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REVIEW

lncRNA PVT1 identified as an independent biomarker for prognosis surveillance of solid tumors based on transcriptome data and meta-analysis

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Xiaoliang Chen,[1,*] Yueying Yang,[2,*] Yong Cao,[1,*] Changjun Wu,[3] Shuxian Wu,[3] Zhan Su,[1] Hongwei Jin,[1] Dongli Wang,[1] Gengxin Zhang,[3] Wei Fan,[4] Jinbo Lin,[5] Yunhong Zeng,[3] Dongsheng Hu[6]

[1]The Center for Chronic Disease Control and Prevention, Shenzhen Guangming District Center for Disease Control and Prevention, Shenzhen, China; [2]Science and Education Department, Shenzhen School of the Affiliated High School of Renmin University of China, Shenzhen, China; [3]Department of Oncology, Guangming District People's Hospital of Shenzhen, Shenzhen, China; [4]Division of Digestive and Liver Disease, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [5]Department of Oncology, Longgang Central Hospital of Shenzhen Affiliated to Zunyi Medical College, Shenzhen, China; [6]School of Medicine, Shenzhen University, Shenzhen, China

*These authors contributed equally to this work

Correspondence: Jinbo Lin
Department of Oncology, Longgang Central Hospital of Shenzhen Affiliated to Zunyi Medical College, 6082 Longgang Avenue, Longgang District, Shenzhen 518116, China
Tel +86 755 84802448
Fax +86 755 84802448
Email 20222523@qq.com

Yunhong Zeng
Department of Oncology, Guangming District People's Hospital of Shenzhen, 339 Songbai Road, Guangming District, Shenzhen 518106, China
Tel +86 755 27166080
Fax +86 755 27166080
Email 1249655007@qq.com

Purpose: Long noncoding RNA PVT1 is dysregulated in some human tumors and has been found to increase the risk of tumor progression and poor prognosis. This study aimed to reanalyze the effect of PVT1 on tumorous prognosis.

Materials and methods: The effect of PVT1 on metastasis and survival were analyzed by univariate logistic regression and Cox proportional hazards model for 32 types of cancer in the Cancer Genome Atlas database (TCGA), and the relationship between PVT1 level and expression of relative genes was assessed by Pearson correlation analysis. RevMan5.3 and STATA14.0 were used to estimate pooled effects of PVT1 on cancer prognosis with data from TCGA and published studies.

Results: In TCGA data, high PVT1 expression tended to increase the risk of TNM progression and decreased the overall survival (OS) time in most of cancers. The pooled effect of PVT1 on TNM (pooled-OR=1.46, 95% CI: 1.29–1.65) and OS (pooled HR=1.32, 95% CI: 1.22–1.43), calculated from 37 and 48 cohorts, identified that high PVT1 expression promoted the metastasis and poor prognosis of cancer. Furthermore, the pooled ORs of 2.77 (95% CI: 1.65–4.66), 4.32 (95% CI: 1.99–9.36), 1.35 (95% CI: 1.01–1.80), 1.62 (95% CI: 1.21–2.18) and 1.48 (95% CI: 1.02–2.15) provided evidence that PVT1 played a role in lymph node metastasis, depth of invasion, distant metastasis, differentiation and lymphatic invasion; while the expression of 24 identified target genes was significantly associated with PVT1 level, and high PVT1 expression dependently decreased the OS time under the influence of co-expression genes (OR=1.29, 95% CI: 1.25–1.32) in high-throughput RNA sequencing merging data. In addition, the expression of PVT1 could be upregulated by smoking, with the pooled OR being 1.09 (95% CI 1.01–1.16).

Conclusion: PVT1 is a dependent biomarker for tumorous prognosis surveillance. However, the reference value of PVT1 needs further study.

Keywords: PVT1, Cancer, biomarker, survive, metastasis

Introduction

Cancer is a major public health problem worldwide.[1] Although a decrease of overall cancer mortality has been observed in the last two decades,[2] it still causes 22% of noncommunicable disease deaths,[3] due to the complex pathogenesis and few target treatments. Numerous experimental studies have attempted to reveal the mechanisms of tumorigenesis to provide clues for prevention, early diagnosis and target treatment. Developments in biotechnology have gradually unveiled some of the mysteries of cancer, with the identification of abundant DNA biomarkers, transcripts, protein and

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epigenetics. Noncoding RNAs (ncRNAs), which are the largest component of human genome transcripts, especially long noncoding RNAs (lncRNAs), have been confirmed as participating in diverse cellular processes from normal development to cancer.[4] Increasing evidence suggests that lncRNAs could be the key regulators interacting with other components such as proteins, RNAs and DNAs;[5,6] while regulating lncRNAs have been shown to have aberrant expression in tumor tissues.[7–9] To date, overwhelming numbers of cancer-related lncRNAs have been reported in the database of the Cancer Genome Atlas (TCGA) project[10,11] as well as the noncode database (http://www.noncode.org) and LNCipedia (http://www.lncipedia.org). Because of being involved in the onset and development of cancer, some key lncRNAs are expected to play a crucial role in cancer detection, diagnosis and therapy.

lncRNA PVT1, homologous to the mouse plasmacytoma variant translocation gene (Pvt1), lies in human chromosome 8q24.21 and has attracted widespread attention.[12] Recent studies showed that PVT1 was dysregulated in some human tumors, such as gastric cancer, nonsmall-cell lung cancer, colorectal cancer, esophageal cancer, pancreatic cancer, and hepatocellular carcinoma.[10,13,14] High PVT1 expression was further found to increase the risk of tumor progression and poor prognosis.[13,15–17] Furthermore, studies of its mechanism suggested that aberrant level of PVT1 was linked to proliferation, angiogenesis and metastasis in human malignancies.[18,19] PVT1 might act as an effective biomarker for tumorous prognosis surveillance. Nevertheless, the association between PVT1 expression and cancer prognosis is still not clear. Moreover, no meta-analysis has investigated the common effect of PVT1 on prognosis of most cancers based on multisource data.

The present study aimed to analyze the pooled effect of PVT1 on cancer prognosis by meta-analysis and further explore possibly common target genes of PVT1 in most cancers.

Materials and methods

TCGA sequencing data

High-throughput RNA sequencing (RNA-Seq) and clinical data of different cancers were downloaded from https://portal.gdc.cancer.gov/projects/ (TCGA database). Because it did not show in RNA-Seq data of most cancers, PVT1 expression level was redownloaded from https://xenabrowser.net/heatmap/ (TCGA database). All the expression data were transformed into the format of $\log_2$ (Illumina Hiseq Pancan normalized numbers+1) after deleting the samples with no PVT1 data or where PVT1 was detected in corresponding normal tissues. Only the samples with clinical and PVT1 expression data were further enrolled for prognosis analysis.

Literature search strategy

English or Chinese studies on the role of PVT1 in human cancer were searched in PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases with the keywords PVT1 and cancer. The references of retrieved papers and conference reports were also searched to identify relevant studies. The last search date was May 8, 2017.

Selection criteria of reported research

The titles and abstracts of searched articles were checked by 4 authors (YC, CW, ZS, and DW) after duplicates were removed. Then, the full text of eligible articles was retrieved. Eligible articles should have the following criteria: 1) the expression of PVT1 was analyzed by prognosis of human cancer; 2) the expression of PVT1 was detected in cancer tissue or circulating blood by reverse transcription polymerase chain reaction (RT-PCR), fluorescence in-situ hybridization or RNA-Seq; 3) the high and low groups of PVT1 expression were divided by the mean/median or ROC curve; and 4) HRs for survival (overall survival [OS], recurrence-free survival [RFS], disease-free survival [DFS], and progression-free survival [PFS]) or ORs for metastasis (tumor-node-metastasis [TNM], lymphatic invasion [LI], lymph node metastasis [LNM], depth of invasion [DOI], distant metastasis [DM], and differentiation [DIF]) were provided or could be calculated from the available data. Furthermore, if more than 1 report from the same cohort was published, only the most recent publication was included. Consensus in searching and exclusion was resolved by discussion of 3 other investigators (XC, YZ, and DH) if needed.

Data extraction and quality assessment

Four authors (YY, SW, HJ, and GZ) extracted the following data by an extraction form: first author's name, published year, region of cohort, cancer type, sample size, and HRs/ORs (95% CI). The quality of studies was assessed by Newcastle–Ottawa Scale (NOS) and the score ≥ 6 was considered as high quality.

Statistical methods

Univariate logistic regression was applied to analyze the risk of high PVT1 expression on metastasis as well as the effect of smoking on PVT1 expression, whereas the PVT1 effects on

OS of 32 types of cancer were assessed by the Cox proportional hazards model with TCGA data. In the meta-analysis, the heterogeneity among studies was tested by inconsistency (I^2) and Q tests (chi-square test). The fixed effects model was used to estimate the pooled effect with no statistical heterogeneity found (I^2<50%, P_Q>0.05); otherwise, a random effects model was used. Publication bias was assessed by Begg's and Egger's tests, as trim and fill analysis was used to adjust the pooled effects, if necessary.[20] In addition, Engauge Digitizer 4.1 was used to analyze HRs and 95% CIs, when they were not provided directly in some studies. The correlations between PVT1 and other genes were estimated by Pearson correlation analysis. All tests, being considered statistically significant with P<0.05, were two sided and performed by STATA 14.0 and Review Manager 5.3 (Cochrane network).

Results

The effect of PVT1 on prognosis of TCGA cancers

The 9,451 patients with 32 types of cancer were divided into high and low groups with the cutoff point being the median of the PVT1 level which was stably detected in tissues. As shown in Table 1, high PVT1 expression tended to deteriorate the prognosis of most cancers. Furthermore, it significantly increased the risk of TNM progression of

Table 1 The effect of PVT1 on TNM and survival as well as smoking on PVT1 expression

Cancer types	Cases (high/low)	TNM ([III+IV]/[I+ II])		Overall survival (high/low)		Smoking (yes/no)	
		P value	OR (95% CI)	*P* value	HR (95% CI)	*P* value	OR (95% CI)
ACC	79 (39/40)	0.050	1.611 (1.000–2.595)	0.001	1.953 (1.293–2.949)	NR	NR
BLCA	407 (203/204)	0.282	1.103 (0.923–1.317)	0.258	1.079 (0.946–1.232)	0.736	0.972 (0.822–1.148)
BRCA	1,095 (547/548)	0.022	1.168 (1.023–1.333)	0.927	0.993 (0.850–1.160)	NR	NR
CESC	302 (151/151)	NR	NR	0.395	1.106 (0.877–1.395)	0.372	1.112 (0.881–1.404)
CHOL	36 (18/18)	0.050	2.450 (0.999–6.012)	0.750	0.946 (0.672–1.331)	NR	NR
COAD	283 (141/142)	NR	NR	0.343	1.157 (0.856–1.562)	NR	NR
DLBC	48 (24/24)	NR	NR	0.869	1.057 (0.454–2.548)	NR	NR
ESCA	184 (92/92)	0.670	1.076 (0.770–1.504)	0.627	1.060 (0.839–1.338)	0.265	0.839 (0.617–1.142)
GBM	153 (76/77)	NR	NR	0.274	1.118 (0.915–1.365)	NR	NR
HNSC	520 (260/260)	<0.001	1.947 (1.464–2.590)	0.102	1.126 (0.976–1.299)	0.256	1.119 (0.922–1.359)
KICH	66 (33/33)	0.058	1.383 (0.989–1.934)	0.174	1.365 (0.871–2.139)	0.308	1.222 (0.831–1.798)
KIRC	533 (266/267)	<0.001	1.593 (1.309–1.938)	<0.001	1.508 (1.279–1.777)	0.806	0.952 (0.645–1.406)
KIRP	290 (145/145)	<0.001	1.841 (1.450–2.338)	0.056	1.245 (0.994–1.560)	0.007	1.319 (1.078–1.614)
LGG	515 (257/258)	NR	NR	<0.001	1.519 (1.333–1.731)	NR	NR
LIHC	371 (185/186)	0.790	0.981 (0.854–1.128)	0.346	1.049 (0.949–1.160)	NR	NR
LUAD	515 (257/258)	0.552	1.060 (0.875–1.285)	0.346	0.941 (0.829–1.068)	0.034	1.205 (1.015–1.430)
LUSC	501 (250/251)	0.975	1.004 (0.795–1.267)	0.434	0.947 (0.826–1.086)	0.827	0.972 (0.757–1.249)
MESO	87 (43/44)	0.696	0.883 (0.471–1.652)	0.467	1.129 (0.814–1.568)	NR	NR
OV	304 (152/152)	NR	NR	0.923	0.994 (0.884–1.118)	NR	NR
PAAD	178 (89/89)	0.551	0.839 (0.471–1.494)	0.002	1.292 (1.101–1.515)	0.582	1.071 (0.839–1.367)
PCPG	179 (90/89)	NR	NR	0.960	0.981 (0.463–2.078)	NR	NR
PRAD	497 (248/249)	NR	NR	0.041	2.010 (1.028–3.929)	NR	NR
READ	93 (46/47)	0.206	1.461 (0.812–2.628)	0.345	1.344 (0.728–2.480)	NR	NR
SARC	259 (129/130)	NR	NR	0.043	1.235 (1.007–1.516)	NR	NR
SKCM	469 (234/235)	0.562	1.063 (0.866–1.304)	0.334	1.076 (0.927–1.250)	NR	NR
STAD	415 (207/208)	0.123	1.171 (0.958–1.433)	0.046	0.848 (0.721–0.997)	NR	NR
TGCT	134 (67/67)	0.423	1.190 (0.777–1.822)	0.597	1.237 (0.562–2.179)	NR	NR
THCA	505 (252/253)	0.904	1.012 (0.828–1.237)	0.006	1.741 (1.171–2.590)	NR	NR
THYM	120 (60/60)	NR	NR	0.005	2.329 (1.286–4.217)	NR	NR
UCEC	176 (88/88)	NR	NR	<0.001	1.471 (1.310–1.652)	NR	NR
UCS	57 (28/29)	NR	NR	0.077	1.276 (0.974–1.673)	NR	NR
UVM	80 (40/40)	0.086	1.604 (0.935–2.753)	<0.001	3.718 (1.956–7.067)	NR	NR

Abbreviations: ACC, adrenocortical cancer; BLCA, bladder cancer; BRCA, breast cancer; CESC, cervical cancer; CHOL, bile duct cancer; COAD, colon cancer; DLBC, large B-cell lymphoma; ESCA, esophageal cancer; GBM, glioblastoma; HNSC, head and neck cancer; KICH, kidney chromophobe; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LGG, lower grade glioma; LIHC, liver cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian cancer; NR, not reported; PAAD, pancreatic cancer; PCPG, pheochromocytoma & paraganglioma; PRAD, prostate cancer; READ, rectal cancer; SARC, sarcoma; SKCM, melanoma; STAD, stomach cancer; TGCT, testicular cancer; THCA, thyroid cancer; THYM, thymoma; UCEC, endometrioid cancer; UCS, uterine carcinosarcoma; UVM, ocular melanoma.

breast cancer, head and neck cancer, kidney clear cell carcinoma (KIRC), and kidney papillary cell carcinoma (KIRP), with ORs being 1.168 (P=0.022), 1.947 (P<0.001), 1.593 (P<0.001) and 1.841 (P<0.001), and significantly decreased the OS time of adrenocortical cancer, KIRC, lower grade glioma, pancreatic cancer, prostate cancer, sarcoma, thyroid cancer, endometrioid cancer, and ocular melanomas (UVM) with the HRs being 1.953 (P=0.001), 1.508 (P<0.001), 1.519 (P<0.001), 1.292 (P=0.002), 2.010 (P=0.041), 1.235 (P=0.043), 1.741 (P=0.006), 2.329 (P=0.005), 1.471 (P<0.001), and 3.718 (P<0.001). Conversely, the OS time of stomach cancer was significantly increased with high PVT1 expression (HR=0.848, P=0.046). In addition, smoking significantly increased the expression of PVT1 in KIRP (OR=1.319, P=0.007) and lung adenocarcinoma (OR=1.205, P=0.034).

Published studies of PVT1 on tumorous prognosis

The literature search resulted in 22 published studies eligible for the meta-analysis (Figure S1), 19 from China,[13,15,16,18,19,21–34] and 3 from Japan,[35] USA,[17] and Italy.[36] These studies involved 2,376 patients and 11 types of cancers, whose PVT1 level was detected in tumor tissue and circulating blood by RT-PCR. The main characteristics of each study are summarized in Table S1. In addition, the included studies had high quality, with NOS scores of more than 6 for each study (data not shown).

Pooled effect of PVT1 on tumorous prognosis

Pooled effect of PVT1 on progression

Seventeen cohorts from published studies and 20 from TCGA provided the ORs of PVT1 on TNM progression in 8,128 patients. Under the random effects model, the pooled effect (pooled OR=1.46, 95% CI: 1.29–1.65) showed that high PVT1 significantly increased the risk of TNM progression (Table 2, Figure S2). Moreover, high PVT1 expression also significantly promoted the development of LNM, DOI and DM with pooled ORs of 2.77 (95% CI: 1.65–4.66), 4.32 (95% CI: 1.99–9.36) and 1.35 (95% CI: 1.01–1.80) under the random effects model (Table 2, Figure S3A–C). Furthermore, the risks of poor differentiation (pooled OR=1.62, 95% CI: 1.21–2.18) and lymphatic invasion (pooled OR=1.48, 95% CI: 1.02–2.15) were significantly increased in patients with high PVT1 expression under the fixed effects model (Table 2, Figure S3D–E).

Table 2 The effect of high PVT1 expression on metastasis

Type of metastasis	Cohorts	Cases	*P* value of heterogeneity	Pooled OR	95% CI
TNM	37	8,128	<0.0001	1.46	1.29–1.65
LNM	11	1,130	0.001	2.77	1.65–4.66
DOI	6	498	0.007	4.32	1.99–9.36
DM	8	884	0.008	1.35	1.01–1.80
DIF	8	1,116	0.500	1.62	1.21–2.18
LI	4	543	0.130	1.48	1.02–2.15

Abbreviations: LNM, lymph node metastasis; DOI, depth of invasive; DM, distant metastasis; DIF, differentiation; LI, lymphatic invasion.

Table 3 The effect of high PVT1 expression on prognosis

Type of prognosis	Cohorts	Cases	*P* value of heterogeneity	Pooled OR	95% CI
OS	48	11,022	<0.0001	1.32	1.22–1.43
DFS	8	975	0.750	1.77	1.46–2.13
PFS	3	304	0.110	1.71	1.45–2.00

Abbreviations: OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

Pooled effect of PVT1 on survival

Forty-eight cohorts, 16 from published studies and 32 from TCGA, showed data for OS by PVT1 level in 11,022 patients. The pooled effect (pooled HR=1.32, 95% CI: 1.22–1.43) indicated that high PVT1 expression significantly decreased the OS time under the random effects model (Table 3, Figure S4). Similar effects have been shown on DFS (pooled HR=1.77, 95% CI: 1.46–2.13) and PFS (pooled HR=1.71, 95% CI: 1.45–2.00) which were reported in more than 2 cohorts (Table 3, Figure S5).

Pooled effect of smoking on PVT1 expression

In addition, the effects of smoking on PVT1 expression were also reported in 12 cohorts within 3,600 patients. Figure 1 depicts that smoking significantly increased the level of PVT1 expression under the fixed effect model (pooled OR=1.09, 95% CI: 1.01–1.16).

Correlation of PVT1 and relative genes in TCGA cancers

Thirty-four relative genes of PVT1 in cancers were summarized by systematic review. Besides 6 co-expression genes in 8q24, 28 target genes of transcriptional regulation of PVT1 were identified by functional experiments in a variety of human cell lines.[30–33,35,37–50] The correlations between them and PVT1 were assessed with the merging RNA-Seq data of 32 types of cancers in TCGA. The PVT1 level

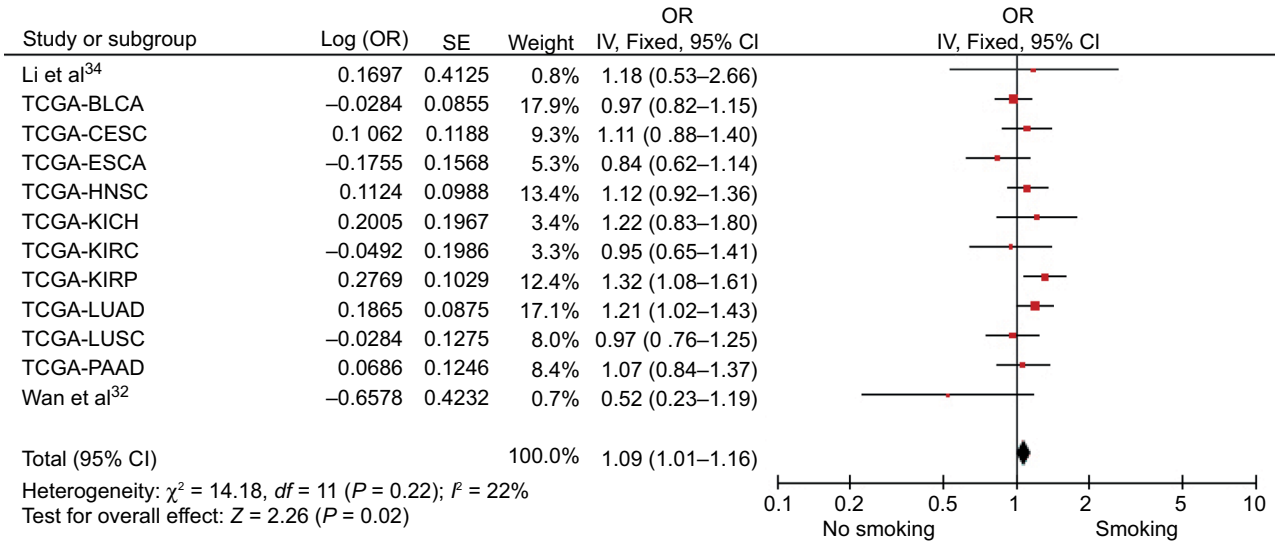

Figure 1 Pooled OR of smoking on PVT1 expression.
Abbreviations: SE, standard error; IV, inverse variance methods; BLCA, bladder cancer; CESC, cervical cancer; ESCA, esophageal cancer; HNSC, head and neck cancer; KICH, kidney chromophobe; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic cancer; TCGA, the Cancer Genome Atlas database.

was positive relative to the expression of 30 genes except for miR-30a (r=0.0196, P=0.06384), whereas miR-1206, miR-146a and miR-195 could not be detected by RNA-Seq technique (Table 4). However, the relative coefficient of miR-152 (r=0.0382, P=0.00031) and TSHR (r=0.0897, P<0.00001) was <0.1, which was considered as no correlation. Because of significant correlations between PVT1 and co-expression genes, the effects of PVT1 on OS time were further assessed by Cox proportional hazards model by controlling the expression of MYC, miR-1207, miR-1208, miR-1205, miR-1205 and miR-1204 in 9451 patients of 32 types of cancer; as shown in Table 5, high PVT1 expression still decreased the OS time with the HR being 1.29 (95% CI: 1.25–1.32).

Sensitivity analysis

Sensitivity analysis was conducted for the association between PVT1 expression and TNM as well as OS. Each diagnosis test was deleted in turn to examine the influence of the removed data on the overall OR/HR. High PVT1 expression still significantly increased the risk of TNM and OS throughout (data not shown).

Publication bias

Publication bias was checked for the effects of PVT1 expression on TNM and OS (Figure 2). Begg's test showed significant rank correlation in studies of PVT1 effect on TNM (Z=2.45, Pr> |z|=0.015) and OS (Z=3.01, Pr>|z|=0.003). Given this result, we performed Egger's test where evidence of significance publication bias was found for TNM (r=1.81, 95% CI: 0.98–2.64, P<0.0001) and OS (r=1.85, 95% CI: 0.95–2.74, P<0.0001). Consequently, we performed trim and fill analysis; the adjusted pooled-OR of TNM and pooled-HR of OS were 1.31 (95% CI: 1.16–1.49) and 1.15 (95% CI: 1.11–1.18) with P<0.0001 for heterogeneity of both.

Discussion

This study aimed to assess the effect of PVT1 expression on cancer prognosis. The pooled effect showed that high PVT1 expression significantly increased the risk of poor differentiation and cancer metastasis, and significantly decreased the survival time of patients. Furthermore, the expression of PVT1 was significantly correlated to that of genes playing important roles in tumorigenesis. PVT1 could act as an effective biomarker for tumorous prognosis surveillance.

lncRNAs have been shown to act as master regulators of gene expression and thus could play a critical role in various biological functions and disease processes including cancer. With the advances in the RNA-Seq technique and improvement of bioinformatics, a large number of tumor associated lncRNAs have recently been discovered through genomics studies. However, only a few lncRNAs have been fully explored to understand the role in cancers such as regulation of transcription, translation, protein modification and the formation of RNA–protein or protein–protein complexes. PVT1 has been identified as an oncogene and highly correlated with Myc which participates in oncogene activation through Akt/c-Myc signaling pathway.[12,13,51,52] Further research into the

Table 4 The characteristic of identified genes and correlation with PVT1 in 8,927 patients of 32 cancers

Gene name	Genes identified in systematic review			Correlation with PVT1	
	Gene type	Relationship	Cancers identified	Coefficient	*P* value
MIR1204	miRNA	Co-expression	NR	0.2234	0.00000
MIR1205	miRNA	Co-expression	NR	0.2664	0.00000
MIR1206	miRNA	Co-expression	NR	–	–
MIR1208	miRNA	Co-expression	NR	0.1430	0.00000
MYC	mRNA	Co-expression	NR	0.1918	0.00000
MIR1207(-5p)	miRNA	Co-expression and target	BRCA	0.1982	0.00000
BCL2	mRNA	Target	OS*	0.1666	0.00000
CASP3	mRNA	Target	CRC	0.1722	0.00000
CCND1	mRNA	Target	OS*	0.1774	0.00000
CD151	mRNA	Target	GC	0.1761	0.00000
CDKN1A(p21)	mRNA	Target	PAAD, NSCLC	0.1735	0.00000
CDKN2A(p16)	mRNA	Target	GC	0.1766	0.00000
CDKN2B(p15)	mRNA	Target	NSCLC, GC	0.1661	0.00000
DDB2	mRNA	Target	NSCLC	0.1755	0.00000
EZH2	mRNA	Target	CESC, THCA, NSCLC	0.1799	0.00000
FASN	mRNA	Target	OS*	0.1769	0.00000
FGF2	mRNA	Target	GC	0.1384	0.00000
HIF1A(HIF1α)	mRNA	Target	GC	0.1667	0.00000
LASP1	mRNA	Target	ESCC	0.1714	0.00000
LATS2	mRNA	Target	NSCLC	0.1700	0.00000
MIR146A	miRNA	Target	PRAD	–	–
MIR152	miRNA	Target	GC	0.0382	0.00031
MIR186	miRNA	Target	GC	0.1146	0.00000
MIR195	miRNA	Target	CESC, OS*	–	–
MIR200B	miRNA	Target	CESC	0.1965	0.00000
MIR203A	miRNA	Target	ESCC	0.1381	0.00000
MIR30A	miRNA	Target	GC	0.0196	0.06384
MIR424	miRNA	Target	CESC	0.1641	0.00000
SMAD3	mRNA	Target	CESC	0.1713	0.00000
SMAD4	mRNA	Target	CRC	0.1673	0.00000
SNAI1	mRNA	Target	GC	0.1752	0.00000
TIMP1	mRNA	Target	OV	0.1800	0.00000
TP53(p53)	mRNA	Target	OV	0.1759	0.00000
TSHR	mRNA	Target	THCA	0.0897	0.00000

Abbreviations: NR, not reported; BRCA, breast cancer; OS*, osteosarcoma; CRC, colorectal cancer; GC, gastric cancer; PAAD, pancreatic cancer; NSCLC, nonsmall-cell lung cancer; CESC, cervical cancer; THCA, thyroid cancer; ESCC, esophageal squamous cell carcinoma; PRAD, prostate cancer; OV, ovarian cancer; CRC, colorectal cancer.

Table 5 The effect of PVT1 and coexpression genes on OS time under Cox proportional hazards model

Gene	Wald	*P* value	HR (95% CI)
MYC	71.07	<0.0001	1.077 (1.058–1.095)
miR-1207	5.933	0.015	1.011 (1.002–1.019)
miR-1208	3.985	0.046	1.011 (1.001–1.021)
miR-1205	19.593	<0.0001	1.017 (1.009–1.025)
miR-1204	313.171	<0.0001	0.847 (0.831–0.862)
PVT1	263.402	<0.0001	1.285 (1.247–1.324)

mechanism found PVT1 could target genes such as LASP1, p15, p16, EZH2, TSHR, and FOXM1 to promote tumor cell proliferation, migration and invasive capability in some cancers.[25,28,34,48] Moreover, PVT1 was confirmed to promote protein stability of MYC, RSPO1, NOP2 and increase the level of them.[52–54] High PVT1 expression was also linked to poor prognosis of some cancers with most patients from China (Table S1). The relationship between PVT1 expression and cancer prognosis is still ambiguous and should be identified by more samples from other groups. For stable detection in 32 types of TCGA cancer, it was found that PVT1 tended to increase the risk of TNM progression and decrease the OS time in most of them.

To further explore the unbiased effect of PVT1 on cancer prognosis, we performed a meta-analysis with the cohorts from TCGA and other published studies. The adjusted pooled OR of 1.31 (95% CI: 1.16–1.49) and pooled HR of 1.15 (95% CI: 1.11–1.18) indicated that

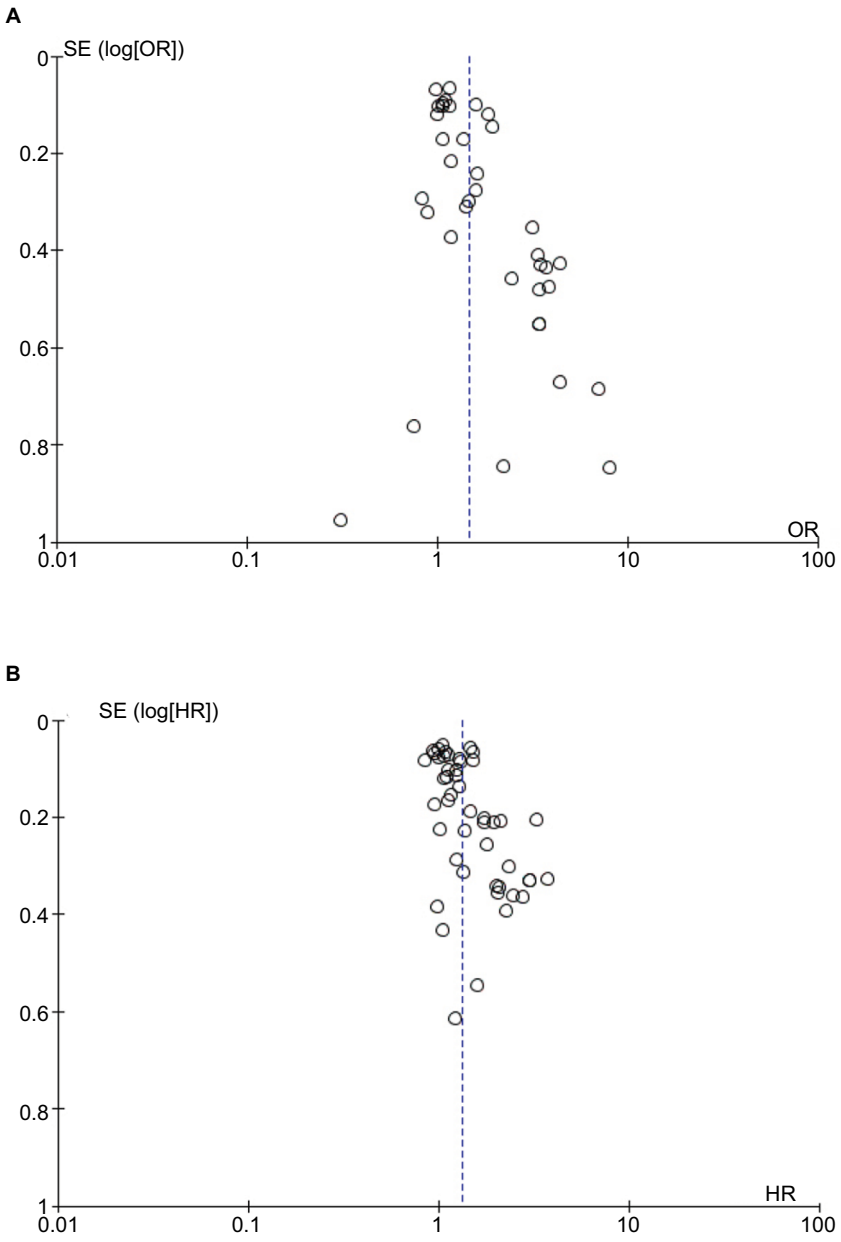

Figure 2 Funnel plots to evaluate the publication bias of PVT1 expression on **(A)** TNM and **(B)** OS.
Abbreviations: OS, overall survival; SE, standard error.

high PVT1 increased the risk of TNM progression and decreased the overall survival time. The effect of high PVT1 on depth of invasive, lymph node metastasis, distant metastasis as well as poor differentiation and lymphatic invasion also provided direct and epidemiological evidence of PVT1 participating in cancer metastasis. Furthermore, five co-expression genes and 24 identified target genes were significantly associated with PVT1 in all TCGA cancers; although the relative coefficients of them were too small to declare a high degree of correlation, which might be caused by heterogeneity of huge samples of data. Moreover, high PVT1 expression dependently decreased the OS time of patients by controlling the influence of co-expressed genes. In addition, it was shown that the expression of PVT1 could be upregulated by smoking to deteriorate the cancer prognosis.[55–57] This suggested that PVT1 expression was an effectively common biomarker for human tumorous prognosis surveillance.

Some meta-analyses focused on the association between lncRNAs such as BANCR,[58] HOTTIP,[59] CCAT2,[60] and metastasis as well as prognosis of cancer; all based on lncRNAs detected by RT-PCR from the cohorts of published studies. To search for an applicably common biomarker for prognosis surveillance, we focused on the effect of PVT1 expression, detected by RT-PCR and RNA-Seq on metastasis and survival as well as the correlation of PVT1 and possible target genes in all common cancer. In the present study, a new way was provided to improve the traditional meta-analysis, by which useful information not published in the literature could be found through published databases to provide more comprehensive evidence. More importantly, the possible mechanism and the common effect of PVT1 on prognosis of all cancers was proved. Furthermore, we provide coefficient references for correlation analysis of gene expression with huge amounts of RNA-Seq data. To our best knowledge, this is the first improved meta-analysis of PVT1 effect on cancer prognosis with the data from the cohorts of TCGA and published studies.

Our study also contains some limitations. Since PVT1 was identified as a common biomarker for cancer prognosis surveillance, there was no reference value to distinguish poor prognosis patients with PVT1 expression detected by RT-PCR or RNA-Seq. Second, although 24 possible target genes were proved to be significantly related to PVT1 expression in most cancers by pooled analysis, the mechanism of their involvement in PVT1 deteriorating cancer prognosis was still clear. Therefore, studies are needed to explore the reference value of PVT1 expression detected by RT-PCR/RNA-Seq to distinguish poor prognosis as well as the role of PVT1 target genes in cancer prognosis.

Conclusion

This improved meta-analysis is the first to demonstrate the effect and possible mechanism of PVT1 on cancer prognosis. The expression of PVT1 could be a biomarker for tumorous prognosis surveillance.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

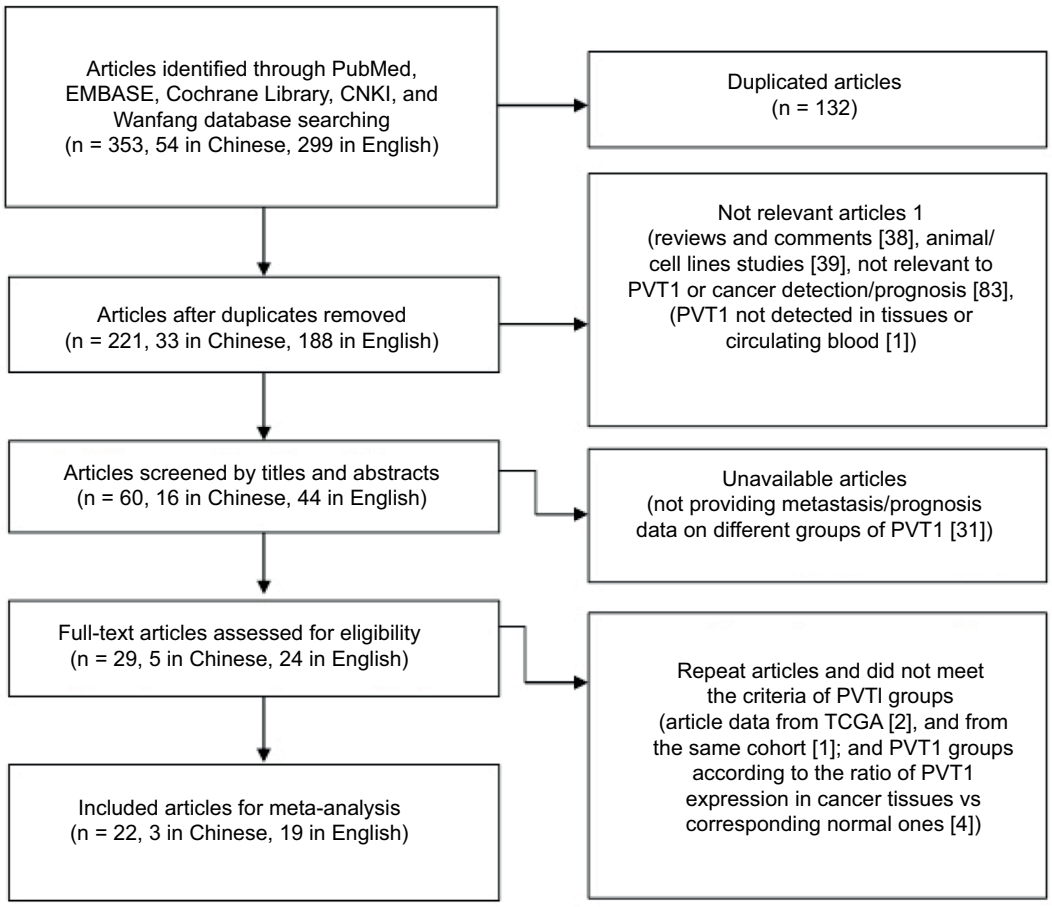

Figure S1 The flow chart of meta-analysis.

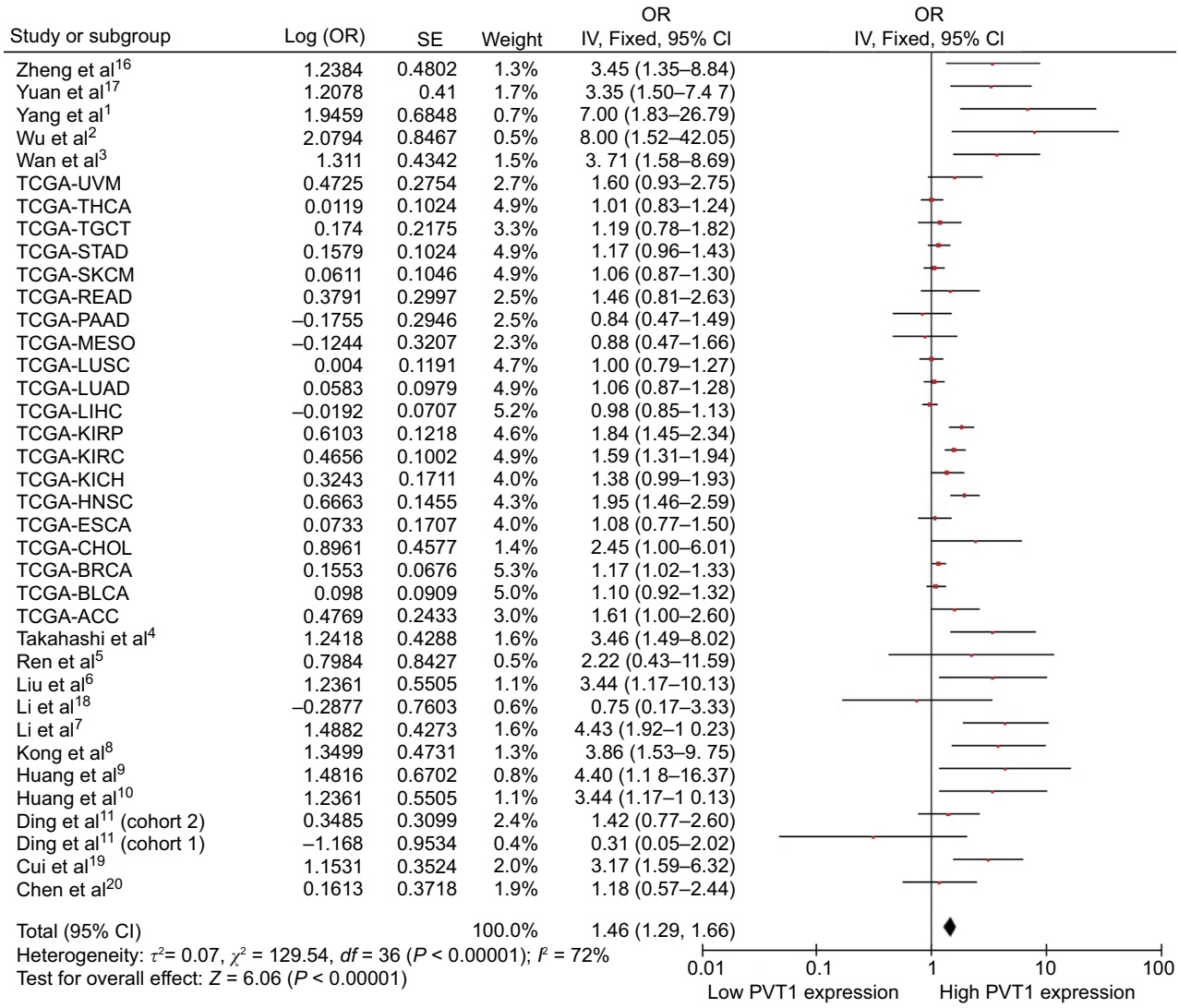

Figure S2 The pooled effect value of PVT1 on TNM.

Abbreviations: IV, inverse variance methods; SE, standard error; UVM, ocular melanoma; SKCM, melanoma; STAD, stomach cancer; TGCT, testicular cancer; THCA, thyroid cancer; READ, rectal cancer; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; LIHC, liver cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; HNSC, head and neck cancer; ESCA, esophageal cancer; ACC, adrenocortical cancer; BLCA, bladder cancer; BRCA, breast cancer; CHOL, bile duct cancer; TCGA, the Cancer Genome Atlas database.

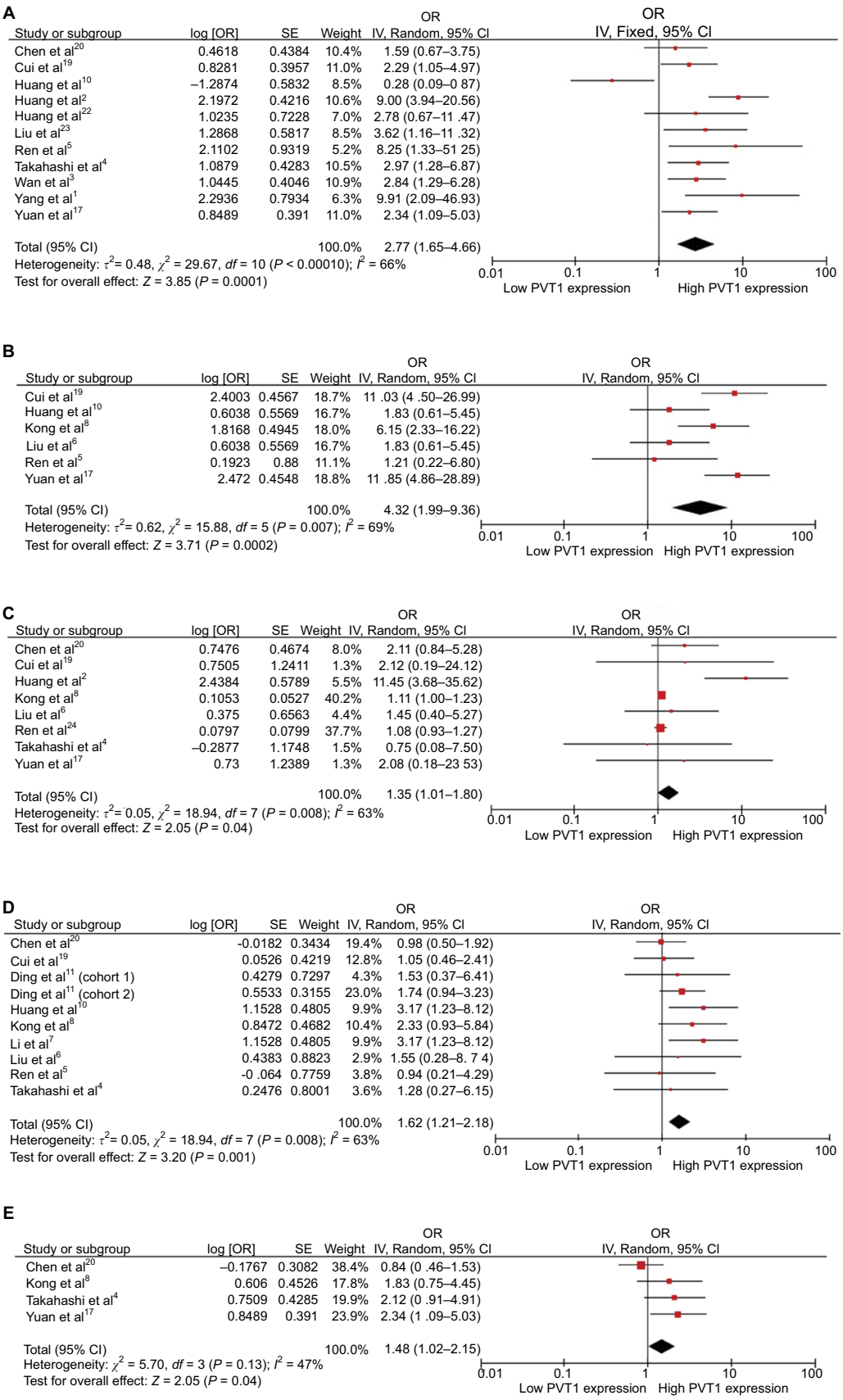

Figure S3 The pooled effect value of PVT1 on **(A)** LNM, **(B)** DOI, **(C)** DM, **(D)** DIF, and **(E)** LI.

Abbreviations: DIF, differentiation; DM, distant metastasis; DOI, depth of invasive; IV, inverse variance methods; LI, lymphatic invasion; LNM, lymph node metastasis; SE, standard error.

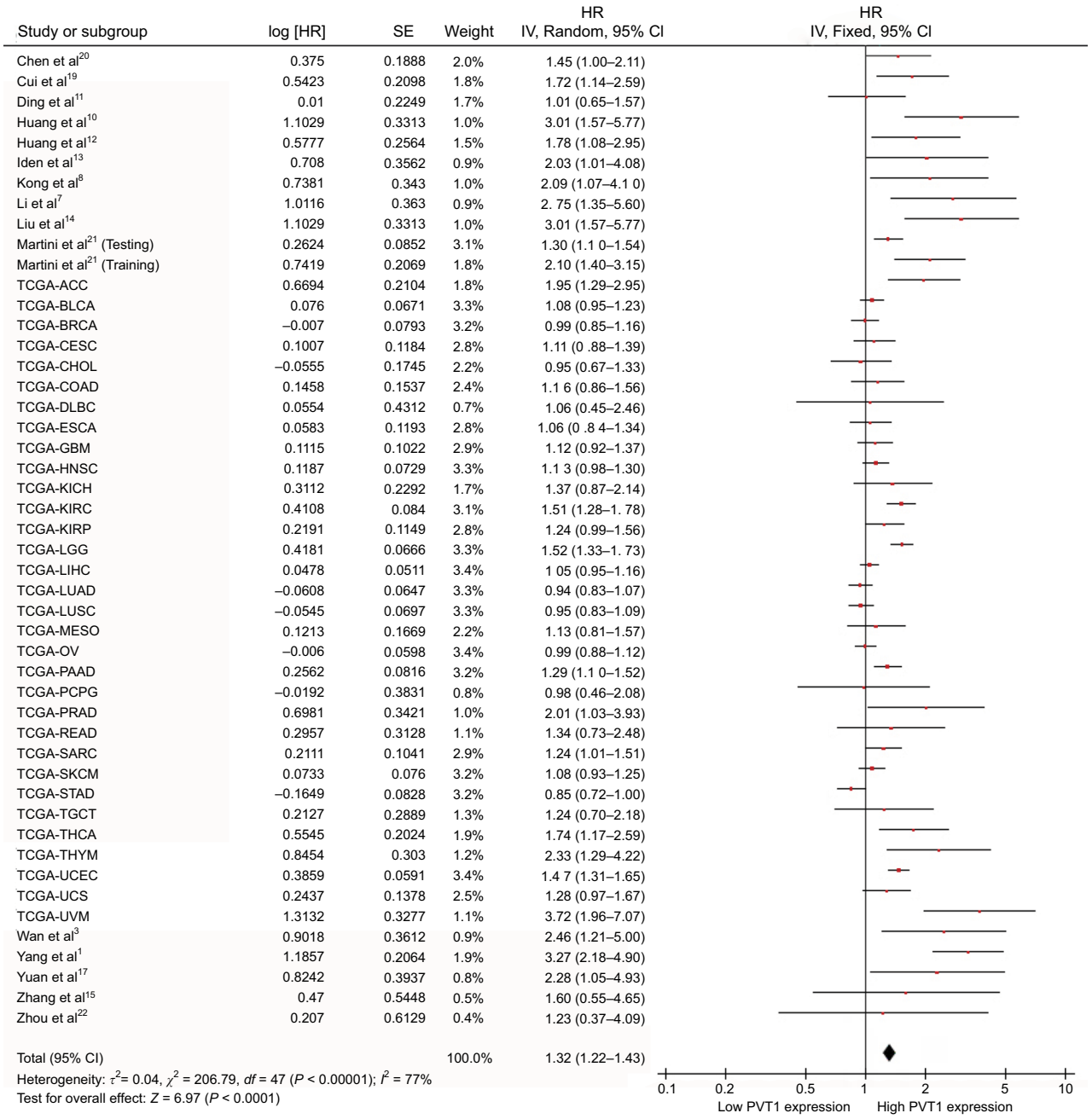

Figure S4 The pooled effect value of PVT1 on OS.

Abbreviations: IV, inverse variance methods; OS, overall survival; SE, standard error; ACC, adrenocortical cancer; BLCA, bladder cancer; BRCA, breast cancer; CESC, cervical cancer; CHOL, bile duct cancer; COAD, colon cancer; DLBC, large B-cell lymphoma; ESCA, esophageal cancer; GBM, glioblastoma; HNSC, head and neck cancer; KICH, kidney chromophobe; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LGG, lower grade glioma; LIHC, liver cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian cancer; PAAD, pancreatic cancer; PCPG, pheochromocytoma & paraganglioma; PRAD, prostate cancer; READ, rectal cancer; SARC, sarcoma; SKCM, melanoma; STAD, stomach cancer; TGCT, testicular cancer; THCA, thyroid cancer; THYM, thymoma; UCEC, endometrioid cancer; UCS, uterine carcinosarcoma; UVM, ocular melanoma.

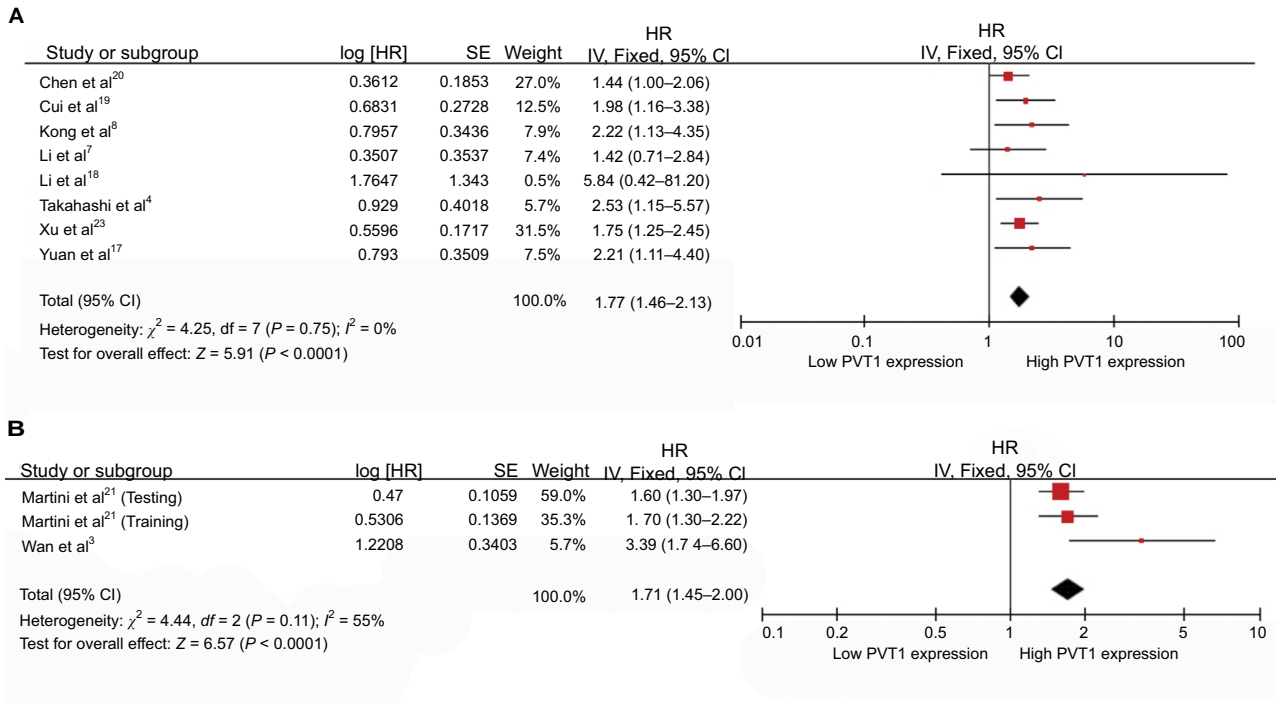

Figure S5 The pooled effect value of PVT1 on **(A)** DFS and **(B)** PFS.
Abbreviations: DFS, disease-free survival; IV, inverse variance methods; PFS, progression-free survival; SE, standard error.

Table S1 Basic data for all included studies in the meta-analysis

Author	Year	Country	Cancer type	Case (high/low)	Metastasis						Prognosis		Smoking on PVT1 OR (95% CI)
					TNM	LI	LNM	DOI	DM	DIF	Outcomes	HR (95% CI)	
					OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)			
Yuan et al[17]	2015	China	GC (tissue)	112 (55/56)	3.346 (1.498–7.475)	2.337 (1.086–5.030)	2.337 (1.086–5.030)	11.846 (4.858–28.884)	2.075 (0.183–23.573)	NR	OS	2.280 (1.054–4.930)	NR
											DFS	2.210 (1.111–4.395)	
Cui et al[19]	2015	China	NSCLC (tissue)	108 (53/55)	3.168 (1.588–8.243)	NR	2.289 (1.054–4.972)	11.026 (4.505–26.983)	2.118 (0.186–24.073)	1.054 (0.461–2.408)	OS	1.72 (1.14–3.25)	Irrelevant data
											DFS	1.98 (1.16–4.35)	
Xu et al[23]	2016	China	GC (tissue)	190 (96/94)	NR	NR	NR	NR	NR	NR	DFS	1.75 (1.25–2.56)	NR
											DSS	1.64 (1.15–2.39)	
Takahashi et al[4]	2014	Japan	CRC (tissue)	164 (133/31)	3.462 (1.494–8.022)	2.119 (0.915–4.908)	2.968 (1.282–6.870)	NR	0.750 (0.075–7.451)	1.281 (0.267–6.149)	DFS	2.532 (1.152–10.747)	NR
Li et al[18]	2016	China	CRC (tissue)	30 (15/15)	0.750 (0.169–3.327)	NR	NR	NR	NR	NR	DFS	5.84 (0.42–81.19)	NR
Zheng et al[16]	2015	China	ESCA (tissue)	77 (39/38)	3.450 (1.346–8.841)	NR	NR	NR	NR	NR	NR	NR	NR
Huang et al[10]	2015	China	PAAD (tissue)	85 (67/18)	3.442 (1.170–10.127)	NR	0.276 (0.088–0.863)	1.829 (0.614–5.444)	NR	1.550 (0.275–8.738)	OS	3.013 (1.574–6.673)	NR
Yang et al[1]	2014	China	NSCLC (tissue)	82 (65/17)	7.000 (1.829–26.788)	NR	9.911 (2.093–46.925)	NR	NR	NR	OS	3.273 (2.184–6.937)	NR
Huang et al[12]	2016	China	SCLC (tissue)	120 (60/60)	NR	NR	9.000 (3.939–20.566)	NR	11.455 (3.683–35.628)	NR	OS	1.782 (1.078–2.945)	NR
Martini et al[21]	2016	Italy	EOC (tissue)	Training 73 (NR)	NR	NR	NR	NR	NR	NR	OS	2.10 (1.40–3.30)	NR
											PFS	1.70 (1.30–2.20)	
				Testing 126 (NR)	NR	NR	NR	NR	NR	NR	OS	1.30 (1.10–1.60)	
											PFS	1.60 (1.30–1.90)	
Kong et al[8]	2015	China	GC (tissue)	80 (40/40)	3.857 (1.526–9.750)	1.833 (0.755–4.455)	NR	6.152 (2.334–16.211)	1.111 (1.002–1.232)	2.333 (0.932–5.839)	OS	2.092 (1.068–4.096)	NR
											DFS	2.216 (1.130–4.345)	
Ding et al[11]	2015	China	HCC (tissue)	58 (49/9)	0.311 (0.048–2.2028)	NR	NR	NR	NR	1.534 (0.367–6.412)	NR	NR	NR
				214 (157/57)	1.417 (0.772–2.603)	NR	NR	NR	NR	1.739 (0.937–3.228)	RFS	1.653 (1.019–2.681)	NR
											OS	1.01 (0.65–1.56)	
Zhang et al[15]	2016	China	CESC (tissue)	90 (45/45)	NR	NR	NR	NR	NR	NR	OS	1.60 (0.55–4.66)	NR
Wu et al[2]	2017	China	PAAD (tissue)	30 (15/15)	8.000 (1.5224–2.042)	NR	Unuseful data	NR	NR	Unuseful data	NR	NR	NR
Ren et al[5]	2016	China	GC (serum)	28 (13/15)	2.222 (0.426–11.603)	NR	8.250 (1.328–51.263)	1.212 (0.216–6.800)	1.083 (0.926–1.267)	0.938 (0.205–4.294)	NR	NR	NR
Wan et al[3]	2016	China	NSCLC (tissue)	105 (56/49)	3.710 (1.584–8.694)	NR	2.842 (1.286–6.282)	NR	NR	NR	OS	2.464 (1.214–4.999)	0.518 (0.226–1.186)
											PFS	3.39 (1.74–6.63)	
Zhou et al[22]	2016	China	OS* (tissue)	53 (29/24)	NR	NR	NR	NR	NR	NR	OS	1.23 (0.37–4.05)	NR

(*Continued*)

Table S1 (*Continued*)

Author	Year	Country	Cancer type	Case (high/low)	Metastasis						Prognosis		Smoking on PVT1 OR (95% CI)
					TNM	LI	LNM	DOI	DM	DIF	Outcomes	HR (95% CI)	
					OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)			
Iden et al[13]	2016	USA	CESC (tissue)	121 (63/58)	NR	NR	NR	NR	NR	NR	OS	2.03 (1.01–4.08)	NR
Li et al[7]	2017	China	ESCC (tissue)	104 (52/52)	4.429 (1.917–10.229)	NR	NR	NR	NR	3.167 (1.235–8.117)	OS DFS	2.75 (1.35–5.59) 1.42 (0.71–2.87)	1.185 (0.528–2.662)
Liu et al[6]	2016	China	CESC (tissue)	85 (67/18)	3.442 (1.170–10.127)	NR	3.621 (1.158–11.323)	1.829 (0.614–5.444)	1.455 (0.402–5.260)	1.550 (0.275–8.738)	OS	3.013 (1.574–6.673)	NR
Huang et al[9]	2015	China	RC (tissue)	54 (39/15)	4.400 (1.183–16.367)	NR	2.783 (0.675–11.477)	NR	NR	NR	NR	NR	NR
Chen et al[20]	2016	China	GC (serum)	187 (112/75)	1.175 (0.567–2.434)	0.838 (0.458–1.532)	1.587 (0.672–3.751)	NR	2.112 (0.845–5.278)	0.982 (0.501–1.927)	OS DFS	1.455 (1.005–2.105) 1.435 (0.998–2.061)	NR

Abbreviations: LI, lymphatic invasion; LNM, lymph node metastasis; DOI, depth of invasive; DM, distant metastasis; DIF, differentiation; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; DSS, disease specific survival; RFS, recurrence free survival; NR, no report; GC, gastric cancer; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; ESCA, esophageal carcinoma; PAAD, pancreatic cancer; SCLC, small-cell lung cancer; EOC, epithelial ovarian cancer; HCC, hepatocellular carcinoma; CESC, cervical cancer; OS*, osteosarcoma; ESCC, esophageal squamous cell carcinoma; RC, renal carcinoma.

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