Original Paper

Overexpression of LncRNA PVT1 Predicts Advanced Clinicopathological Features and Serves as an Unfavorable Risk Factor for Survival of Patients with Gastrointestinal Cancers

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Key Words

Pvt1 • LncRNA • Digestive system cancer • Pathological features • Prognosis

Abstract

Background/Aims: Many studies have reported that PVT1 played important roles in diverse cancer types. But the systematic analysis of PVT1 in gastrointestinal cancers has not been inspected. Thus, we aimed to investigate clinical value of the long noncoding RNA PVT1 (lncRNA) expression in digestive system cancers. **Methods:** Eligible studies were collected from a number of databases (PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure and Wanfang database). Pooled hazard ratio (HR) or odds ratio (OR) with 95 % confidence interval (95 % CI) were applied to assess the clinical significance of PVT1. **Results:** Data from 15 articles were included with a total of 2585 patients. Elevated PVT1 expression were significantly related to poor overall survival (OS) [HR = 1.86, 95% CI (1.44, 2.28); p<0.0001] in digestive system cancers. The same association was also observed between PVT1 expression with outcomes, including disease free survival (DFS), disease specific survival (DSS) and relapse free survival (RFS). The lncRNA PVT1 could also be predicative for some clinicopathological features. **Conclusions:** This meta-analysis revealed that PVT1 may serve as a prognostic predictor and pathological biomarker in digestive system cancers.

Introduction

Digestive system malignancies, consisting mainly of esophageal cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma, pancreatic cancer and gallbladder cancer, have F. Liu and Q. Dong contributed equally to this work.

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been emerged as the main causes for all the cancer-related mortality worldwide [1, 2]. Although great achievements and progress have been made in the diagnosis and treatment of digestive system cancers [3-6], the prognosis of these cancers have been still unfavorable, especially for those with invasion and metastasis [7, 8]. More accurate prognosis prediction for the patients with digestive system cancers should be developed to contribute to better clinical treatment and management. However, no specific prognostic markers have been routinely applied in clinical practices. Thus, it has been clinically significant to explore reliable molecular markers to predict the prognosis in digestive system malignant cancers.

Nowadays, long noncoding RNAs (lncRNAs), one kind of noncoding RNA molecules with a length of longer than 200 nucleotides but without protein-coding potential [9, 10], have become research hotspots in the fields of life science. Enormous studies have revealed that lncRNAs have participated in a variety of biological processes and have been closely related to carcinogenesis and tumor progression [11-13]. Plasmacytoma variant translocation 1 (PVT1) has been a rising star among lncRNAs, it was transcribed by the human PVT1 gene located in chromosomal 8q24.21 [14, 15]. lncRNA PVT1 was reported to play an important role in various cancers [16-18] and function as an oncogene in the development of tumors through promoting cell proliferation, inhibiting cell apoptosis and enhancing cell migration [16-19].

A number of researches have been performed to explore the association between lncRNA PVT1 and the pathological features or prognosis in digestive system malignancies [20-22]. The impact of PVT-1 expression on the prognosis of 164 colorectal cancer patients were studied in Takahashi's study [20]. The mechanism of lncRNA PVT1 on proliferation and stem cell-like property of hepatocellular carcinoma cells were explained from the regulation of the lncRNA hPVT1/NOP2 pathway [21]. The expression of lncRNA PVT1 was also studied in both human tissues and cell lines [22]. In the above studies, there were more single-center clinical study or single-pathway mechanism study. The sample size was small and the results from individual studies was inconclusive.

For more precisely evaluate the prognostic value of PVT1 in digestive system malignancies, this quantitative meta-analysis has been performed to summarize the results of published studies. The relationship between PVT1 expression and pathological features in digestive system malignancies have been further explained.

Materials and Methods

Search strategy and study selection

To collect articles eligible for this meta-analysis, we retrieved the database of PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database. The literature search was conducted from their establishment to Apr. 15, 2017 [23, 24]. The search strategy was performed with the combination of the following keywords: "Plasmacytoma Variant Translocation 1" or "PVT1" or "lncRNA PVT1" or "long noncoding RNA PVT1", "cancer" or "carcinoma" or "tumor" or "neoplasm", "pathological feature" or "pathology" or "prognosis" or "survival" or "clinical outcome". The reference lists of relevant articles were also hand-searched. The full-text articles written in English and Chinese were included in this meta-analysis.

Studies that met the following standards were considered eligible: (1) patients included were diagnosed with digestive system cancers; (2) the expression of lncRNA PVT1 in tissue specimens was reported in the studies; (3) the associations between lncRNA PVT1 expression and prognosis or clinicopathologic features of digestive system cancers were reported; (4) sufficient data was provided for calculating the hazard ratio (HR) with 95% confidence intervals (CI) for survival rates, or odds ratios (ORs) with 95% CI for pathological features.

Studies that met exclusion criteria were excluded and exclusion criteria were as follows: (1) patients suffered from the digestive system benign tumor; (2) reviews, meta-analysis, case reports and duplicate articles; (3) the studies without usable data for survival and pathological features.

Data extraction and quality assessment

With standardized information collection forms, the relevant data from all eligible articles was strictly extracted by two authors (LFT and DQ) independently. Any disagreements were resolved by consensus. The extracted data included the following items: first author's name, publication year, country, cancer type, sample size, tumor stage, follow-up period, conditions of PVT1 expression, detection methods, clinicopathological features (gender, tumor invasion depth, histopathological grade, lymph node metastasis, distant metastasis and tumor-node-metastasis (TNM) stage), the cut-off value, and HR as well as corresponding 95% CI.

A study provided the detailed HRs and 95% CIs for survival and the data would be obtained directly. Or the HRs was estimated from sample size, survival rate at specified times, log-rank statistic and p-value. Otherwise, if a study only provides Kaplan-Meier curves, the HRs with 95% CIs and survival rate at specified times would be calculated. Two individual investigators extracted the data and calculated the required values with the Engauge Digitizer version 4.1[25, 26].

The quality of all included studies was evaluated using the Newcastle-Ottawa quality assessment scale (NOS), which has a score ranging from 0 to 9 points [27, 28]. A score equal or more than 6 was regarded as high quality, which indicating lower risks of bias. In the current meta-analysis, the quality of all included studies was varied from 5 to 9, with a mean value of 6.5.

Statistical analysis

Statistical analysis of HRs for Overall survival (OS), Disease free survival (DFS), Disease specific survival (DSS) and Relapse free survival (RFS) were estimated by Stata statistical software version 12.0 (Stata Corporation, College Station, Texas, USA) to explore the prognostic value of lncRNA PVT1 in digestive system cancers. Odd ratios (ORs) for clinicopathological parameters were calculated with RevMan5.3 software (Cochrane Collaboration).

The variations in patient groups and clinical settings etc in individual trial would increase the variability of results. Thus, the between-studies heterogeneity has been evaluated by performing *Chisquare*-based Q test and I^2 statistics. If the P-value was less than 0.05 and/or the I^2 -value was greater than 50%, a random-effects model was used because the heterogeneity existed. Conversely, the fixed-effects model was applied in the analysis [29, 30]. Subgroup analysis and sensitivity analysis were also performed. The publication bias was common issue in meta-analysis. The positive results would tend to be published, which could not be representative of all populations. In our study, publication bias was assessed using the Begg's funnel plot and Egger's test [31, 32] for estimating the number of missing studies that might exist in a meta-analysis.

Results

Literature search and study characteristics

A total of 15 eligible publications [20-22, 33-44] were finally included in the meta-analysis according to the inclusion and exclusion criteria. A total of 2585 participants were included with a maximum sample size of 593 and a minimum sample size of 30. Among the 15 articles, the digestive system malignancies assessed in these studies included esophageal carcinoma (2 articles) [39, 44], gastric cancer (6 articles) [22, 33,

Fig. 1. Flowchart showing the process of study search and selection.

38, 40-42], colorectal cancer (2 articles) [20, 37], hepatocellular carcinoma (2 articles) [21, 34], pancreatic cancer (3 articles) [35, 36, 43]. Among the eligible articles, one came from Japan [20], one came from Portugal [36] and the rest of 13 articles were came from China [21-22, 33-35, 37-44]. The participants in all the studies could be classified into high PVT1 expression group and low PVT1 expression group. The publication period of 15 articles were ranged from 2014 to 2017. The detailed process of study search and selection was presented (Fig. 1). The main characteristics of all included studies were summarized (Table 1).

Association between PVT1 expression and prognosis in digestive system malignancies

OS associated with PVT1 expression in digestive system malignancies. A total of 10 studies reported the OS of 1179 patients according to PVT1 expression levels in tissues [20, 21, 33-38,

Table 1. Main characteristics of all studies included in the meta-analysis, CRC: colorectal cancer; EC: esophageal carcinoma; PC: pancreatic cancer; HCC: hepatocellular carcinoma; GC: gastric cancer; OS: overall survival; RFS: recurrence-free survival; DFS: disease-free survival; DSS: disease-specific survival; qRT-PCR: quantitative real-time-polymerase chain reaction; NA, Not available

First author, Year	Country	Cancer type	Sample Size	Sample Type	Tumor stage	Follow-up	High expression N (%)	Cut-off value	Detection method	Outcome measures	Multivariate analysis
Takahashi Y, 2014 [20]	Japan	CRC	164	cancer & matched-normal tissues	0-IV	≥5 years	131(79.88)	20 percentiles value	qRT-PCR	OS	Yes
Wang F, 2014 [21]	China	HCC	89	cancer & matched-normal tissues	I-IV	<5 years	45(50.56)	the median value	qRT-PCR	OS, RFS	No
Ding J, 2015[22]	China	GC	31	cancer & matched-normal tissues	I-IV	NA	19(61.29)	Cancer tissue /non-cancerous (1.0)	qRT-PCR	NA	NA
Kong R, 2015[33]	China	GC	80	cancer & matched-normal tissues	I-IV	<5 years	40(50.00)	median value	qRT-PCR	OS, DFS	Yes
Ding C-1, 2015[34]	China	HCC	214	cancer & matched-normal tissues	I-IV	≥5 years	157(73.36)	from the ROC curve analysis	qRT-PCR	OS, RFS	OS-No, RFS-Yes
Ding C-2, 2016[34]	China	HCC	58	cancer & matched-normal tissues	I-IV	NA	49(84.48)	from the ROC curve analysis	qRT-PCR	NA	NA
Huang C, 2015[35]	China	PC	85	cancer & matched-normal tissues	I-IV	<5 years	67(78.82)	mean value	qRT-PCR	OS	Yes
Posa I, 2016[36]	Portugal	PC	115	unmatched normal-cancer tissues	NA	≥5 years	NA	median value	NA	OS	No
Li Q, 2016[37]	China	CRC	30	cancer & matched-normal tissues	II-III	<5 years	15(50.00)	NA	qRT-PCR	OS	No
Yuan CL, 2016 [38]	China	GC	111	cancer & matched-normal tissues	I-IV	<5 years	55(49.55)	median value	qRT-PCR	OS, DFS	Yes
Zheng X, 2016[39]	China	EC	77	cancer & matched-normal tissues	I-IV	NA	39(50.65)	median value	qRT-PCR	NA	NA
Xu MD-1, 2016[40]	China	GC	190	cancer & matched-normal tissues	I-IV	≥5 years	96(50.53)	from the ROC curve analysis	qRT-PCR	DFS, DSS	Yes
Xu MD-2, 2016[40]	China	GC	359	cancer & matched-normal tissues	NA	≥5 years	128(35.65)	NA	NA	DFS	No
Xu MD-3, 2016[40]	China	GC	593	cancer & matched-normal tissues	NA	≥5 years	315(53.12)	NA	NA	DSS	No
Huang T, 2017[41]	China	GC	68	cancer & matched-normal tissues	I-IV	NA	30(44.11)	mean ratio	qRT-PCR	NA	NA
Chen J, 2017[42]	China	GC	187	cancer & matched-normal tissues	I-IV	≥5 years	112(59.89)	NA	qRT-PCR	OS, DFS	Yes
Wu BQ, 2017[43]	China	PC	30	unmatched normal-cancer tissues	I-IV	NA	15(50.00)	median value	qRT-PCR	NA	NA
Li PD, 2017[44]	China	EC	104	cancer & matched-normal tissues	I-III	≥5 years	52 (50.00)	median value	qRT-PCR	OS, DFS	OS-Yes, DFS-No

42, 44]. Since no significant heterogeneity was observed among studies ($I^2 = 0.0\%$, $P_h = 0.752$), the fixed-effects model was applied to calculate the pooled HR with corresponding 95% CI. Overall, the results revealed that there was a significant association between high PVT1 expression and poor OS in digestive system malignancies [HR = 1.86, 95% CI (1.44, 2.28); $p < 0.0001$] (Fig. 2).

The subgroup meta-analysis was further performed based on the tumor type, ethnicity, analysis type, sample size and follow-up times (Table 2). From the subgroup results by tumor type (for all online supplementary

material, see www.karger.com/doi/10.1159/000481719, Fig. S1), we found that PVT1 could be served as a significant prognostic indicator of OS for patients with colorectal cancer (CRC) [HR=2.68, 95% CI (1.22, 4.15); $p < 0.0001$], pancreatic cancer (PC) [HR=2.70, 95% CI (1.35, 4.05), $p < 0.0001$] and gastric cancer (GC) [HR=1.58, 95% CI (1.08, 2.08); $p < 0.0001$]. However, no statistical significance but strong trends association was also found in hepatocellular carcinoma (HCC) [HR=2.05, 95% CI (0.49, 3.61)]. All cancer types could be generally classified into 2 categories (Gastrointestinal(GI) tract and Non-GI tract) (see supplementary material, Fig. S2), a similar result was found in cancers from GI tract [HR=1.74, 95% CI (1.28, 2.21); $p < 0.0001$] and cancers from Non-GI tract [HR=2.42, 95% CI (1.40, 3.44); $p < 0.0001$].

Additionally, we detected a significant relationship between PVT1 expression and OS of patients with digestive system malignancies in Asian [HR= 1.80, 95% CI (1.37, 2.24); $p < 0.0001$] (see supplementary material, Fig. S3). PVT1 was also found to be significantly associated with OS of patients in studies with sample size both equal or greater than 100 [HR=1.70, 95% CI (1.21, 2.18); $p < 0.0001$] and less than 100 [HR: 2.37, 95% CI (1.51, 3.22); $p < 0.0001$] (see supplementary material, Fig. S4). The association between PVT1 and OS of patients was significant in studies reported in multivariate analysis [HR=1.70, 95% CI (1.22, 2.17); $p < 0.0001$] and non-multivariate analysis [HR=2.44, 95% CI (1.54, 3.35); $p < 0.0001$] (see supplementary material, Fig. S5). In addition, a significant relationship between PVT1 expression and OS of patients was observed in studies with follow-up times both equal or greater than 5 years [HR=1.66, 95% CI (1.16, 2.16); $p < 0.0001$] and less than 5 years [HR=2.35, 95% CI (1.57, 3.14); $p < 0.0001$] (see supplementary material, Fig. S6).

Finally, in order to assess the stability of the results, the sensitivity analysis was performed by sequential omission of individual studies, and the pooled result was not obviously influenced by any single study, which suggested the robustness of the results. However, the shape of funnel plot was asymmetrical (Fig. 3), which was confirmed in Egger's test ($P = 0.029$). Then the "trim and fill method" was also applied to replace five missing studies (Fig. 4). After correction, the adjusted pooled HR was 1.742 (95 % CI:1.464-2.073, $p < 0.0001$) [31, 32].

Fig. 2. Forest plot of HR for the relationship between high PVT1 expression and OS. The pooled HR with corresponding 95% CI was calculated with fixed-effects model. the results revealed that there was a significant association between high PVT1 expression and poor OS in digestive system malignancies [HR = 1.86, 95% CI (1.44, 2.28); $p < 0.0001$].

Table 2. Results of subgroup analysis of pooled hazard ratios (HRs) of overall survival (OR) of patients with high PVT1 expression

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	p-value	Heterogeneity	
					I ² (%)	P-value
[1] Tumor type						
1) CRC	2	194	2.68(1.22-4.15)	<0.0001	0.0	0.948
PC	2	200	2.70(1.35-4.05)	<0.0001	0.0	0.778
HCC	2	303	2.05(0.49-3.61)	>0.05	0.0	0.976
GC	3	378	1.58(1.08-2.08)	<0.0001	0.0	0.566
EC	1	104	2.75(1.35-5.59)	0.011	-	-
2) GI tract	6	676	1.74(1.28-2.21)	<0.0001	0.0	0.548
Non-GI tract	4	503	2.42(1.40-3.44)	<0.0001	0.0	0.927
[2] Ethnicity						
Asian	9	1064	1.80(1.37-2.24)	<0.0001	0.0	0.754
Caucasian	1	115	2.58(1.28-4.47)	0.002	-	-
[3] Sample size						
≥ 100	6	895	1.70(1.21-2.18)	<0.0001	0.0	0.643
< 100	4	284	2.37(1.51-3.22)	<0.0001	0.0	0.873
[4] Analysis type						
Multivariate	6	731	1.70(1.22-2.17)	<0.0001	0.0	0.632
Non-multivariate	4	448	2.44(1.54-3.35)	<0.0001	0.0	0.944
[5] Follow-up time						
≥5 years	5	784	1.66(1.16-2.16)	<0.0001	0.0	0.559
<5 years	5	395	2.35(1.57-3.14)	<0.0001	0.0	0.951
CRC: colorectal cancer; PC: pancreatic cancer; HCC: hepatocellular carcinoma; GC: gastric cancer; EC: esophageal carcinoma; GI tract: Gastrointestinal tract

Fig. 3. Funnel plots of publication bias on the correlation between PVT1 and OS. The asymmetrical shape of funnel plot indicated that there were missing studies [31].

DFS/DSS/RFS associated with PVT1 expression in digestive system malignancies. Six studies reported the association between PVT1 and DFS in patients with digestive system malignancies and 1031 patients were included. The pooled results suggested that there was

Fig. 4. Filled funnel plot of meta-analysis with “trim-and-fill” method for correction the publication bias [31, 32]. The pooled HR was corrected after replacing five missing studies. $\circ$ indicates observed studies; $\blacksquare$ indicates missed studies.

Fig. 5. Forest plot of HR for the relationship between high PVT1 expression and DFS. The pooled results suggested that there was a significant association between PVT1 expression and DFS in digestive system malignancies [HR=1.68, 95% CI (1.40, 1.97); $p < 0.0001$] with no heterogeneity ($I^2=0.0\%$, $P_h=0.720$).

a significant association between PVT1 expression and DFS in digestive system malignancies [HR=1.68, 95% CI (1.40, 1.97); $p < 0.0001$] with no heterogeneity ($I^2=0.0\%$, $P_h=0.720$) (Fig.

Fig. 6. Forest plot of HR for the relationship between high PVT1 expression and RFS. High PVT1 expression was a negative factor for RFS in patients with Hepatocellular cancer [HR=1.76, 95% CI (1.13, 2.39); $p < 0.0001$] with no heterogeneity ($I^2 = 0.0\%$, $P_h = 0.705$).

5). Particularly, PVT1 could be serve as a prognostic predictor for DFS in in GC [HR=1.72, 95% CI (1.42, 2.02); $p < 0.0001$] (Fig. 5).

Only two studies provided the results of RFS were included for analysis [21, 34]. A total of 303 patients were involved, both in hepatocellular carcinoma. The HR with 95% CI were 1.90 (1.18-3.12) and 1.65 (1.02-2.68), respectively. In our study, the pooling HRs with 95% CI were calculated from those two studies, which was 1.76 (1.13-2.39). The HR was higher than 1.0 in both individual study and pooling results. It indicated that high level of PVT1 expression was a negative factor for RFS in patients with HCC [HR=1.76, 95% CI (1.13, 2.39); $p < 0.0001$] with no heterogeneity ($I^2 = 0.0\%$, $P_h = 0.705$) (Fig. 6).

For the relationship between PVT1 and DSS, only two studies including 783 patients reported HRs for DSS in gastric cancer; the overall results revealed that upregulation of PVT1 expression was associated with poor DSS in GC [HR=1.30, 95% CI (1.07, 1.53); $p < 0.0001$] with no significant heterogeneity ($I^2 = 25.7\%$, $P_h = 0.246$) (Fig. 7).

Because the included studies were small and no between-studies heterogeneity was found, the publication bias and sensitivity analyses were not conducted for DFS/DSS/RFS.

Association between PVT1 expression and clinical characteristics in digestive system malignancies

Gender. A total of 14 studies that reported the relationship between PVT1 expression and gender in digestive system cancers. No significant heterogeneity across-studies was observed ($I^2 = 0.0\%$; $P_h = 0.53$), the fixed-effects model was applied to calculate the pooled OR and corresponding 95% CI. The result showed that there was no significant association between PVT1 expression and gender [OR = 1.05, 95% CI (0.81, 1.37), $p = 0.71$] (see supplementary material, Fig. S7). In the subgroup analysis, no significant association was observed between PVT1 expression and gender in GC, CRC, HCC, PC or EC patients (see supplementary material, Fig. S7).

Tumor invasion depth. Only 5 studies reported the relationship between PVT1 expression and tumor invasion depth. Because there was significant heterogeneity ($I^2 = 67\%$; $P_h = 0.02$), the random effects model was applied. The pooled result suggested that the group of high PVT1 expression had a higher risk of deep tumor invasion (T3 stage or more) than that of in the group of low PVT1 expression in digestive system cancers [OR = 3.54, 95% CI (1.52, 8.20), $p = 0.003$] (see supplementary material, Fig. S8). In the subgroup analysis, a significant association was also observed between PVT1 expression and tumor invasion depth in GC patients (see supplementary material, Fig. S8).

Fig. 7. Forest plot of HR for the relationship between high PVT1 expression and DSS in gastric cancer. The upregulation of PVT1 expression was associated with poor DSS [HR=1.30, 95% CI (1.07, 1.53); $p < 0.0001$] with no significant heterogeneity ($I^2=25.7\%$, $P_h=0.246$).

Histopathological grade. 8 studies reported the relationship between PVT1 expression and histopathological grade. The heterogeneity between studies was not significant ($I^2 = 35\%$; $P_h = 0.15$), therefore the fixed-effects model was applied to analyze the pooled OR with corresponding 95% CI, which was significantly different [OR = 1.37, 95% CI (1.02, 1.86), $p=0.04$] (see supplementary material, Fig. S9). It revealed that patients with digestive system cancers detected with high PVT1 expression had a poorer histopathological grade than those of with low PVT1 expression. However, in the subgroup analysis, no significant association was observed between PVT1 expression and histopathological grade in GC or HCC patients (see supplementary material, Fig. S9).

Lymph node metastasis. 7 studies reported the relationship between PVT1 expression and lymph node metastasis. There was no significant heterogeneity among studies ($I^2 = 0\%$; $P_h = 0.50$), so the fixed-effects model was applied. The pooled result revealed that there was a significant association between UCA1 expression and lymph node metastasis [OR = 2.94, 95% CI (2.02, 4.28), $p < 0.00001$] (see supplementary material, Fig. S10). The patients of digestive system malignancies detected with high PVT1 expression had a higher risk of lymph node metastasis than those of with low PVT1 expression. In the subgroup analysis, a significant association was also observed between PVT1 expression and lymph node metastasis in GC, or PC patients (see supplementary material, Fig. S10).

Distant metastasis. A total of 6 studies reported the association between PVT1 expression and distant metastasis. Due to no significant heterogeneity observed among studies ($I^2 = 0\%$; $P_h = 0.44$), the fixed effects model was applied to calculate the pooled OR and corresponding 95% CI, which showed significant difference [OR = 3.27, 95% CI (1.79, 5.97), $p = 0.0001$] (see supplementary material, Fig. S11). It suggested that the patients with high PVT1 expression had more risk of distant metastasis than that of with low PVT1 expression. In the subgroup analysis, a significant association was also observed between PVT1 expression and distant metastasis in GC patients (see supplementary material, Fig. S11).

TNM stage. There were 14 studies investigated the association between PVT1 expression and TNM stage (II-IV vs. 0-II). The across-studies heterogeneity was not significant ($I^2 = 45\%$; $P_h = 0.03$), the fixed effects model was applied. The result showed that high PVT1 expression was linked with advanced TNM stage [OR = 2.48, 95% CI (1.93, 3.17), $p < 0.00001$] (see

supplementary material, Fig. S12). In the subgroup analysis, a significant association was also observed between PVT1 expression and TNM stage in CRC, GC, PC or EC patients (see supplementary material, Fig. S12), however, no significant association was observed between PVT1 expression and TNM stage in HCC patients (see supplementary material, Fig. S12).

For the clinicopathological value of PVT1 in digestive system malignancies, except for tumor invasion depth, there was no significant heterogeneity among studies for histopathological grade, lymph node metastasis and distant metastasis. Given the small number of the studies ($n < 10$), we didn't conduct publication bias and sensitivity analyses for those clinicopathological features. However, publication bias and sensitivity analyses were performed for the gender and TNM stage, the results showed that there was no significant publication bias, and as each study was omitted sequentially, the pooled results did not be significantly altered neither.

Discussion

Plasmacytoma variant translocation 1 (PVT1) was a functional lncRNA, which was originally discovered as an activator of MYC in murine plasmacytoma variant translocations [45, 46]. Recently, accumulating studies have found the aberrant expression of lncRNA PVT1 in lesion tissues, which played a crucial role in digestive system malignancies. Ding et al. [22] showed that the expression level of PVT1 was remarkably higher in cancerous tissues compared with that of in corresponding adjacent non-tumor tissues. It was associated with a higher serum α -fetoprotein expression level and shorter recurrence-free survival in hepatocellular carcinoma. Kong et al. [33] demonstrated that elevated expression of PVT1 in gastric cancer was associated with advanced clinicopathological features and poor prognosis.

Many studies have investigated the roles of lncRNA PVT1 in pathological factors and prognosis in digestive system cancers. However, the potential application of lncRNA PVT1 as a novel prognostic biomarker for digestive system cancers was still unclear. Therefore, it was significant to conduct a comprehensive meta-analysis which combined previous studies about the significantly role of PVT1 in digestive system malignancies. To our knowledge, this is the first meta-analysis to clarify the clinical significance and prognostic value of lncRNA PVT1 in digestive system malignancies.

Here we performed this meta-analysis with a total of 2585 patients from 15 articles to provide evidences that the high expression of lncRNA PVT1 could predict advanced clinicopathological features and serve as a negative risk factor for survival of patients with digestive system cancers. Our research on the association between PVT1 and digestive system cancers suggested that enhanced PVT1 expression negatively correlated with poor OS in digestive system cancers. The fixed-effects model was applied since there was no significant heterogeneity. Subgroups analysis further showed that lncRNA PVT1 was significantly associated with OS for CRC, GC and PC. The result would not be altered by other factors, such as ethnicity, sample size, analysis type and follow-up times. Besides that, we performed analysis of DFS, DSS and RFS in digestive system malignancies. The pooled results demonstrated that increased PVT1 expression was negatively associated with DFS and DSS in GC. In addition, elevated lncRNA PVT1 was associated with poor RFS in HCC.

Further, the association between expression of lncRNA PVT1 and clinicopathological features was explored in patients with digestive system malignancies. The pooled results verified that the group with high lncRNA PVT1 expression was associated with deeper tumor invasion, worse histopathological grade and more advanced TNM stage. The patients detected with overexpressed lncRNA PVT1 may have a higher risk of developing lymph node metastasis and distant metastasis. No significant association was observed between PVT1 expression and gender. It's worth noting that in the subgroup analysis, the similar results were also found to be stratified by the cancer types.

Recent studies have provided novel insights into the functions of lncRNA in the pathogenesis and clinicopathological processes of digestive system cancers [39-48]. In a study on esophageal cancer, unregulated PVT1 may induce epithelial-to-mesenchymal transition (EMT) by regulating the expression levels of EMT markers (E-cadherin, N-cadherin and vimentin), promoting the invasion of esophageal cancer cells [39]. When exploring the underlying roles of PVT1 in human gastric cancer, Yuan et al. [38] demonstrated that upregulated PVT1 expression was significantly correlated with some advanced pathological features (invasion depth, TNM stage, lymph nodes metastasis) and poor OS and DFS rate, indicating that PVT1 might participate in the progression of GC. Another research further explored the biological role of lncRNA PVT1 in GC, and confirmed that lncRNA PVT1 could accelerate cell proliferation through epigenetically regulating p15 and p16 [33]. PVT1 enhanced cancer cell proliferation and invasion *in vitro* and *in vivo*, through the positive feedback loop of PVT1-FOXO1, suggesting that PVT1 could be a potential therapeutic target for gastric cancer [40].

Another study showed that the development of HCC would be affected by PVT1 through the TGF- β 1/ hPVT1/NOP2 pathway. With gene expression microarray analysis, Takahashi et al. [30] demonstrated that the TGF- β signaling pathway and apoptotic signals would be upregulated by PVT-1 knockdown, leading to the significant loss of CRC proliferation and invasion capabilities. Although much attention has been paid to the roles of PVT1 in gastrointestinal cancers, the biological function and mechanism of PVT1 remained unclear, more experimental studies should be performed to further elucidate the mechanism of PVT1 in digestive system malignancies.

Originating from systematically reviewing, the relationships between PVT1 expression with pathology and prognosis in digestive cancers have been discussed. PVT1 may be served as a candidate for substantially improving prognosis estimation. However, there were still some limitations in our research. First, most of studies included were from Asian countries, the number of studies from other countries were small, which might limit the application value for other ethnic populations. Second, only 2585 participants from 15 publications were included and the sample size needed to be further enlarged. Third, some other cancer types of digestive system were not investigated, such as gallbladder carcinoma and gastrointestinal stromal tumors. And studies with positive results tend to be published more easily than that of with negative results, thus publication bias may exist in OS. Finally, the cut-off values for differentiating high and low PVT1 expression varied among studies.

Taken together, our meta-analysis clearly clarified that PVT1 was capable of predicting for clinical outcomes in digestive cancers. In another word, PVT1 may play a significant clinicopathological and prognostic role in digestive system cancers. Considering the limitations of our study, further well-designed studies with larger sample sizes are necessary for further confirming the investigation findings.

Disclosure Statement

The authors declared that there was no conflict of interest regarding the publication of this paper.

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