

The prognostic value of long non-coding RNA PlncRNA-1 in patients with cancers: a systematic review and meta-analysis

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Abstract

Background

We performed this meta-analysis to elucidate whether the expression of PlncRNA-1 might serve as an effective prognostic marker for various cancers.

Methods

We conducted a database search of PubMed, ScienceDirect, Embase, Web of Science and CNKI database (up to Oct 31, 2019). The pooled hazard ratio (HR), odds ratio (OR) and 95% confidence interval (CI) were used to estimate the strength of the relationship between PlncRNA-1 expression and the clinical prognosis of cancer patients.

Results

The results showed that elevated PlncRNA-1 expression predicted a poor OS with pooled HRs of 1.43 (95% CI: 1.25-1.63, I² =63.1%, P=0.004). Likewise, we found that advanced tumour stages were associated with upregulated PlncRNA-1 expression in various cancer types (III-IV vs I-II: OR=2.79, 95% CI: 1.76-4.41, I² =0%, P=0.822), patients with high PlncRNA-1 expression might have an increased risk of large tumours (OR=2.03, 95% CI: 1.31-3.14, I² =67.1%, P=0.028).

Conclusions

PlncRNA-1 might be used as a prognostic biomarker and as a tool for the early detection of various tumours.

1. Background

Long non-coding RNAs (lncRNAs) are a group of transcribed RNAs longer than 200 nt, that cannot be translated into proteins[1, 2]. lncRNAs are being continually discovered by high-throughput sequencing[3, 4]. Emerging evidence has identified lncRNAs in various human tissues and has shown lncRNAs to play an important role in the occurrence and development of diseases[5–8]. For example, lncRNAs participate in tumorigenesis with oncogenic or tumour-suppressive effects by regulating gene expression at the transcriptional and post-transcriptional levels[9]. lncRNAs regulate gene expression in many ways, such as by interfering with the promoters of genes, inducing histone modification, chromatin reorganization, the regulation of subcellular localization and the production of endogenous siRNAs[10, 11]. The dysregulation of lncRNAs has been shown to be related to tumour formation, progression, invasion and metastasis in various types of cancer, such as breast cancer, colorectal cancer and ovarian cancer[12–14]. Some lncRNAs have been used as potential biomarkers for cancer diagnosis and as therapeutic and prognostic targets for cancer treatment[15, 16]. However, the majority of the biological functions of lncRNAs are still unknown.

Prostate Cancer-Upregulated Long Non-coding RNA 1 (PlncRNA-1), also referred to as CBR3 Antisense RNA 1 (CBR3-AS1), is located on 21q22.12. It consists of five exons and was first identified in prostate cancer. PlncRNA-1 is ubiquitously expressed in the prostate, salivary glands and 25 other tissues. It has been shown that PlncRNA-1 plays an important role in various cancer types, including prostate cancer, colorectal cancer, osteosarcoma, glioma and oesophageal squamous carcinoma[17–26]. Accumulating evidence has demonstrated that PlncRNA-1 acts as a transcriptional regulator to modify various developmental processes. For example, upregulated PlncRNA-1 expression can modulate apoptosis and proliferation and induce epithelial-mesenchymal transition[17–25]. More recently, a study reported that the overexpression of PlncRNA-1 predicted unfavourable prognosis and promoted tumorigenesis in osteosarcoma[22], suggesting that PlncRNA-1 may serve as a prognostic biomarker for patients with osteosarcoma. In these studies, PlncRNA-1 was identified as a prognostic biomarker in malignant tumour patients. However, due to limitations of small patient samples and discrete outcomes, the evidence to prove the relationship between PlncRNA-1 and cancers remains insufficient. Therefore, to elucidate whether the expression of PlncRNA-1 serves as an effective prognostic marker for various cancers, we performed this meta-analysis by comprehensively analysing all previously published data.

2. Methods

2.1 Literature retrieval strategy

The selected publications were identified by using up-to-date electronic databases, including PubMed, ScienceDirect, Embase, Web of Science and CNKI database. The literature search included all relevant studies published until Oct 31, 2019. The following key words were used in combination for the search: "PlncRNA-1", "CBR3-AS1", "lncRNA CBR3-AS1", and "cbr3-as1".

2.2 Selection criteria

The inclusion criteria were as follows: (1) PlncRNA-1 expression was assessed in human cancer tissues or blood. (2) According to the expression levels of PlncRNA-1, the patients were divided into low- and high- expression groups. (3) The hazard ratios (HRs) and 95% confidence intervals (CIs) for survival time were available or could be calculated from the survival curve.

The exclusion criteria were as follows: (1) studies without usable data; (2) duplicate publications; (3) studies with overlapping data; and (4) reviews, case reports, letters, and expert opinions.

2.3 Quality assessment

The assessment was performed by two authors, who had already reached an agreement on all items assessed. The quality of the papers was assessed as previously reported[27, 28]. Briefly, the assessment system consisted of four items: scientific design, laboratory methodology, generalizability and results analysis. Each part was scored as follows: 2 points (if it was clearly defined in the article), 1 point (if its description was incomplete or unclear) and 0 point (if it was not defined or was inadequate). The final quality score was calculated using the sum of the total points divided by 44 and multiplied by 100. Half of the investigated studies defined 85% of the quality score as the cut-off point. Higher scores represented high methodological quality. The work was reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.4 Data extraction

Two investigators independently extracted data from the included studies. Any problems were discussed between them. If these problems could not be overcome, a third investigator was consulted. For each eligible study, the following information was extracted: first author, year of publication, cancer type, sample size, PlncRNA-1 detection method, number of low-PlncRNA-1-expression groups and high-PlncRNA-1-expression groups, tumour stage, cut-off value, follow-up duration, and results of multivariate or univariate analyses, HR with the corresponding 95% CI for overall survival (OS) and HR retrieval method. The HRs were extracted by two methods. In method 1, the HRs were obtained directly from the corresponding articles. In method 2, the HRs were extracted from Kaplan–Meier curves[27].

2.5 Statistical analysis

The extracted data were analysed with STATA software version 12.0 (STATA Corporation, College Station, TX, USA). HRs with 95% CIs were used to estimate the strength of the relationship between PlncRNA-1 and the clinical prognosis of cancer patients. In this meta-analysis, some HRs and their 95% CIs could not be extracted directly from original texts; thus, we calculated HRs with Kaplan–Meier curves using Engauge Digitizer version 4.1. Other HRs and their 95% CIs were collected from eligible articles. In this study, the heterogeneity among the included studies was quantified by the chi-squared test and I^2 statistics[29]. If $I^2 > 50\%$ or $P < 0.1$, a random-effects model was applied (it indicated strong heterogeneity across studies). If $P > 0.1$ and $I^2 < 50\%$, a fixed-effects model was applied (it indicated nonsignificant heterogeneity among studies). Subgroup analyses were carried out according to cancer type, quality score, sample size, HR estimation method and follow-up duration. Begg's funnel plots were employed to evaluate the publication bias. A Galbraith radial plot was used to illustrate the sources of heterogeneity across the studies. As usual, $P < 0.05$ was considered statistically significant.

3. Results

3.1 Study characteristics

A total of seven studies and 829 patients were finally included in the meta-analysis based on the screening criteria. The mean patient sample size was 118 (range 70–318). The flowchart of the meticulous process of study retrieval is shown in Fig1 (PRISMA 2009 Flow Diagram). The published period of eligible studies ranged from 2016 to 2019, suggesting that the prognostic value of PlncRNA-1 is a novel field of research. Among the seven articles, six studies were from China, while the other study was from Iran. In this meta-analysis, patients with eight types of cancer were enrolled, including digestive system malignancies (colorectal cancer, hepatocellular carcinoma and gastric cancer), neurologic system tumours (glioma and glioblastoma multiforme) and other system carcinomas (osteosarcoma, breast cancer, and lung adenocarcinoma). According to PlncRNA-1 expression, the patients were divided into two groups, namely, high- and low-PlncRNA-1-expression groups. The main features of and data from the eligible studies are summarized in Table1.

3.2 Association between PlncRNA-1 expression and OS

A total of seven studies assessed the HRs for OS. In three studies (Dong 2016, Zhang 2018 and Song 2019), HRs were obtained directly from their corresponding articles (method 1), while HRs were extracted using method 2 in the remaining four studies (Wang 2018, Song 2017, Zohreh 2017 and Xu 2019). The results showed that elevated PlncRNA-1 expression predicted a poor outcome for OS (HR = 1.43, 95% CI: 1.25–1.63). However, there was significant heterogeneity across studies ($\chi^2 = 24.39$, $df = 9$, $P = 0.004$; $I^2 = 63.1\%$) (Fig2). Therefore, a random-effects model was employed to pool the association of PlncRNA-1 expression with OS across multiple malignancies.

Subgroup analyses were performed on the basis of the HR estimation method, cancer type, sample size, quality of the paper and follow-up duration. The results are summarized in Table2.

The subgroup analysis based on the HR estimation method showed a significant difference between the two methods (method 1: HR = 2.49, 95% CI: 1.83–3.38; method 2: HR = 1.28, 95% CI: 1.05–1.56), with no significant heterogeneity (method 1: $I^2 = 0\%$, $P = 0.634$; method 2: $I^2 = 23.3\%$, $P = 0.251$) (Fig3a).

For the subgroups based on cancer type, we classified all tumours into two categories (digestive system malignancies and other system malignancies). The results showed that there was a significant association between poor OS and digestive system malignancies (HR = 2.28, 95% CI: 1.50–3.45), with no significant heterogeneity ($I^2 = 7.5\%$, $P = 0.356$), while there was high heterogeneity ($I^2 = 66.7\%$, $P = 0.010$) in other system malignancies (HR = 1.47, 95% CI: 1.10–1.95) (Fig3b).

In the subgroups analysed by sample size, PlncRNA-1 was found to be obviously correlated with patient survival in studies with sample size ≤ 100 (HR = 1.71, 95% CI: 1.12–2.63) and ≥ 100 (HR = 1.68, 95% CI: 1.11–2.55), with significant heterogeneity (sample size ≤ 100 : $I^2 = 59.5\%$, $P = 0.060$; sample size ≥ 100 : $I^2 = 70.4\%$, $P = 0.005$) (Fig3c).

Next, we evaluated the relationship between the quality of the selected paper in the studies and OS. We found that the scores did not influence the result of the estimated HR (score $\geq 85\%$: HR = 2.00, 95% CI: 1.24–3.23, $I^2 = 79.4\%$, $P = 0.002$; score $< 85\%$: HR = 1.36, 95% CI: 1.00–1.86, $I^2 = 36.0\%$, $P = 0.167$) (Fig3d).

Finally, the subgroup analysis based on follow-up duration revealed that there was a significant association between poor OS and follow-up duration ≥ 60 months (HR = 1.76, 95% CI: 1.29–2.39), with obvious heterogeneity ($I^2 = 66.0\%$, $P = 0.004$), while follow-up duration ≤ 60 months displayed no statistically significant association (HR = 1.46, 95% CI: 0.62–3.41) (Fig3e).

3.3 Association between PlncRNA-1 expression and tumour stage

In this study, five studies (a total of 688 cancer patients) investigated the correlation between PlncRNA-1 expression and tumour stage. These studies focused on colorectal cancer, hepatocellular carcinoma, osteosarcoma, and gastric cancer. There was no significant association between tumour stage and PlncRNA-1 expression (III–IV vs I–II: OR = 1.29, 95% CI: 0.94–1.78, $I^2 = 83.4\%$, $P = 0.000$) (Fig4a). Next, we carried out a sensitivity analysis of heterogeneity. When we omitted the study by Zohreh et al, the result and heterogeneity across studies was markedly changed (III–IV vs I–II: OR = 2.79, 95% CI: 1.76–4.41, $I^2 = 0\%$, $P = 0.822$) (Fig4b). This finding suggested that the study by Zohreh et al was the cause of high heterogeneity. Therefore, the results revealed a significant correlation between PlncRNA-1 expression and advanced tumour stage.

3.4 Association between PlncRNA-1 expression and tumour size

Four studies with a total of 370 patients were used to estimate the correlations between PlncRNA-1 expression levels and tumour size. A strong relationship was observed between high PlncRNA-1 expression and large tumours with high heterogeneity (OR = 2.03, 95% CI: 1.31–3.14, $I^2 = 67.1\%$, $P = 0.028$) (Fig5). Therefore, the result also showed that patients with high PlncRNA-1 expression might have an elevated risk of large tumours.

3.5 Sensitivity analysis and publication bias

We conducted sensitivity analyses to investigate the reliability of our pooled estimates by omitting one study at a time. The results showed that the pooled HRs of OS were reliable, regardless of which study was excluded, and the significance of the HRs did not change (Fig6). To illustrate the sources of heterogeneity across the studies, we employed a Galbraith radial plot. As shown in Fig7, the study by Zhang et al played an important role in the generation of significant heterogeneity.

Begg's funnel plot was used to evaluate the potential bias across the studies. The shape of the funnel plot showed no obvious publication bias for the HR assessments of OS ($P = 0.074$) (Fig8).

4. Discussion

Accumulating evidence has demonstrated that abnormal expression of lncRNAs plays an important role in the development and progression of tumours[30, 31]. lncRNAs have become a hot topic as diagnostic markers of diseases. The transcriptional level of PlncRNA-1 is significantly elevated in multiple malignancies, and PlncRNA-1 acts as a transcriptional regulator of various developmental processes[17–25]. In several human tumours, overexpression of PlncRNA-1 is related to poor OS, high TNM classification, advanced clinical stage, low histological differentiation, and poor vital status[20, 22, 24, 32–34]. The present meta-analysis was conducted to clarify the prognostic value of PlncRNA-1 expression in all cancer types and to examine its correlation with the main clinicopathological characteristics.

A total of 7 studies with 829 patients were finally included in this meta-analysis. Consistently, combining HRs from Cox multivariate and univariate analyses demonstrated shorter OS in the high-PlncRNA-1-expression group compared to those with low-PlncRNA-1-expression group. Subgroup analyses showed that the association between PlncRNA-1 expression and OS existed across all subgroups. Moreover, the pooled data illustrated that PlncRNA-1 expression was also remarkably correlated with tumour stage and tumour size in these patients. All results suggested that high levels of PlncRNA-1 were related to poor OS in cancer patients. Therefore, PlncRNA-1 can be used as a prognostic biomarker in malignant tumour patients.

At present, the function and role of PlncRNA-1 in the occurrence and development of cancer have been extensively investigated. Although researchers have not stopped exploring, the underlying mechanism of the effect of PlncRNA-1 overexpression on poor outcomes remains unknown. PlncRNA-1 was first identified in prostate cancer. Cui et al reported that the reciprocal regulation of PlncRNA-1 and AR contributed to prostate cancer pathogenesis[18]. This conclusion was consistent with the results of another study showing that PlncRNA-1 could regulate a feed-forward loop (PlncRNA-1 protected AR from microRNA-mediated inhibition by sponging AR-targeting microRNAs) to contribute to the development of prostate cancer[21]. Yang et al investigated the function of PlncRNA-1 and discovered that PlncRNA-1 could regulate the cell cycle and cyclinD1 levels and could also affect apoptosis and proliferation in prostate cancer cells through the Her-2 pathway[19]. Song et al demonstrated that PlncRNA-1 promoted colorectal cancer cell progression by regulating the PI3K/Akt signalling pathway[20]. Another study noted that the upregulation of PlncRNA-1 indicated poor prognosis and promoted glioma progression by activating the Notch signalling pathway[24]. In this meta-analysis, as shown in Table3, we systematically analysed data regarding PlncRNA-1 and its potential targets, related microRNAs and pathways to provide a reference for exploring its mechanism in cancer and targeted therapy.

Although we tried our best to conduct a comprehensive study, this meta-analysis still has many limitations. First, some of the HRs were calculated indirectly by reconstructing Kaplan–Meier survival curves rather than being extracted directly from the corresponding articles. This may have resulted in bias and heterogeneity. Second, the conclusion may be weak due to the relatively small number of included studies and sample size. Third, PlncRNA–1 might display different biological functions in different malignant tumours, and due to the limited number of included articles, we could not pool the results according to a single type of tumour. Although we performed subgroup analyses, heterogeneity was still unavoidable. Fifth, the majority of the included studies were from Asia which might reduce the applicability of the results across different ethnicities. In addition, the tendencies of positive outcomes in the publications might give rise to potential selection and publication bias.

5. Conclusions

In summary, this meta-analysis revealed that high expression of lncRNA PlncRNA–1 represents a significant risk factor for survival outcomes in the development of tumours in patients with different types of cancer and could develop as an independent factor for predicting the prognosis of cancer patients.

Abbreviations

HR: hazard ratio

OR: odds ratio

CI: confidence interval

OS: overall survival

lncRNA: long non-coding RNA

PlncRNA–1: Prostate Cancer-Upregulated Long Non-coding RNA 1

CBR3-AS1: CBR3 Antisense RNA 1

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Guarantor of integrity of entire study: HJ Yang

Study concepts and design: HJ Yang, LJ Lei

Literature research: LJ Lei, LB Sheng

Data acquisition and analysis: LJ Lei, LY Wu, JJ Liu

Statistical analysis: LJ Lei, B Wei, S Liu

Manuscript preparation: LJ Lei, LB Sheng, ZW Xue

Manuscript revision: HJ Yang

Manuscript final version approval: HJ Yang, LJ Lei

All authors read and approved the final manuscript.

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Not applicable

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Tables

Table1. Characteristics of PlncRNA-1 studies included in the meta-analysis

Study [year]	Region	Tumor type	No.of patients	Tumor stage	Laboratory method	PT	SO	Cut-off value	M	Survival analysis	P value	Follow-up (month)	Quality score(%)
Wang et.al 2018	China	glioma	104	I-II	qRT-PCR	NO	OS,PFS	Median	2	Univariate	0.009	36	82
Zohreh 2017	Iran	gastric cancer	318	I-II	qRT-PCR	NA	OS	Median	2	Univariate	0.778	67	84
Zohreh 2017	Iran	breast invasive carcinoma	318	I-II	qRT-PCR	NA	OS	Median	2	Univariate	0.002	200	84
Zohreh 2017	Iran	glioblastoma multiforme	318	I-II	qRT-PCR	NA	OS	Median	2	Univariate	0.039	50	84
Zohreh 2017	Iran	lung adenocarcinoma	318	I-II	qRT-PCR	NA	OS	Median	2	Univariate	0.005	100	84
Song et.al 2017	China	colorectal cancer	77	I-II	qRT-PCR	NO	OS	Mean	2	Univariate	P=0.05	60	82
Dong et.al 2016	China	hepatocellular carcinoma	84	I-II	qRT-PCR	NO	OS	Mean	1	Univariate Multivariate	P=0.001	60	98
Zhang et.al 2018	China	osteosarcoma	132	I-II	qRT-PCR	NO	OS	Median	1	Univariate Multivariate	P=0.001	72	96
Song et.al 2019	China	colorectal cancer	77	I-II	qRT-PCR	NO	OS	Median	1	Univariate	0.0020	120	97
Xu et.al 2019	China	breast cancer	70	I-II	qRT-PCR	NA	OS	Median	2	Univariate	0.0415	80	96

M=method (1=HRs obtained directly from publications,2=HRs extracted from Kaplan–Meier curves); NA, not available; OS, overall survival; PFS, progression-free survival; PT, preoperative treatment; SO, survival outcome.

Table2. Results of subgroup analysis of pooled HRs for OS

Subgroup analysis	No. of studies	No. of patients	Pooled HR (95% CI)	Heterogeneity	
				I ² (%)	P-value
Total	7	829	1.43(1.25-1.63)	63.1	0.004
HR estimation method					
Method1	3	293	2.49(1.83-3.38)	0	0.634
Method2	4	536	1.28(1.05-1.56)	23.3	0.251
cancer type					
digestive system malignancies	4	523	2.28(1.50-3.45)	7.5	0.356
other system malignancies	4	591	1.47(1.10-1.95)	66.7	0.010
sample size					
<100	4	308	1.71(1.12-2.63)	59.5	0.060
≥100	3	521	1.68(1.11-2.55)	70.4	0.005
the quality of the selected paper					
score ≥85%	4	363	2.00(1.24-3.23) 2.49(1.83-3.38) 2.49(1.83-3.38)	79.4	0.002
score <85%	3	466	1.36(1.00-1.86)	36.0	0.167
follow-up duration (month)					
≥60	6	725	1.76(1.29-2.39)	66.0	0.004
<60	2	389	1.46(0.62-3.41)	52.9	0.145

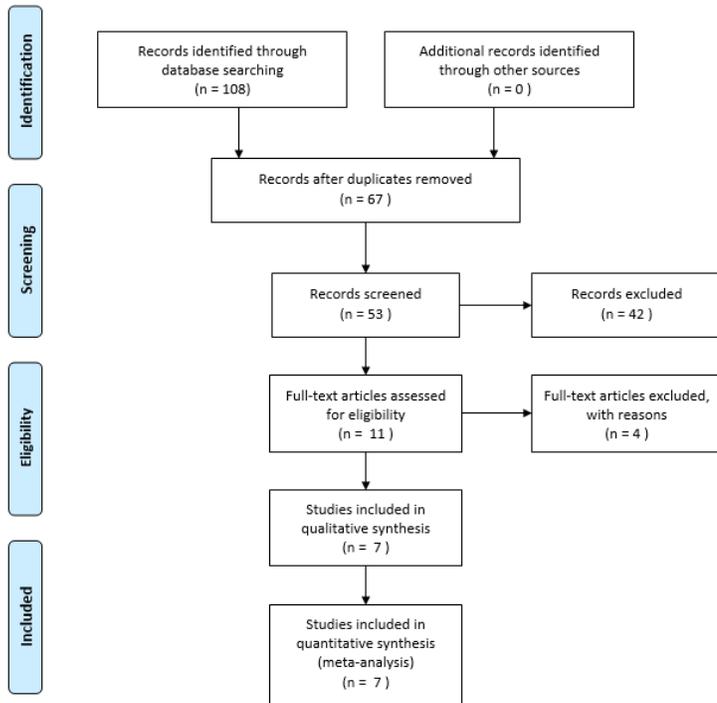
Table3. Summary of PlncRNA-1 with their potential targets, pathways and related microRNAs

Potential targets	Pathways	Related microRNAs	Cancer type	Reference
PI3K,Akt	PI3K/Akt	NA	colorectal cancer	[15]
MMP9	Wnt/β-catenin	miR-204	colorectal cancer	[18]
Notch-1, Jag-1, Hes-1	Notch	NA	glioma	[19]
NA	EMT signaling	NA	hepatocellular carcinoma	[21]
CyclinD1,N-Cadherin,E-cadherin	TGF-β1	NA	prostate cancer	[12]
AR	AR-signaling	NA	prostate cancer	[13]
Her-2, cyclinD1	Her-2	NA	prostate cancer	[14]
AR	NA	miR-34c ,miR-297	prostate cancer	[16]

Figures



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Figure 1

PRISMA 2009 Flow Diagram

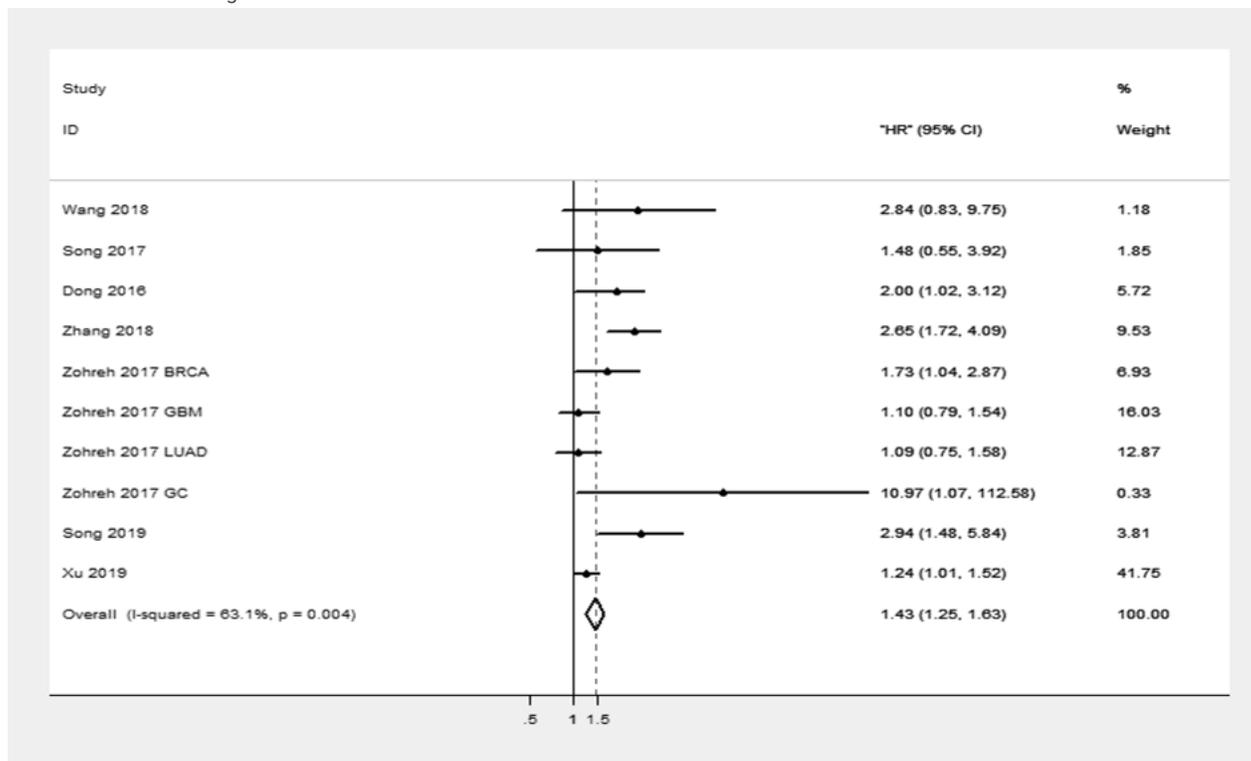


Figure 2

Forest plot showing association between overall survival (OS) and elevated PlncRNA-1 expression in cancer patients GC: gastric cancer, BRCA: breast invasive carcinoma, LUAD: lung adenocarcinoma, GBM: glioblastoma multiforme.

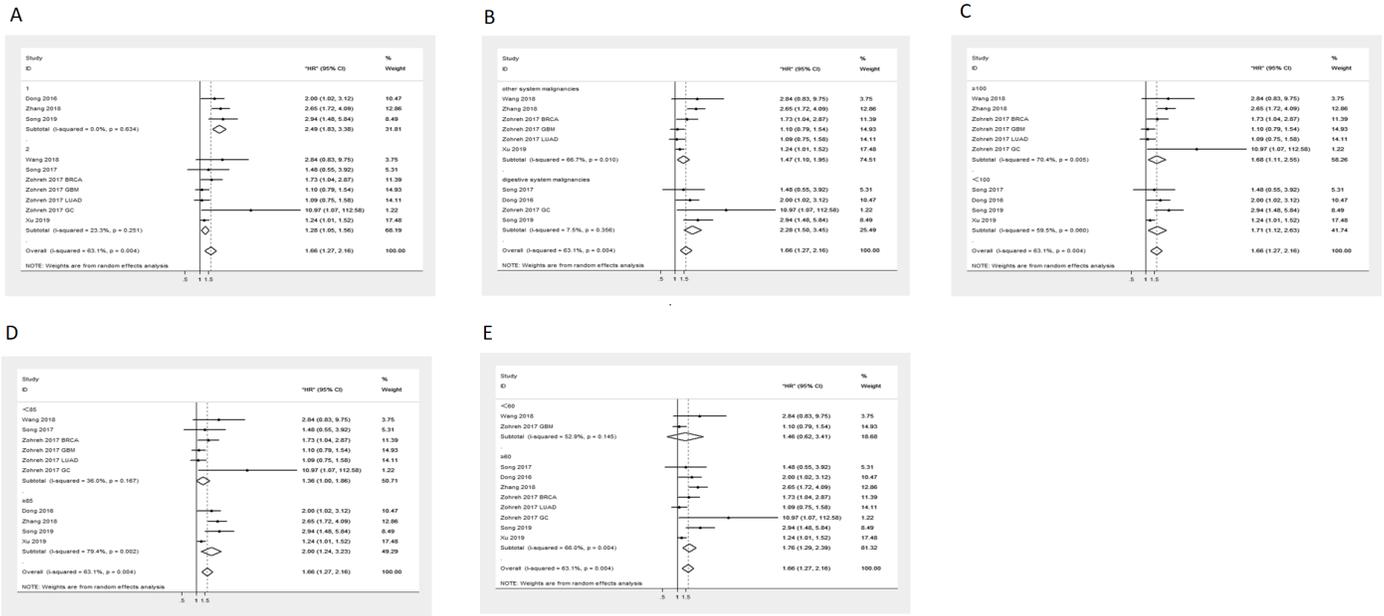
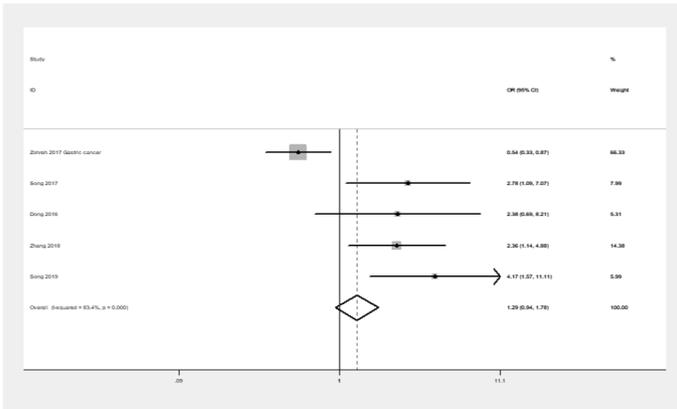


Figure 3

Forest plot showing the subgroup analyses of the pooled HRs with elevated PlncRNA-1 expression in the different types of cancer. Values of P and I2 and the HRs with their 95% CI of overall survival (OS) were analysed by the factors of HR estimation method(a), cancer type(b), sample size(c), the quality of the paper(d) and follow-up duration(e) a: 1=method1, 2=method2.

A



B

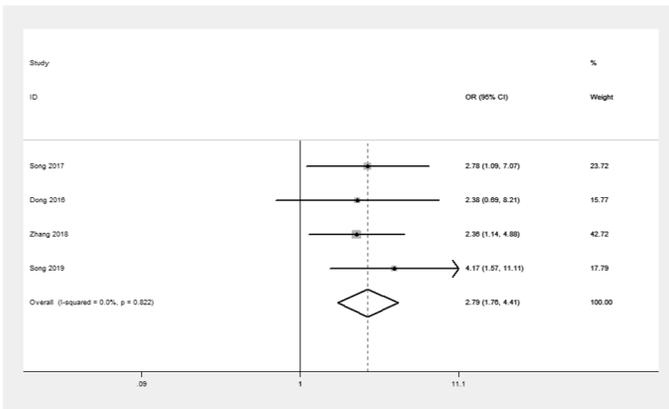


Figure 4

Forest plot showing association between PlncRNA-1 expression and tumour stage (a) all of the four eligible studies, (b) omitted the study by Zohreh et al

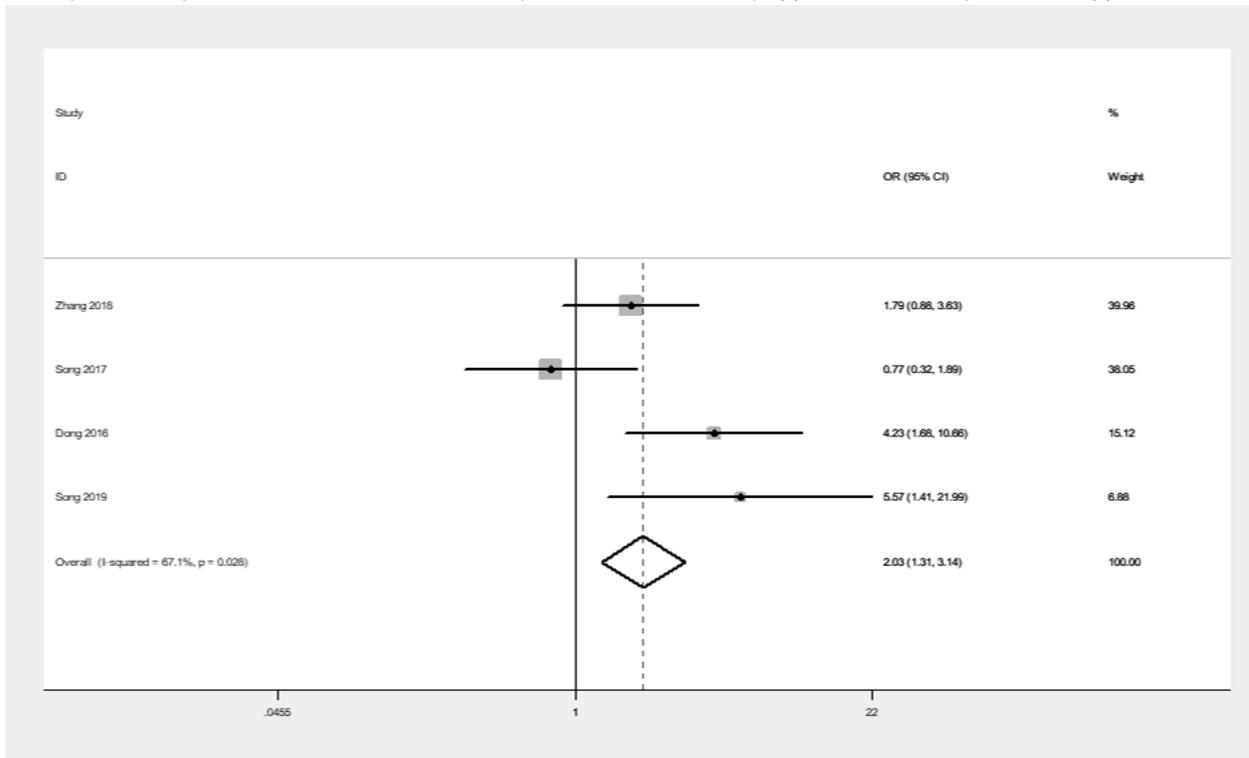


Figure 5

Forest plot showing association between PlncRNA-1 expression and tumour size.

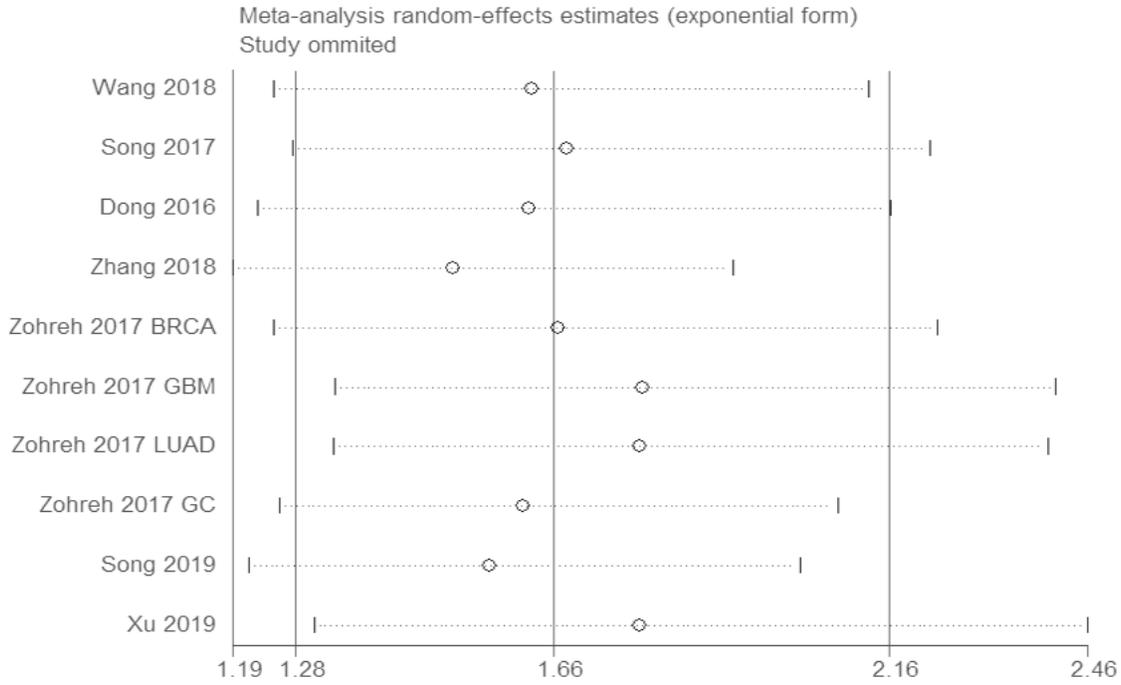


Figure 6

Sensitivity analysis of the effect of the individual study on the pooled HRs for the correlation between PlncRNA-1 expression and overall survival (OS)

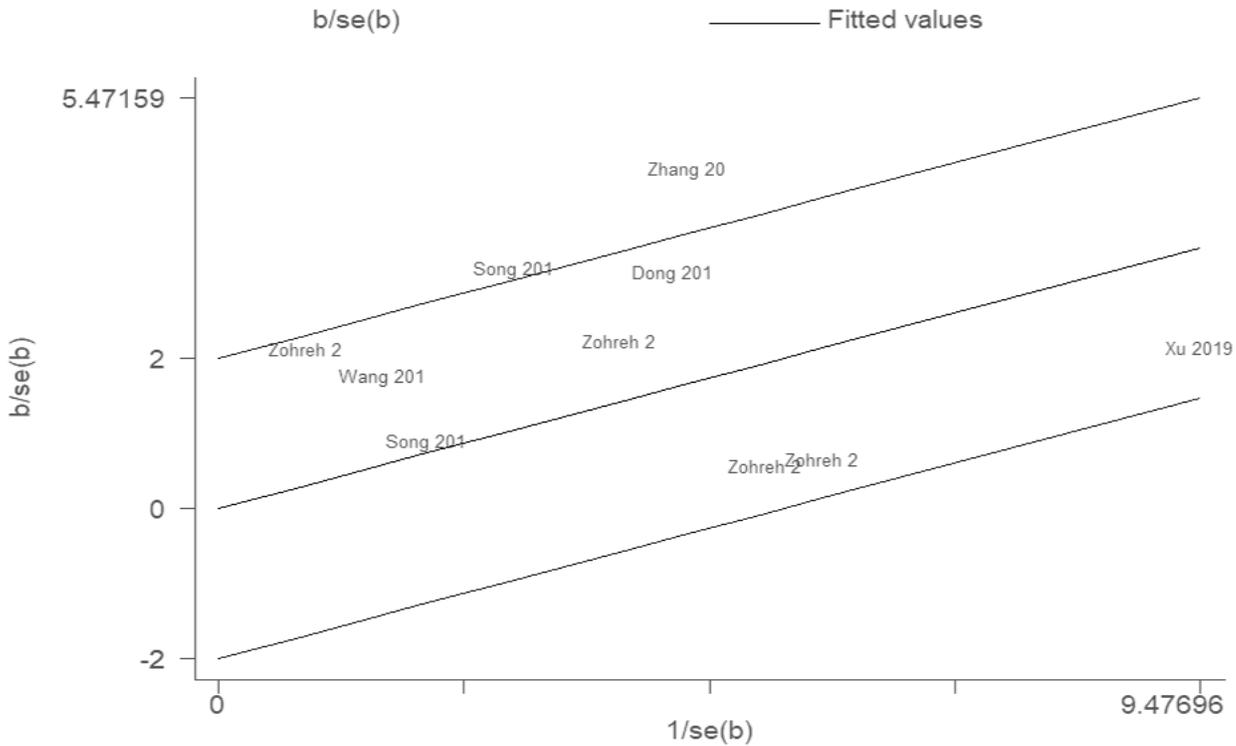


Figure 7

Galbraith radial plot analysis to illustrate the sources of heterogeneity across the studies

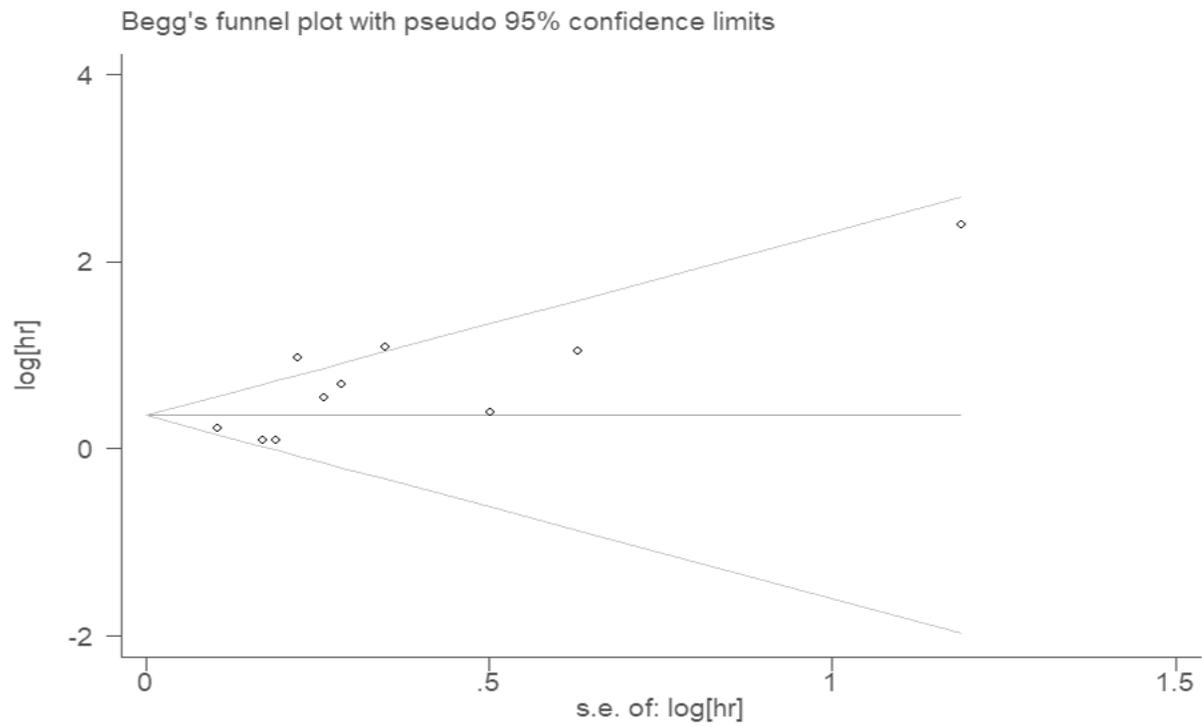


Figure 8

Begg's funnel plot of publication bias

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2009checklist.doc](#)