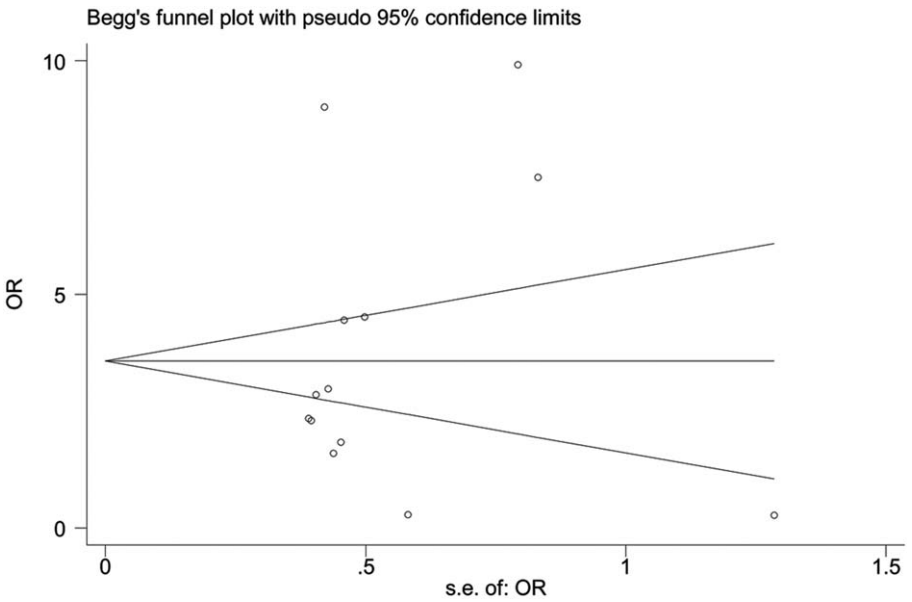

Figure 9. Begg's funnel plot showing the publication bias for PVT1 expression and lymph node metastasis. PVT1 = Plasmacytoma variant translocation 1.

of PVT1 in cancer patients were investigated. Detecting genes closely related to prognosis and tissue differentiation would help to better understand the mechanism of tumorigenesis. This meta-analysis would provide a foundation for research into the therapeutic value of PVT1 in cancers.

A total of 2350 cancer patients from twenty-three eligible studies were collected and analyzed in this study. The most related lncRNA studies were from China after retrieving the three global science databases. According to the inclusion and exclusion criteria, 10 tumor types in 23 eligible studies, including 22 from China and 1 from Japan, had met the criteria. Consequently, the results might be only suitable for the Han population or Asian population. Thus, studies from other ethnicities or countries are needed to determine whether the results are applicable to all populations. A random effects model or fixed effects model was used in this meta-analysis depending on the results of heterogeneity analysis. It was found that high PVT1 expression might indicate poorer prognosis for cancer patients. HRs from Cox multivariate analyses were combined, and a significant difference was found in OS between high and low PVT1 expression groups. It was found that high PVT1 expression was remarkably associated with DFS and RFS in different types of cancer. Furthermore, it was revealed in this meta-analysis that high PVT1 expression was evidently correlated with larger tumor size, poor differentiation grade, advanced tumor stage, LNM, and DM. The heterogeneity discovered in this

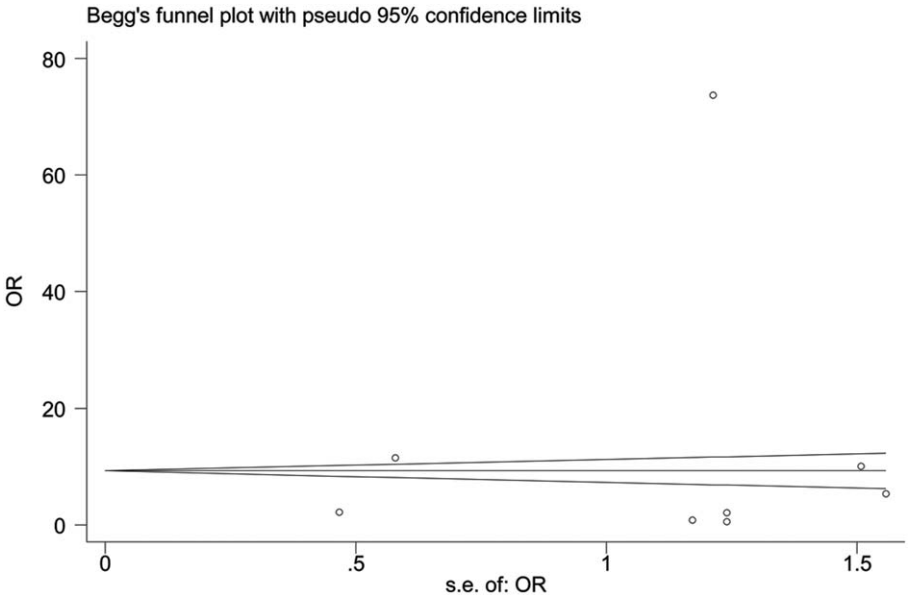

Figure 10. Begg's funnel plot showing the publication bias for PVT1 expression and distant metastasis. PVT1 = Plasmacytoma variant translocation 1.

study could mainly be attributed to the various types of cancers in this meta-analysis. Taken together, our meta-analysis suggested that PVT1 might be used as an unfavorable prognostic biomarker for most cancers.

5. Limitations

Several limitations must be taken into account while interpreting the conclusions of this meta-analysis. Firstly, most included studies were from China, and only one was from Japan; therefore, our data might not be globally applicable. Secondly, only small sample size of cancer type and number was included in this meta-analysis, so larger-scale studies would be necessary to verify the obtained results. Thirdly, the criteria for high expression differed among these studies, and it was difficult to obtain the same value. Consequently, further study will be needed to confirm the function of PVT1 in various cancers.

6. Conclusions

Taken together, our findings indicate that a high PVT1 expression level is correlated with poor OS, DFS, RFS, LNM, DM, differentiation grade, larger tumor size, and tumor stage in multiple cancers. Therefore, PVT1 expression is a potentially useful biomarker to predict the prognosis and metastasis for cancer patients.

Author contributions

CM and XGN search the electronic databases of Pubmed, OVID and Web of Science. CM and YLW evaluated all of the included studies and extracted the data independently. CM and DPW extracted and examined the data from the original articles independently. QDL resolved the disagreements in the literature assessment and CM was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Investigation: Chao Ma, Xing-Guo Nie, Yan-Li Wang, Da-Peng Wu, and Qiu-dong Liang.
Methodology: Chao Ma, Xing-Guo Nie, Yan-Li Wang, Da-Peng Wu, and Qiu-dong Liang.
Project administration: Chao Ma.
Software: Chao Ma, Xing-Guo Nie, and Qiu-dong Liang.
Supervision: Qiu-dong Liang.
Writing – original draft: Chao Ma.
Writing – review & editing: Qiu-dong Liang.

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