Original Article

Long non-coding RNA LINC-PINT is associated with favorable prognosis in cancer patients: a systematic review and meta-analysis

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Background: There is growing evidence that long non-coding RNA long iatrogenic non-protein-coding RNA p53-induced transcript (LINC-PINT) is highly expressed in cancer tissue and is associated with the prognosis of cancer patients. The present study systematically analyzed the prognostic significance of LINC-PINT expression in cancer patients. We aimed to reveal the association between LINC-PINT expression and survival in cancer patients.

Methods: We collected eligible studies through the PubMed, Embase, and Cochrane library searches until February 1, 2024. We collected the following data from the enrolled studies: first author, publication year, country, cancer type, case number, cancer stage, detection method and cut-off value of LINC-PINT expression, follow-up period, and survival outcome. The prognostic significance of LINC-PINT expression was evaluated by conducting a meta-analysis. StataSE17 (Stata, College Station, TX, USA) was used for all analyses.

Results: Eleven eligible studies with 2,876 cancer patients were collected. The pooled results revealed that LINC-PINT expression was associated with favorable overall survival (OS) and disease-free survival (DFS) in cancer patients [for OS, hazard ratio (HR) =0.72, 95% confidence interval (CI): 0.64–0.80, P<0.001; for DFS, HR =0.70, 95% CI: 0.60–0.82, P<0.001].

Conclusions: LINC-PINT expression was associated with favorable OS and DFS, and it may serve as a valuable prognostic marker in cancer patients.

Keywords: Cancer; long iatrogenic non-protein-coding RNA p53-induced transcript (LINC-PINT); long non-coding RNA (lncRNA); meta-analysis; prognosis

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Introduction

Cancer has emerged as a major health problem worldwide. Despite several developments in cancer diagnosis and treatment, the survival rate of cancer patients remains low (1). Therefore, it is imperative to develop biomarkers that can help in early diagnosis and prognostic stratification, and serve as therapeutic targets for cancer patients (2).

Long non-coding RNAs (lncRNAs) are defined as non-coding RNAs longer than 200 nucleotides (3). LncRNAs regulate local protein-coding gene expression at the level

of chromatin remodeling, transcriptional control, and post-transcriptional processing (4). There is increasing evidence for the involvement of lncRNAs in various human diseases due to aberrant lncRNA function in differentiation and developmental processes (3,4).

Recently, some lncRNAs have been identified as cancer-related molecules (5). The lncRNA long iatrogenic non-protein-coding RNA p53-induced transcript (LINC-PINT) is abnormally expressed in various cancer (6). Moreover, lncRNA LINC-PINT is identified tumor suppressor with down-regulated expression in many types of cancer cells (7). For example, LINC-PINT acts as a tumor suppressor by sponging microRNA in lung cancer (6). Furthermore, current studies have demonstrated that LINC-PINT is associated with prognosis in cancer patients, but its exact prognostic role has not been quantitatively investigated (6-16). Hence, we integrated eligible studies to explore the relationship between lncRNA LINC-PINT expression and the prognosis of cancer patients. We present this article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-627/rc)

Methods

Literature search

We searched eligible studies through the PubMed, Embase, and Cochrane library searches until February 1, 2024 using the following terms: (LncRNA LINC-PINT or Long non-coding RNA LINC-PINT) and (cancer or tumor or carcinoma or neoplasm or malignancy) and (prognostic or predictive or prognosis or survival or outcome). We also performed a manual search.

Highlight box

Key findings

- Long iatrogenic non-protein-coding RNA p53-induced transcript (LINC-PINT) expression was associated with survival in cancer patients.

What is known and what is new?

- LINC-PINT expression was associated with prognosis in cancer patients.
- LINC-PINT expression was associated with favorable survival in cancer patients.

What is the implication, and what should change now?

- LINC-PINT expression may serve as a valuable prognostic marker in cancer patients.

Inclusion and exclusion criteria

We enrolled studies that coincide with the following qualifications: (I) studies evaluating the relationship between LINC-PINT expression and survival, and (II) LINC-PINT expression evaluating in human cancer tissue. Reviews, case reports, letters, conference abstracts, non-English articles, and duplicate articles were excluded.

Data extraction

Both authors individually collected the following data from the enrolled studies: first author, publication year, country, cancer type, case number, cancer stage, detection method and cut-off value of LINC-PINT expression, follow-up period, and survival outcome. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from Kaplan-Meier plots. Differences in the data were agreed by reaching a consensus through a discussion.

Quality assessment

Both authors individually evaluated the quality of the enrolled studies by the Newcastle-Ottawa Scale (NOS). Differences in the quality evaluation were agreed by reaching a consensus through a discussion.

Statistical analysis

The relationship between LINC-PINT and survival outcome was assessed by calculating HR with 95% CI, and the heterogeneity of the enrolled studies was evaluated using I^2 statistics. The subgroup analysis was also evaluated. The funnel plot with Egger's test was performed to check for publication, and the sensitivity analysis was carried out to reveal the consistency of the pooled results. StataSE17 (Stata, College Station, TX, USA) was used for all analyses. The P value <0.05 was considered statistically significant.

Results

Study characteristics

We reviewed a total of 86 articles and selected 11 eligible studies (*Figure 1*). The basic data of the enrolled studies are

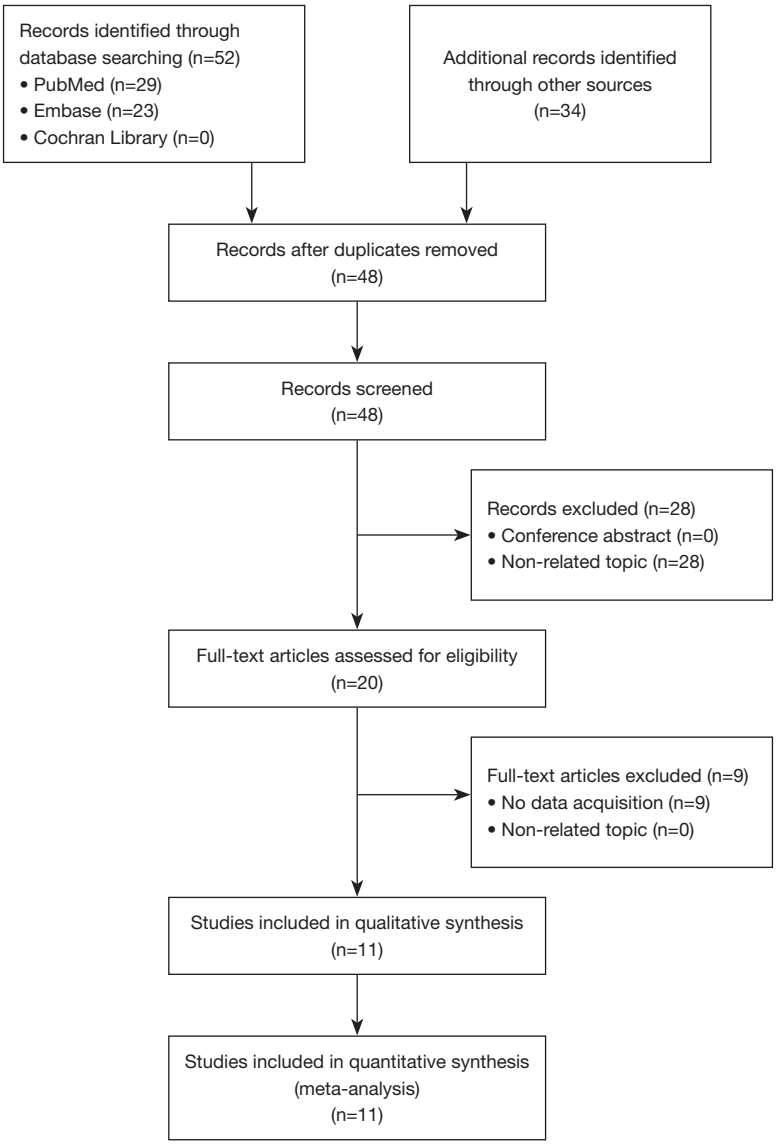

Figure 1 Flow diagram of the study selection.

shown in *Table 1*. All studies were published in China, and the publication years ranged from 2016 to 2021. Enrolled cases included gastric cancer (n=2), laryngeal squamous cell carcinoma (n=1), lung cancer (n=1), glioblastoma (n=1), breast cancer (n=1), ovarian cancer (n=1), renal cancer (n=1), melanoma (n=1), esophageal cancer (n=1), and pancreatic cancer (n=1). These studies enrolled a total of 2,876 cancer patients. The NOS scores of the included studies suggested relatively good quality, ranging from 7 to 8.

Association between LINC-PINT expression and overall survival (OS)

Eleven studies with a total of 2,876 cancer patients assessed a relationship between LINC-PINT expression and OS. The heterogeneity (I^2=44.86%, P=0.05) between the studies was moderate that the pooled HR was evaluated by the fixed effects model. The pooled HR was 0.72 (95% CI: 0.64–0.80, P<0.001), suggesting that LINC-PINT expression was

Table 1 Characteristics of studies enrolled in this meta-analysis

Study	Country	Cancer type	Case number (high/low)	Stage (case number)	Detection method	Cut-off value	Follow-up (months)	Survival outcome	Survival analysis	NOS
Yang *et al.* [2021] (14)	China	Laryngeal squamous cell carcinoma	15/15	I–II/III–IV (12/18)	RT-PCR	Median	40	OS	KM	7
Zhang *et al.* [2021] (6)	China	NSCLC	58/64	I–II/III–IV (56/66)	RT-PCR	NR	60	OS	KM, MVA	8
Zhu *et al.* [2021] (16)	China	Glioblastoma	338/338	NR	GEPIA database	NR	200	OS, DFS	KM	7
Chen *et al.* [2020] (8)	China	Breast cancer	535/535	NR	GEPIA database	NR	300	OS, DFS	KM	7
Hao *et al.* [2020] (10)	China	Ovarian cancer	20/52	I–II/III–IV (39/33)	RT-PCR	NR	120	OS	KM	7
Duan *et al.* [2019] (9)	China	CCRCC	41/41	I–II/III–IV (69/13)	RT-PCR	Median	60	OS, DFS	KM	7
Feng *et al.* [2019] (7)	China	Gastric cancer	33/39	I–II/III–IV (19/53)	RT-PCR	Using OriginLab software	60	OS	KM	7
Hong *et al.* [2019] (11)	China	Gastric cancer	38/40	NR	RT-PCR	Youden's index	60	OS	KM	7
Xu *et al.* [2019] (13)	China	Melanoma	138/138	NR	RT-PCR	NR	400	OS, DFS	KM	7
Zhang *et al.* [2019] (15)	China	Esophageal cancer	67/270	T1–T2/T3 (257/80)	RT-PCR	NR	40	OS	KM	7
Li *et al.* [2016] (12)	China	Pancreatic cancer	NR	I–II/III–IV (35/26)	RT-PCR	NR	60	OS	KM, MVA	8

High: high LINC-PINT expression; low: low LINC-PINT expression. CCRCC, clear cell renal cell carcinoma; DFS, disease-free survival; GEPIA, Gene Expression Profiling Interactive Analysis; KM, Kaplan-Meier; MVA, multivariate analysis; NR, no report; NOS, Newcastle-Ottawa Scale; NSCLC, non-small cell lung cancer; OS, overall survival; RT-PCR, reverse transcription polymerase chain reaction.

associated to favorable OS (*Figure 2*). In the subgroup analysis of cancer type and case number, the groups with non-digestive system cancer (HR =0.74, 95% CI: 0.66–0.83, P<0.001) and digestive system cancer (HR =0.61, 95% CI: 0.46–0.81, P=0.001), and the groups with case number <100 (HR =0.56, 95% CI: 0.40–0.79, P=0.001) and >100 (HR =0.74, 95% CI: 0.66–0.83, P<0.001) were statistically significant (*Table 2*, *Figure 3*).

Association between LINC-PINT expression and disease-free survival (DFS)

Four studies with a total of 2,104 cancer patients evaluated a relationship between LINC-PINT expression and DFS. The heterogeneity (I^2=14.52%, P=0.32) between the studies was low that the pooled HR was assessed by the fixed effects model. The pooled HR was 0.70 (95% CI: 0.60–0.82, P<0.001), implying that LINC-PINT expression was associated to favorable DFS (*Figure 4*).

Publication bias

Funnel plot with Egger's test was performed to know for publication bias. For OS, funnel plot showed slightly asymmetric appearance, but the Egger's test revealed that it was not statistically significant (P=0.14) (*Figure 5A*). For DFS, funnel test with Egger's test was not significant (P=0.34) (*Figure 5B*). The trim and fill methods were also evaluated. The pooled results were still significant for OS (HR =0.75, 95% CI: 0.67–0.83) and for DFS (HR =0.69, 95% CI: 0.59–0.81), showing that our initial pooled results were consistent (*Figure 6*).

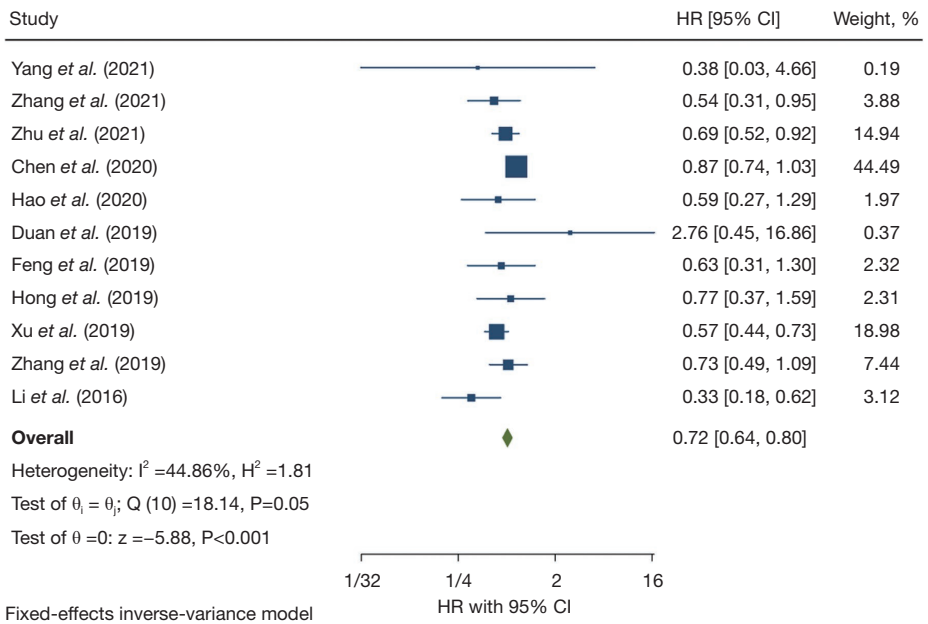

Figure 2 Forest plot of the association between LINC-PINT expression and overall survival. CI, confidence interval; HR, hazard ratio; LINC-PINT, long iatrogenic non-protein-coding RNA p53-induced transcript.

Table 2 Subgroup analysis of the association between LINC-PINT expression and overall survival in cancer patients

Subgroup	Number of studies	Number of patients	Pooled HR (95% CI)	P value	Heterogeneity	
					I^2 (%)	P value
Cancer type						
Non-digestive system cancer	7	2,328	0.74 (0.66–0.83)	<0.001	49.30	0.07
Digestive system cancer	4	548	0.61 (0.46–0.81)	0.001	38.07	0.18
Case number						
Less than 100	6	395	0.56 (0.40–0.79)	0.001	24.90	0.25
More than 100	5	2,481	0.74 (0.66–0.83)	<0.001	56.60	0.06

CI, confidence interval; HR, hazard ratio; LINC-PINT, long iatrogenic non-protein-coding RNA p53-induced transcript.

Sensitivity analysis

The sensitivity analysis was performed that the enrolled studies were omitted one by one to assess the effect of the studies. The results showed that the pooled HR was not significantly affected by any single study for OS (HR =0.72, 95% CI: 0.64–0.80, P<0.001) and for DFS (HR =0.70, 95% CI: 0.60–0.82, P<0.001) (*Figure 7*).

Discussion

LncRNAs, a subset of non-coding RNAs, are defined as transcripts >200 nucleotides in length, with no protein translating potential (17). Although they are not translated, lncRNAs have important functions in various biological processes, such as gene regulation and expression, chromatin dynamics, and cellular growth and differentiation (17). Recently, the aberrant function of lncRNAs was linked to many cancers and diseases (18).

LINC-PINT, a novel lncRNA, has been identified to be expressed in multiple cancers, and is believed to be related to the prognosis of cancer patients (6). For example, the expression of LINC-PINT was demonstrated

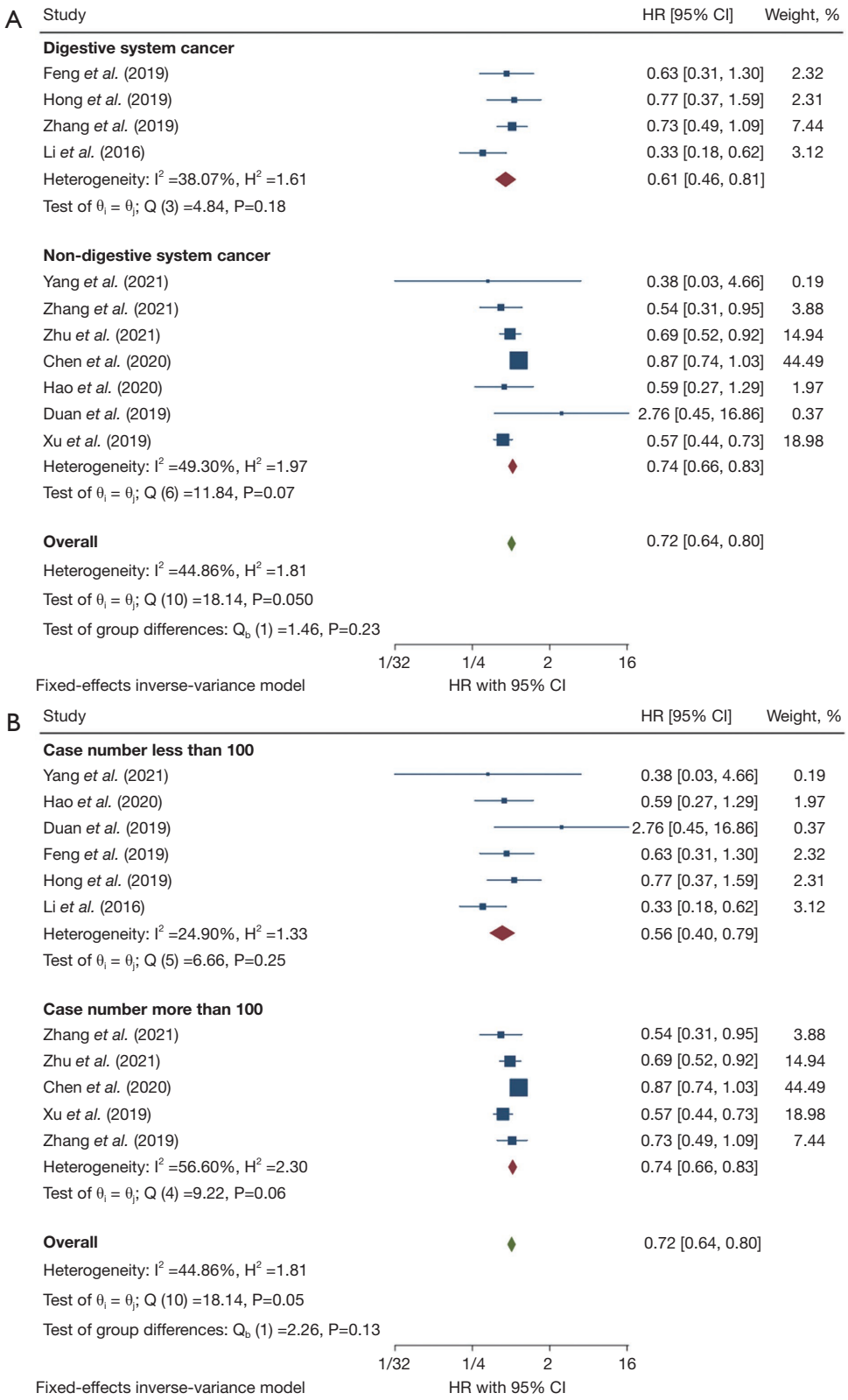

Figure 3 Forest plot of the association between LINC-PINT expression and overall survival stratified by cancer type (A) and case number (B). CI, confidence interval; HR, hazard ratio; LINC-PINT, long iatrogenic non-protein-coding RNA p53-induced transcript.

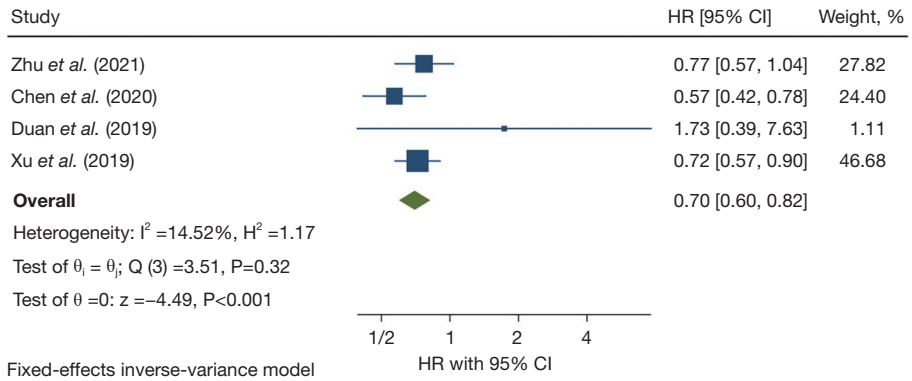

Figure 4 Forest plot of the association between LINC-PINT expression and disease-free survival. CI, confidence interval; HR, hazard ratio; LINC-PINT, long iatrogenic non-protein-coding RNA p53-induced transcript.

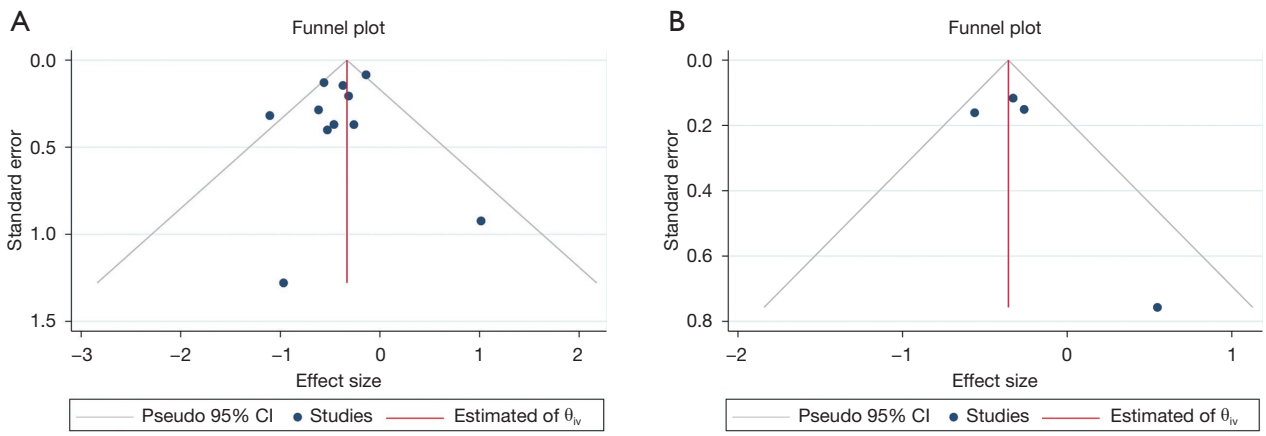

Figure 5 Funnel plot of the association between LINC-PINT expression with overall survival (A) and disease-free survival (B). CI, confidence interval.

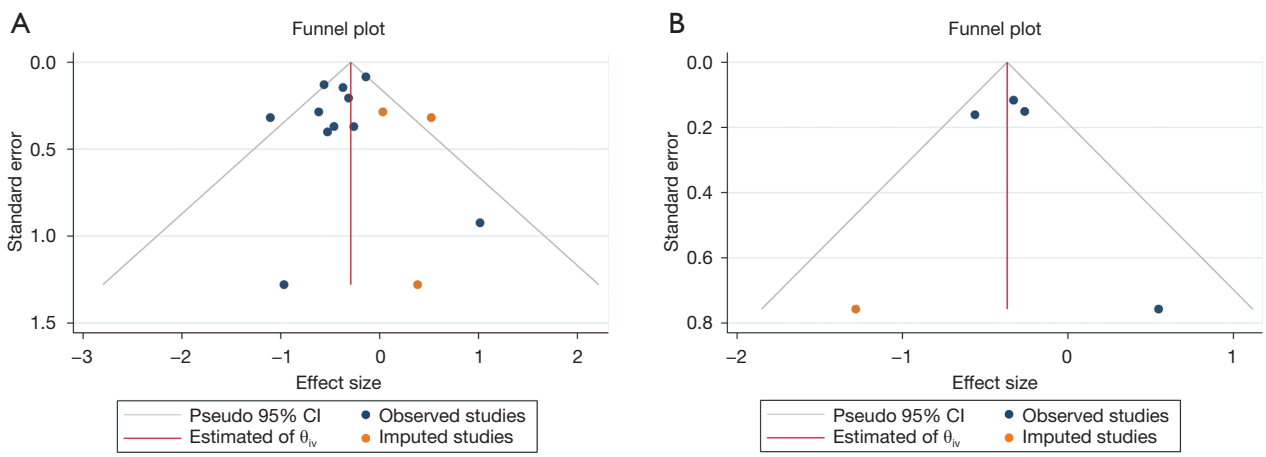

Figure 6 Trim and fill method of the association between LINC-PINT expression with overall survival (A) and disease-free survival (B). CI, confidence interval.

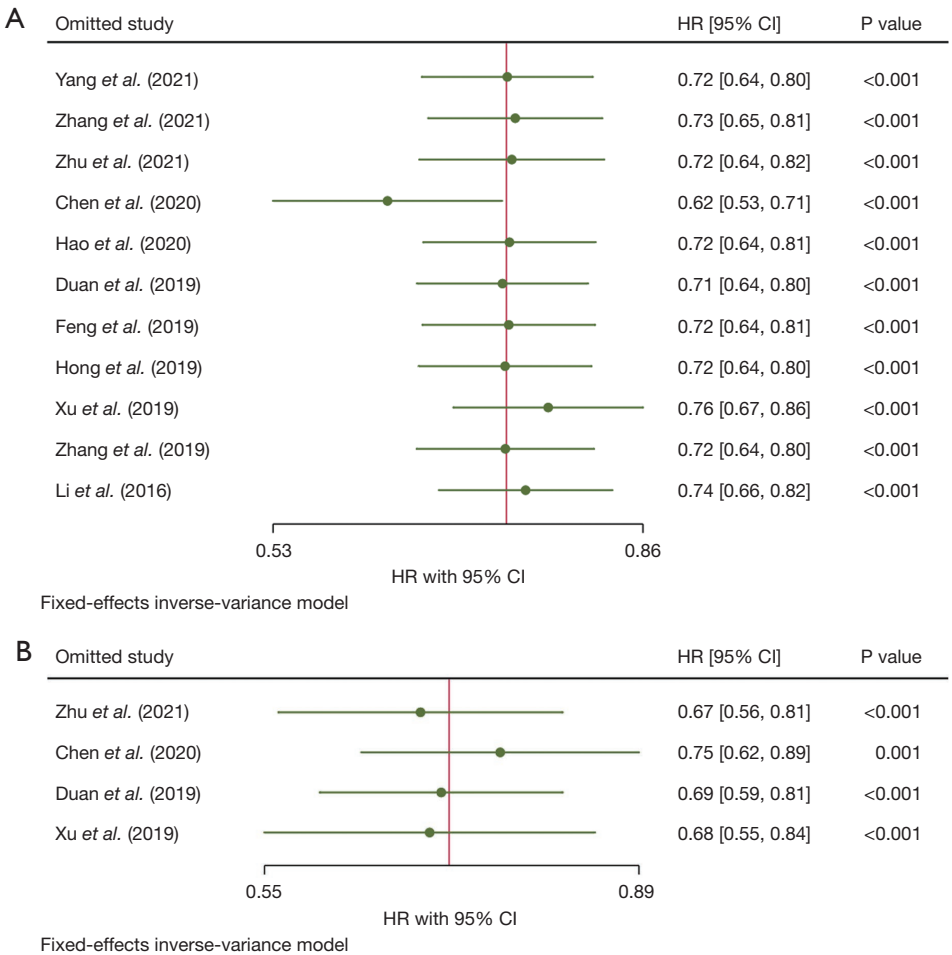

Figure 7 Sensitivity analysis of the association between LINC-PINT expression with overall survival (A) and disease-free survival (B). CI, confidence interval; HR, hazard ratio; LINC-PINT, long iatrogenic non-protein-coding RNA p53-induced transcript.

to suppress the malignant progression of cancer cells in non-small cell cancer (6), triple negative breast cancer (8), gastric cancer (7,11), ovarian cancer (10), pancreatic cancer (12), melanoma (13) and laryngeal squamous cell carcinoma (14) as well as esophageal cancer (15) and glioblastoma (16). LINC-PINT expression has also been associated with prognosis in lung, gastric, breast, ovarian, pancreatic, esophageal, laryngeal, renal, brain cancer, and melanoma (6-16).

In this study, we collected 11 related studies and conducted a meta-analysis. We reported the prognostic significance of LINC-PINT expression in cancer patients. We proved that LINC-PINT expression was significantly related to OS and DFS. Regarding the cancer type and case number, the results were statistically significant.

Most of the studies we collected showed that LINC-PINT expression was associated with favorable survival. Only one study (9) reported that high expression of LINC-PINT was significantly correlated with poor clinical outcomes in patients with clear cell renal cell carcinoma. They advocated that overexpression of LINC-PINT promoted cancer cell proliferation, induced cell cycle progression, and inhibited apoptosis (9). Therefore, we hope that future research will clarify the effects of LINC-PINT on cancer.

The study had some limitations. First, all studies were published in China. Therefore, these results may not be necessarily applicable to other regions. Second, cancer type and case number were small, which led to the inaccuracy of our results. Third, HRs with CIs were calculated by processing survival curves, thus the prognostic significance of LINC-PINT expression might be exaggerated.

Conclusions

In conclusion, this study is the first to demonstrate the prognostic significance of LINC-PINT expression in cancer patients. High expression of LINC-PINT is associated with favorable OS and DFS, and it may serve as a valuable prognostic marker in cancer patients.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-627/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-627/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-627/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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