

The prognostic value of long noncoding RNA activated by TGF- β in digestive system cancers

A meta-analysis

Houyu Duan, MD , Xiang Ding, MD, Hesheng Luo, MD*

Abstract

Background: To systematically evaluate whether the expression level of long non-coding RNA activated by transforming growth factor- β (lncRNA-ATB) is correlated with the prognosis of digestive system cancer (DSC) patients.

Methods: PubMed, Embase, Cochrane Library, Web of Science, Springerlink, Nature, and Karger databases were searched up to April 20, 2019 by 2 experienced researchers independently. The quality of studies was assessed with the Newcastle-Ottawa scale. The Review Manager 5.2 and STATA 12.0 software were used for this meta-analysis.

Result: Eleven studies with 1227 DSC patients were included in the meta-analysis. Except for pancreatic cancer, high expression of lncRNA-ATB was associated with lymph node metastasis (risk ratio (RR) = 1.26, 95% confidence interval (CI): 1.12–1.42, $P < .001$), advanced clinical staging (RR = 1.44, 95%CI: 1.23–1.69, $P < .001$), reduced overall survival rate (OS) (hazard ratio (HR) = 2.33, 95% CI: 1.22–4.50, $P = .01$), and recurrence-free survival (RFS) (HR = 2.61, 95%CI: 1.46–4.65, $P = .001$) compared with low lncRNA-ATB expression in DSCs.

Conclusions: High expression of lncRNA-ATB was significantly correlated with poor prognosis for most DSCs. The expression level of lncRNA-ATB could be a promising prognostic biomarker for DSC patients.

Abbreviations: AKT = protein kinase B, BC = breast cancer, BC¹ = bladder cancer, CC = colon cancer, CC¹ = cervical cancer, CDH1 = cadherin 1, ceRNA = competing endogenous RNA, CIs = confidence intervals, CRCs = colorectal cancers, DFS = disease-free survival, DM = distant metastasis, DSCs = digestive system cancers, EC = endometrial cancer, EMT = epithelial-mesenchymal transition, ERK = extracellular regulated protein kinases, ESCC = esophageal squamous cell carcinoma, GAPDH = glyceraldehyde 3-phosphate dehydrogenase, GCs = gastric cancers, GIC = gastrointestinal cancer, GUSB = β -glucuronidase, HCC = hepatocellular carcinoma, HRs = hazard ratios, IL-11 = interleukin-11, ITGA6 = integrin α 6, KRAS = Kirsten rat sarcoma viral oncogene homolog, lncRNA-ATB = lncRNA activated by transforming growth factor β , lncRNAs = long noncoding RNAs, LNM = lymph node metastasis, miRNAs = microRNAs, mTOR = mammalian target of rapamycin, ncRNAs = noncoding RNAs, NOS = Newcastle-Ottawa scale, NSCLC = Non-small cell lung cancer, OS = overall survival, PC = prostate carcinoma, PCNA = proliferating cell nuclear antigen, P-H3 = phosphorylated histone H3, PI3K = phosphoinositide 3 kinase, piRNAs = piwi-associated RNAs, PRCs = pancreatic cancers, PTC = papillary thyroid cancer, RCC = renal cell carcinoma, RFS = recurrence-free survival, rRNAs = ribosomal RNAs, RRs = risk ratios, RT-qPCR = quantitative reverse transcription-polymerase chain reaction, siRNAs = small interfering RNAs, snoRNAs = small nucleolar RNAs, snRNAs = small nuclear RNAs, STAT3 = signal transducer and activator of transcription 3, TGF = transforming growth factor, tRNAs = transfer RNAs, ZEB1 = zinc-finger E-box binding homeobox 1, ZEB2 = zinc-finger E-box binding homeobox 2, ZNF-217 = zinc finger protein 217.

Keywords: cancer, digestive system, lncRNA-ATB, meta-analysis, prognosis

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1. Introduction

Digestive system cancers (DSCs) are the most common malignancies, accounting for nearly 30% of all cancers. According to GLOBOCAN 2018, DSCs accounted for 4.76 million newly diagnosed cases and 3.39 million deaths in the year 2018, which comprise a higher proportion than cancers in other systems.^[1] Based on data from the report, colorectal cancers (CRCs), gastric cancers (GCs), liver cancers, esophageal cancers, and pancreatic cancers (PRCs) were the top 5 DSCs respectively in morbidity as well as mortality rates.^[1] Many advanced diagnostic and treatment modalities have been investigated recently, but the 5-year survival rate has not improved. Surgical resection, radiotherapy, chemotherapy, and other supportive treatments are the mainstream treatments for DSCs; however neither their therapeutic effects nor the patient prognosis is completely satisfactory. Due to the lack of sufficient sensitivity and specificity amongst the currently available cancer biomarkers, researchers are searching for new molecular markers that will help in the early diagnosis and prediction of the prognosis of

DSCs in clinical practice. As demonstrated by the human genome project,^[2] the majority of genome sequences are transcribed into a category of RNA transcripts that lack the potential for protein coding and are therefore called noncoding RNAs (ncRNAs). ncRNAs are divided into housekeeping ncRNAs and regulatory ncRNAs.^[3,4] Housekeeping ncRNAs include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), which are usually constitutively expressed.^[3] Short regulatory ncRNAs (<200 nt) primarily consist of microRNAs (miRNAs), small interfering RNAs (siRNAs), and piwi-associated RNAs (piRNAs).^[4] Long noncoding RNAs (lncRNAs) belong to a larger group of regulatory ncRNAs and are generally classified as 200 nt-100 kb long transcripts. They are a relatively well-characterized class of ncRNA molecules, which are further involved in the regulation of various cell processes, including transcription, intracellular trafficking, and chromosome remodeling.^[5,6] lncRNAs comprise more than 80% of all genome transcripts and were considered “noise” in the past.^[7,8] However, the associations between lncRNAs and malignancies have received more attention from researchers in recent years. Recent evidence demonstrated that lncRNAs play an important role in the processes of proliferation, invasion, and metastasis in different types of cancers.^[9–11] Among cancer-related lncRNAs, the lncRNA-AL589182.3 (ENST00000493038) activated by the transforming growth factor (TGF) β (lncRNA-ATB) was first identified by Yuan et al^[12] in 2014. This lncRNA was found to induce epithelial-mesenchymal transition (EMT) and promote the invasion of cancer cells through the signaling pathway for TGF- β /miR-200s/ZEB in hepatocellular carcinoma (HCC). lncRNA-ATB contains 2446 nucleotides and is located on human chromosome 14. Subsequent studies confirmed that lncRNA-ATB was abnormally expressed in DSCs,^[13–22] central nervous system cancers,^[23] urinary system cancers,^[24,25] female reproductive system cancers,^[26,27] and other system cancers.^[28] In addition, the high expression of lncRNA-ATB was further demonstrated to be associated with aggressive clinicopathological features and poor prognosis in patients with DSCs.^[13,15–22] As single-center studies with small sample sizes and discrete outcomes will not provide a clear outcome and conclusion, systematic analysis should be performed to obtain better insight about the role of lncRNA-ATB in the prognosis of DSC patients. However, to the best of our knowledge, no systematic analysis evaluating the prognostic value of lncRNA-ATB in DSC patients has been reported to date. Therefore, the aim and objective of this meta-analysis was to assess the association between the lncRNA-ATB expression level and the clinicopathological features in DSC patients, and further, to evaluate the prognostic significance. Additionally, the molecular mechanisms of lncRNA-ATB in DSCs and other system cancers were also comprehensively summarized. The results of the present study suggest that the expression level of lncRNA-ATB is associated with the clinical outcomes of patients with DSC and is worth recommending as a prognostic biomarker for DSCs.

2. Material and methods

2.1. Literature search strategy

A systematic search was performed in PubMed, Embase, Cochrane Library, Web of Science, Springerlink, Nature, and Karger databases to assess studies that investigated the associa-

tion between the expression of lncRNA-ATB and prognosis in DSC patients. All studies published up to April 20th 2019 in the English language were included in the search. In order to increase the search's sensitivity, a strategy of combing the MeSH terms and free-text words was used in accordance with the Cochrane systematic evaluation manual 5.1. Cross references of some included studies were also evaluated to acquire information ignored at the beginning of the screening process. In the event of insufficient available data, the study authors were contacted through email for the relevant information. Preliminary screening was carried out by reading the titles and abstracts of the retrieved studies. After reading the full text of the study, 2 experienced researchers decided whether the target article could be included in the analysis or not. Disagreements between the 2 researchers regarding the inclusion of an article were resolved by asking the third researcher. The following keywords was used in the search analysis: (“long non-RNA ATB, human” [Mesh]) OR (((lncRNA-ATB [Title/Abstract]) OR Long noncoding RNA ATB [Title/Abstract]) OR ATBlncRNA [Title/Abstract]) OR Lnc-ATB [Title/Abstract]) AND (“Neoplasms” [Mesh]) OR (((Neoplasm [Title/Abstract]) OR Cancer [Title/Abstract]) OR Cancers [Title/Abstract]) OR Tumor [Title/Abstract]) OR Tumors [Title/Abstract]) AND (“Prognosis” [Mesh]) OR (((Prognoses [Title/Abstract]) OR Prognostic, Factor [Title/Abstract]) OR Factor, Prognostic [Title/Abstract]) OR Prognostic, Factors [Title/Abstract]) OR Factors, Prognostic[Title/Abstract])).

2.2. Literature selection

Inclusion criteria: (1) Published clinical retrospective studies available in free text. (2) Manuscripts comprised of histopathologically diagnosed DSC patients. (3) Studies regarding the association between the expression of lncRNA-ATB with clinicopathological features and the prognosis of DSC patients.

Exclusion criteria: (1) Studies that were not published in the English language. (2) Studies that did not involve human subjects. (3) Published manuscripts other than research clinical studies such as literature reviews, duplicate articles, editorials, letters, or case reports. (4) Unavailability of the full text and incomplete studies in which data extraction was not possible.

2.3. Data extraction

The characteristics of the extracted data: (1) Basic information such as the author's first names, year of publication, country, the expression level of lncRNA-ATB, sample size, method of detection, cut-off value, analysis type, etc were collected. (2) Patient clinicopathological features: gender, age, tumor size, depth of invasion, tumor differentiation, clinical stage, vascular invasion, lymphatic invasion, lymph node metastasis, and distant metastasis. (3) Outcome indicators: overall survival (OS) rate, disease-free survival (DFS), and recurrence-free survival (RFS). Some of the outcome indicators were directly extracted from the studies, while some were indirectly extracted from survival curves using the HR digitizer software Engauge Digitizer version 4.1.^[29]

2.4. Quality assessment

The quality of all the included studies was assessed with the Newcastle-Ottawa scale (NOS).^[30] The NOS scores ranged from 0 to 9 and articles with scores greater than 6 were considered high quality.

2.5. Statistical analysis

Review Manager 5.2 and STATA 12.0 software were used for statistical analysis. The associations between lncRNA-ATB expression and clinicopathological features in patients with DSCs were evaluated based on the risk ratios (RRs) with confidence intervals (CIs) at 95%. The association between lncRNA-ATB expression and the survival rate was evaluated based on the hazard ratios (HRs) with 95% CIs. The heterogeneity of the included literature was evaluated with the X^2 -based Q test and the I^2 statistic. A fixed-effects model for the related effect sizes of combination and analysis was used when there was no obvious heterogeneity and the value of P was $>.05$ or I^2 was $<50\%$. If significant heterogeneity was not found, a random-effects model was used for the relevant analysis. In the event of significant heterogeneity, subgroup analysis was performed to find the potential sources of heterogeneity. Sensitivity analysis was also performed to evaluate the stability of statistical results. Potential publication bias was assessed with Begg's and Egger's tests. Both of these tests are considered sensitive tests for evaluating publication bias.^[31] All analyses were based on previous published studies, and therefore approval from the related ethics committee was not required for this meta-analysis. All P values were 2-tailed and were determined using 2-sided tests. The level of significance was kept as $P < .05$.

3. Results

3.1. Characteristics and quality of included studies

Initially, 97 articles were retrieved using the above mentioned search strategy. After preliminary screening of the titles and abstracts, 23 full-text articles were critically evaluated for eligibility. Finally, after a meticulous review, only 11 studies with 1227 DSC patients were included in this meta-analysis.^[12-22] The quality of all included studies was good, with NOS scores ≥ 6 (Table 1). The flow chart for the search strategy and specific screening processes are shown in Figure 1. Among the included studies, 6 were from China,^[12,14,16-18,21] 2 were from Japan,^[13,15] 2 were from South Korea,^[19,20] and 1 was from Iran.^[22] All the included studies were published from the year 2014 to the year 2018, and the most recent published study was dated October 19, 2018. The sample size for the included studies ranged from 37 to 218, and the mean sample size was 111.

Among them, 2 studies were associated with esophageal squamous cell carcinoma (ESCC),^[17,21] 3 studies were related to GC,^[13,18,22] 3 studies were related to HCC,^[12,19,20] 1 study was associated with PRC,^[14] 1 study was associated with CRC,^[15] and 1 study was associated with colon cancer (CC).^[16] All the specimens in the included studies were evaluated histopathologically; however, Lee YR et al evaluated the specimens through serum assessment. The main characteristics of these studies are summarized in Table 1. The expression levels of lncRNAs were assessed by quantitative reverse transcription-polymerase chain reaction (RT-qPCR). The reference genes for the lncRNAs were different amongst the studies. Genes such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH),^[13,15-19,21] β -actin,^[14] β -glucuronidase (GUSB),^[22] and cel-miR-39^[20] were used in the included studies. All patients in the studies were divided into low expression and high expression groups according to the lncRNA cut-off values. The cut-off values in the included studies were not consistent, reflecting both the median expression^[12-17,20-22] and average expression.^[18] In the included studies, related clinicopathological features such as tumor differentiation and depth of invasion were confirmed by histo-pathological examination. The survival outcomes for the DSC patients were assessed by OS,^[12-14,16,17,19-21] DFS,^[16,17] and RFS,^[12,15] which accounted for 73% (8/11), 18% (2/11), and 18% (2/11) of all the included studies, respectively. High expression of lncRNA-ATB was correlated with poor prognosis for DSC patients in most of the included studies.

3.2. The association between the expression level of lncRNA-ATB and clinicopathological features of DSC patients

The associations of the DSC patients' gender (men vs women), age (≤ 60 vs >60 years old), tumor size (≤ 5 vs >5 cm), tumor differentiation (poor vs good/moderate), depth of invasion (T3 +T4 vs T1+T2), vascular invasion (presence vs absence), lymphatic invasion (presence vs absence), lymph node metastasis (presence vs absence), distant metastasis (presence vs absence), and clinical stage (advanced vs early) with the expression level of lncRNA-ATB were systematically evaluated (Table 2). The results revealed that lymphatic metastasis (RR = 1.26, 95% CI: 1.12-1.42, $P < .001$) and advanced clinical stage (RR = 1.44, 95% CI: 1.23-1.69, $P < .001$) were respectively correlated with high

Table 1
Characteristics of studies included in the meta-analysis.

Author and year of publication	Country	Sample size	Sample source	Tumor type	Cut-off value	Detection method	Outcome	Analysis type	NOS scores
Yuan JH 2014 ^[12]	China	86	Tissue	HCC	Median expression	qRT-PCR	CP,OS,RFS	Kaplan-Meier	7
Saito T 2015 ^[13]	Japan	183	Tissue	GC	Median expression	qRT-PCR	CP,OS	Multivariate	8
Qu SB 2015 ^[14]	China	150	Tissue	PRC	Median expression	qRT-PCR	CP,OS	Multivariate	8
Iguchi T 2015 ^[15]	Japan	124	Tissue	CRC	Median expression	qRT-PCR	CP,RFS	Multivariate	7
Yue B 2016 ^[16]	China	60	Tissue	CC	Median expression	qRT-PCR	CP,OS,DFS	Multivariate	7
Li ZW 2017 ^[17]	China	150	Tissue	ESCC	Median expression	qRT-PCR	CP,OS,DFS	Multivariate	6
Chen Y 2017 ^[18]	China	40	Tissue	GC	Average expression	qRT-PCR	CP	NA	6
Jiang SY 2017 ^[19]	SouthKorea	100	Tissue	HCC	NA	qRT-PCR	CP,OS,PFS	Multivariate	7
Lee YR 2018 ^[20]	SouthKorea	79	Serum	HCC	Median expression	qRT-PCR	CP,OS,DPR	Multivariate	6
Xiao W 2018 ^[21]	China	218	Tissue	ESCC	Median expression	qRT-PCR	CP,OS	Multivariate	7
Nourbakhsh N 2018 ^[22]	Iran	37	Tissue	GC	Median expression	qRT-PCR	CP	NA	6

CC = colon cancer, CP = clinicopathological parameters, CRC = colorectal cancer, DFS = disease-free survival, DPR = disease progression rate, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, NA = not available, NOS = Newcastle-Ottawa scale, OS = overall survival, PFS = progression-free survival, PRC = pancreatic cancer, RFS = recurrence-free survival, RT-qPCR = quantitative reverse transcription-polymerase chain reaction.

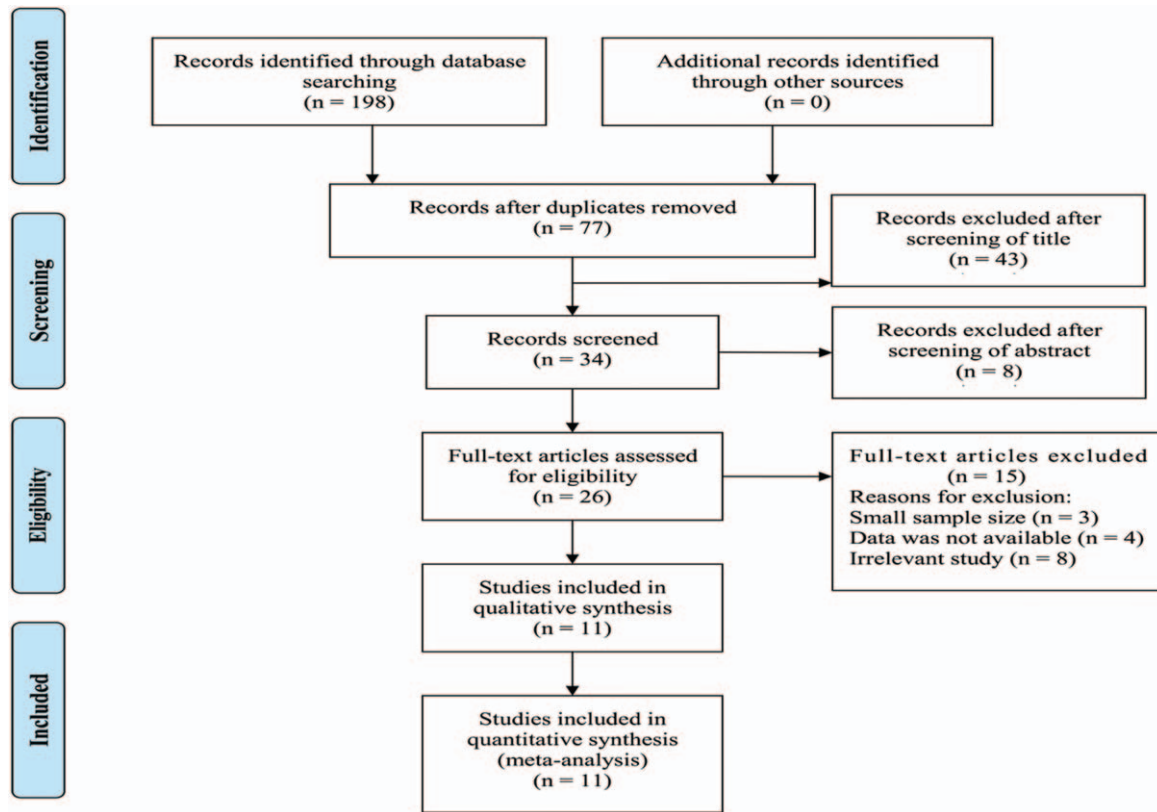


Figure 1. The flow chart of literature search and selection.

expression of lncRNA-ATB in DSCs with statistical significant P values $<.05$. However, non-significant differences between high expression and low expression of lncRNA-ATB were found in PRC. Other clinicopathological features such as gender, age, tumor size, tumor differentiation, depth of invasion, and distant metastasis were not correlated with the expression of lncRNA-ATB ($P >.05$) (Table 2).

3.3. The association between the expression of lncRNA-ATB and OS in DSC patients

Out of the included studies, only 8 studies^[12–14,16,17,19–21] with 1026 patients reported the prognostic significance of lncRNA-

ATB and its association with the OS rate. Most of the studies reported that the increased expression of lncRNA-ATB was significantly correlated with poor prognosis in DSC patients. However, Qu et al obtained opposite results, which indicated the low expression of lncRNA-ATB was correlated with poor OS.^[14] The results for the Q test and I^2 statistic indicated that there was obvious heterogeneity in the included studies, with $I^2=84\%$ and a significance level of $P <.001$; therefore, a random-effects model was applied. Our results revealed that the OS of DSC patients was shorter in the high lncRNA-ATB expression group compared with the low expression group (HR=2.33, 95%CI=1.22–4.46, $P=.01$, $I^2=84\%$) (Fig. 2).

Table 2
The meta-analysis results for the included studies regarding the expression level of lncRNA-ATB and clinicopathological features.

Clinicopathological features	Studies	Patients	Heterogeneity test		Model used	Meta-analysis	
			I^2 (%)	P		RR (95%CI)	P
Gender	9	1017	<0.01	.680	Fixed	1.03 (0.95–1.11)	.458
Age (≤ 60)	4	369	3.10	.377	Fixed	1.08 (0.88–1.32)	.483
Tumor size (≤ 5)	6	635	35.30	.172	Fixed	0.90 (0.79–1.03)	.132
Tumor differentiation	3	492	<0.01	.447	Fixed	1.38 (0.98–1.95)	.067
Depth of invasion	3	156	89.30	.000	Random	1.31 (0.71–2.42)	.392
Vascular invasion	3	393	94.70	.000	Random	1.78 (0.58–5.43)	.313
Lymphatic invasion	3	344	70.80	.033	Random	1.17 (0.77–1.77)	.472
Lymph node metastasis	5	602	49.20	.097	Fixed	1.26 (1.12–1.42)	.000
Distant metastasis	2	223	70.00	.068	Random	3.07 (0.23–41.30)	.399
Clinical stage	7	748	46.70	.080	Fixed	1.44 (1.23–1.69)	.000

CI=confidence interval, RR=risk ratio.

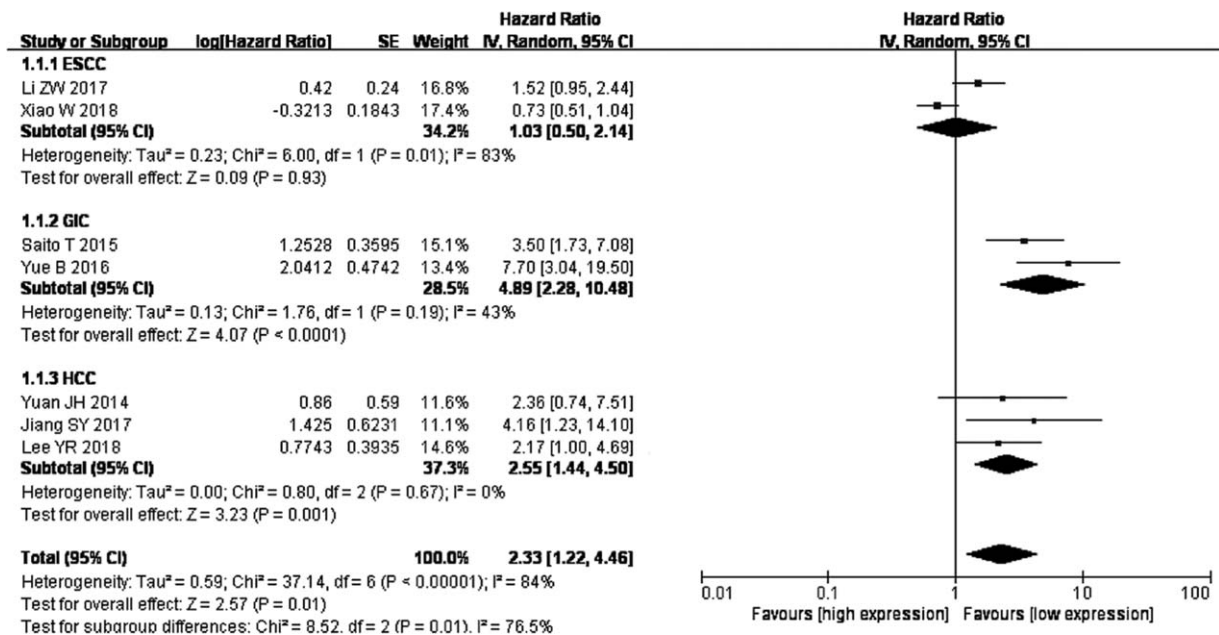


Figure 2. The forest plot for the association between the expression of lncRNA-ATB and OS for DSC patients. DSC=digestive system cancer, ESCC=esophageal squamous cell carcinoma, GIC=gastrointestinal cancer, HCC=hepatocellular carcinoma, OS=overall survival.

Subgroup analysis and meta-regression analysis according to potential confounding factors such as sample size, country, tumor type, cut-off value, data extraction, analysis type, NOS score, and weight were performed. When subgroup analysis for the tumor types was conducted, the results showed that high

expression of lncRNA-ATB could serve as an independent prognostic factor in gastrointestinal cancer (GIC) (GC and CC) (HR=4.89, 95%CI=2.28–10.48, P<.001) and HCC (HR=2.55, 95%CI=1.44–4.50, P=.001) (Fig. 2; Table 3). However, in ESCC, patients with lncRNA-ATB over-expression showed a

Table 3
Subgroup meta-analysis of pooled HRs for OS.

Influence factor	Studies	Patients	Heterogeneity test		Model used	Meta-regression P	Meta-analysis	
			I ² (%)	P			HR (95%CI)	P
[1] OS	7	876	84	<.001	Random		2.33 (1.22–4.46)	.010
[2] Sample size						0.172		
≤100	4	325	37	.190	Fixed		3.44 (2.12–5.59)	<.001
>100	3	551	88	<.001	Random		1.50 (0.65–3.46)	.340
[3] Country						0.483		
China	4	514	88	<.001	Random		1.95 (0.79–4.77)	.150
Other countries	3	362	0	.570	Fixed		2.99 (1.85–4.82)	<.001
[4] Tumor type						0.199		
ESCC	2	368	83	.010	Random		1.03 (0.50–2.14)	.930
GIC	2	243	43	.190	Fixed		4.89 (2.28–10.48)	<.001
HCC	3	265	0	.670	Fixed		2.55 (1.440–4.50)	.001
[5] Cut-off value						0.549		
Median	6	776	85	<.001	Fixed		2.17 (1.09–4.32)	.030
Non-median	1	100	–	–	–		4.16 (1.23–14.10)	.020
[6] Data extraction						0.657		
From article	5	640	89	<.001	Random		2.67 (1.010–7.02)	.050
From survival curve	2	236	0	.490	Fixed		1.62 (1.05–2.50)	.030
[7] Analysis type						0.990		
Multivariate	6	790	86	<.001	Random		2.34 (1.15–4.78)	.020
Non-multivariate	1	86	–	–	–		2.36 (0.74–7.51)	.140
[8] NOS score						0.614		
≤6	2	229	0	.440	Fixed		1.68 (1.12–2.50)	.010
>6	5	647	89	<.001	Random		2.74 (0.97–7.76)	.060
[9] Weight						0.172		
≤15%	4	325	37	.190	Fixed		3.44 (2.12–5.59)	<.001
>15%	3	551	88	<.001	Random		1.50 (0.65–3.46)	.340

ESCC=esophageal squamous cell carcinoma, GIC=gastrointestinal cancer, HCC=hepatocellular carcinoma, HRs=hazard ratios, NOS=Newcastle-Ottawa scale, OS=overall survival.

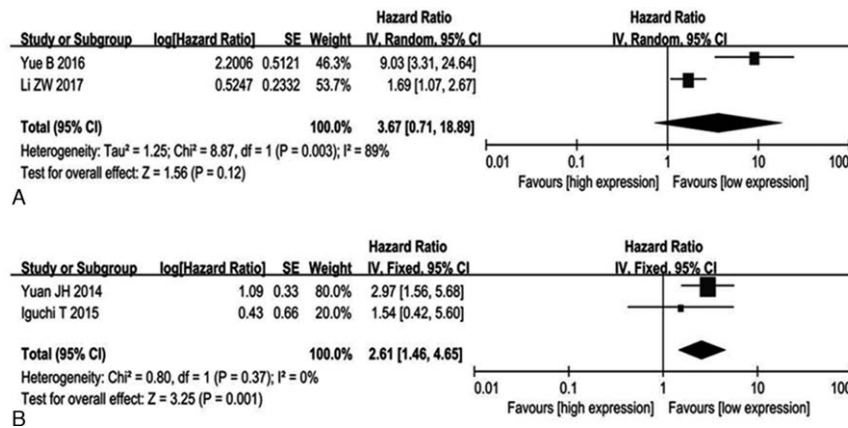


Figure 3. Forest plots for the association between the high expression of lncRNA-ATB and DSS/DFS for DSC patients. (A) DFS; (B) RFS. DFS=disease-free survival, DSC=digestive system cancer, RFS=recurrence-free survival.

greater tendency towards poor OS, though there was no statistical significance (HR = 1.03, 95%CI = 0.50–2.14, $P = .93$). This might be due to the relatively low number of studies on ESCC included in this meta-analysis. Furthermore, subgroup analysis was performed including the sample size, country, analysis type, NOS score, and weight. The results revealed that higher expression of lncRNA-ATB was closely correlated with poorer OS in groups with a small sample size (HR = 3.44, 95%CI = 2.12–5.59, $P < .001$), non-Chinese population (HR = 2.99, 95%CI = 1.85–4.82, $P < .001$), multivariate analysis (HR = 2.34, 95%CI = 1.15–4.78, $P = .020$), NOS score not more than 6 (HR = 1.68, 95%CI = 1.12–2.50, $P = .010$), and weight not more than 15% (HR = 3.44, 95%CI = 2.12–5.59, $P < .001$). The other factors used for subgroup stratification like the cut-off value and data extraction had significantly less influence on the prognostic value of high lncRNA-ATB expression. However, the source of heterogeneity was not revealed by subgroup analysis and meta-regression analysis (Table 3).

3.4. The association between the expression of lncRNA-ATB and DFS/RFS in DSC patients

Only 2 studies with 210 patients reported the DFS.^[16,17] The results of the Q test and I^2 statistic indicated that there was obvious heterogeneity between the 2 studies, with $I^2 = 89\%$ and $P = .003$. A random-effects model was used for the analysis. The results showed that there was no statistical significance for DFS between the high expression and low expression groups for lncRNA-ATB in DSC patients (HR = 3.67, 95%CI = 0.71–18.89, $P = .12$) (Fig. 3A).

There were also 2 studies with 210 patients which reported the prognostic significance of lncRNA-ATB in RFS.^[12,15] The results showed that there was no significant heterogeneity between the 2 studies with $I^2 = 0\%$ and $P = .37$. A fixed-effects model was also used for analysis. Our results revealed that RFS was shorter in the high expression lncRNA-ATB group than in the low expression lncRNA-ATB group, with a statistically significant P value (HR = 2.61, 95%CI = 1.46–4.65, $P = .001$) (Fig. 3B).

3.5. Sensitivity analysis

The I^2 values for the depth of invasion, vascular invasion, and lymphatic invasion in heterogeneity tests were 89.3%, 94.7%,

and 70.8% respectively, indicating heterogeneity amongst these studies (Table 2). The sensitivity analyses were performed using STATA version 12.0 software and were performed on the OS to assess its stability. The results showed that removing any of the included studies had no significant influence on the estimated pooled results, which demonstrated that our analyses were relatively stable and credible (Fig. 4).

3.6. Publication bias

The potential publication bias was evaluated with Begg's funnel plot and Egger's test. The results showed that there may be publication bias in terms of OS ($P > |t| = 0.018$, 95%CI: 1.24–8.23, Fig. 5A). Therefore, the "trim and fill" method was used to estimate the number of missing studies caused by publication bias. The adjusted pooled HR for OS was 1.725 (95%CI: 0.95–3.12, $P = 0.07$), and there was no significant asymmetry in the funnel plot after correction (Fig. 6). However, there was also no obvious asymmetry for DSS+DFS ($P > |t| = 0.481$, Fig. 5B), gender ($P > |t| = 0.747$, Fig. 5C), age ($P > |t| = 0.104$, Fig. 5D), tumor size ($P > |t| = 0.811$, Fig. 5E), lymph node metastasis ($P > |t| = 0.465$, Fig. 5F), and clinical stage ($P > |t| = 0.072$, Fig. 5G) in DSC patients. As a consequence, publication bias assessment indicated the OS results were robust.

4. Discussion

Although advanced treatment modalities have evolved recently, the DSC mortality and morbidity rates are still high due to drug resistance in chemotherapy and the side effects of radiotherapy. The overall prognosis of DSC patients is still unfavorable, which affects their quality of life. Recent studies conducted on the clinical roles of lncRNAs indicated that lncRNAs could be used as molecular biomarkers for predicting the prognosis of DSC patients. By assessing the expression levels of specific lncRNAs in tissue or other body fluids, doctors can not only make appropriate clinical decisions based on the prognoses, but also monitor the therapeutic efficacy of different treatments for each DSC patient. Though many studies^[12–22] have explored the prognostic significance of lncRNA-ATB in DSCs, conflicting results were reported, especially in prognostic analysis. Furthermore, the ability to evaluate the relationship between lncRNA-ATB expression and the prognosis of DSC patients has been

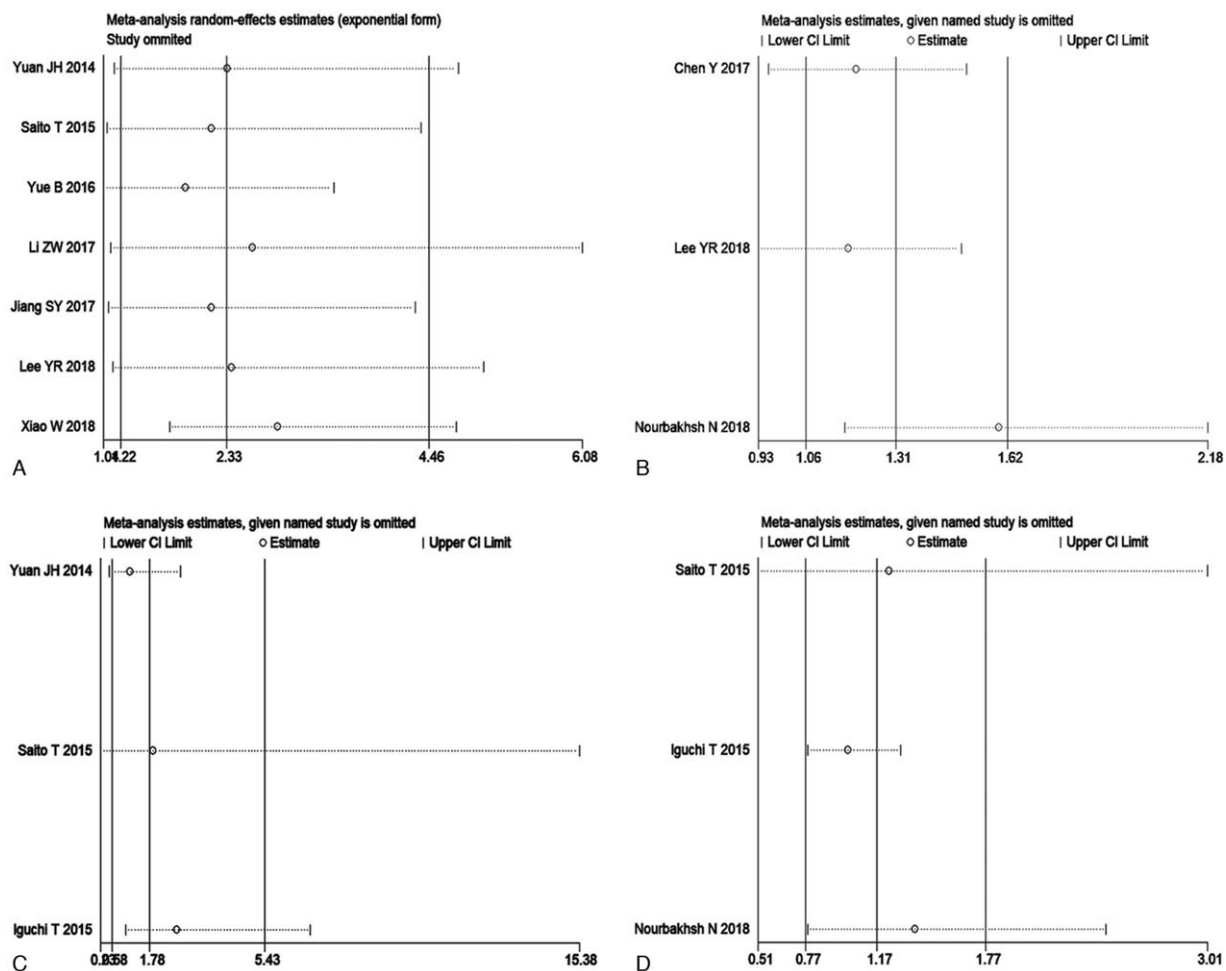


Figure 4. Sensitivity analyses of the studies. (A) OS; (B) depth of invasion; (C) vascular invasion; (D) lymphatic invasion. OS = overall survival.

limited to a single study. Therefore, the prognostic value of lncRNA-ATB needs to be clarified, verified, and summarized in a system review or meta-analysis. Fan et al^[32] in 2017 reported that the high expression of lncRNA-ATB was significantly correlated with lymph node metastasis (LNM), distant metastasis (DM), and advanced tumor staging, as well as poor OS, RFS, and DFS in human cancers excluding PRC. However, Shen et al^[33] in 2018 indicated that the high expression of lncRNA-ATB was associated with poor tumor differentiation, deeper tumor invasion, and earlier vascular invasion, as well as shorter OS, DFS, and PFS compared with low expression in cancer patients. The conclusions from Fan's and Shen's studies were similar in many aspects. However, Shen's study had a larger sample size and revealed additional correlated clinicopathological findings such as clinical staging, PFS, age, gender, tumor size, tumor differentiation, vascular invasion, and subgroup analysis for OS, which were missing in Fan's study. Previously published meta-analyses regarding the expression of lncRNA-ATB in human cancers reported inconsistent results and no proper prognostic value for lncRNA-ATB has been defined. Therefore, this study was conducted to evaluate the association between the expression level of lncRNA-ATB and the prognosis of DSC patients. In ESCC, lncRNA-ATB was confirmed to be an oncogene that functions through dysregulation of the miR-200b/Kindlin-2 signaling pathway, and a high expression of lncRNA-ATB could

predict a poor prognosis for diagnosed patients.^[17,21] In GC cases, high expression of lncRNA-ATB was correlated with aggressive clinicopathological features, and the silencing of lncRNA-ATB inhibited the malignant biological behaviors of GC cells such as proliferation, invasion, and migration.^[18] However, Saito et al^[13] revealed that lncRNA-ATB could accelerate the invasion and metastasis of GC cells through the TGF- β /miR-200s/ZEB axis. In HCC cases, high expression of lncRNA-ATB was observed compared to that in the controls. The increased expression of lncRNA-ATB was correlated with portal vein thrombosis, advanced clinical staging, and poor prognosis for patients with HCC.^[19,20] Qu et al^[14] confirmed through prognostic research on PRC that lower expression of lncRNA-ATB was correlated with a poor OS rate compared to that in patients with high lncRNA-ATB expression. In CRC, the overexpression of lncRNA-ATB was demonstrated to be significantly associated with unfavorable clinicopathological features and poor outcomes in Iguchi's study.^[15] Yue et al^[16] further reported that lncRNA-ATB might regulate the progression of CRC by promoting EMT and inhibiting the expression of E-cadherin. The above mentioned studies indicated that the expression level of lncRNA-ATB has significant prognostic implication in DSCs. After the systematic review of the studies mentioned above, with the exception of PRC, all DSCs were associated with high expression of lncRNA-ATB, albeit with

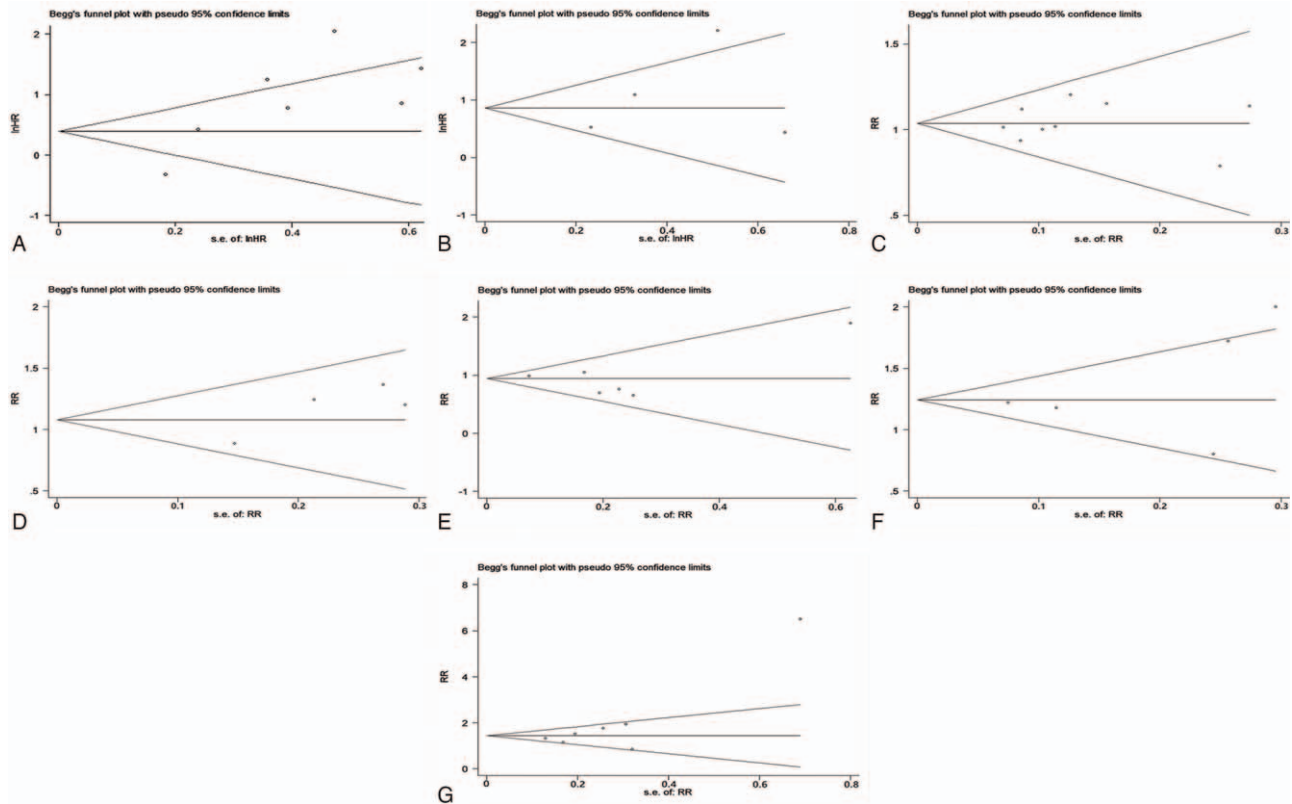


Figure 5. Begg's funnel plots of survival outcomes and clinicopathological parameters. (A) OS; (B) DFS+RFS; (C) gender; (D) age; (E) tumor size; (F) lymph node metastasis; (G) clinical stage. DFS=disease-free survival, OS=overall survival, RFS=recurrence-free survival.

different mechanisms of action. Highly expressed lncRNA-ATB mostly serves as an oncogene and is associated with poor prognosis in DSC patients. However, the specific molecular mechanisms of lncRNA-ATB in the occurrence or progression of DSCs and other system cancers have not been fully elucidated to date. As a consequence, the potential targets and pathways of lncRNA-ATB involved in DSCs^[12,13,16,17], female reproductive system cancers,^[26,27,34,35] urinary system cancers,^[24,25,36] and other system cancers^[23,28,37,38] were summarized in detail in the present study. As shown in Figure 7, the most significant effect of lncRNA-ATB expression on the function of cancer cells was related to proliferation, followed by cell invasion and cell

migration. In addition, the EMT pathway may largely be involved in the regulation of lncRNA-ATB expression in human cancers, since increasing evidence has confirmed the relationship between them in malignancies, especially in DSCs (Fig. 7). As the primary inducers of EMT, ZEB1 and ZEB2 were demonstrated to be involved in the feedback regulation of microRNA-200 family members (miR-200a, miR-200b, miR-200c, miR-141, and miR-429) in studies targeting lncRNA-ATB.^[12,26,28] In practical terms, lncRNA-ATB could function as a competing endogenous RNA (ceRNA) by competitively binding to miR-200s and elevating ZEB1/2 expression, thereby activating the EMT pathway.^[12,26] This further suggests the indispensable role of

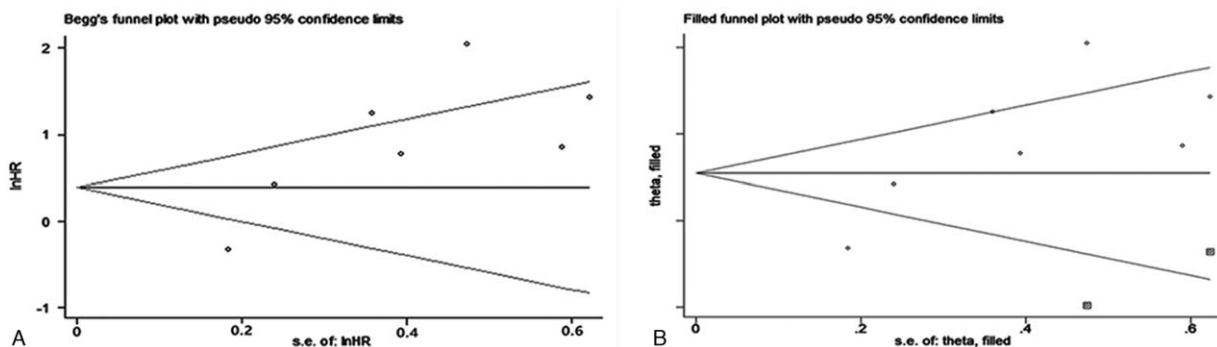


Figure 6. Begg's funnel plots of OS. (A) Begg's funnel plot of OS; (B) filled Begg's funnel plot with "trim and fill" method (O indicates observed studies, ■ indicates missing studies). OS=overall survival.

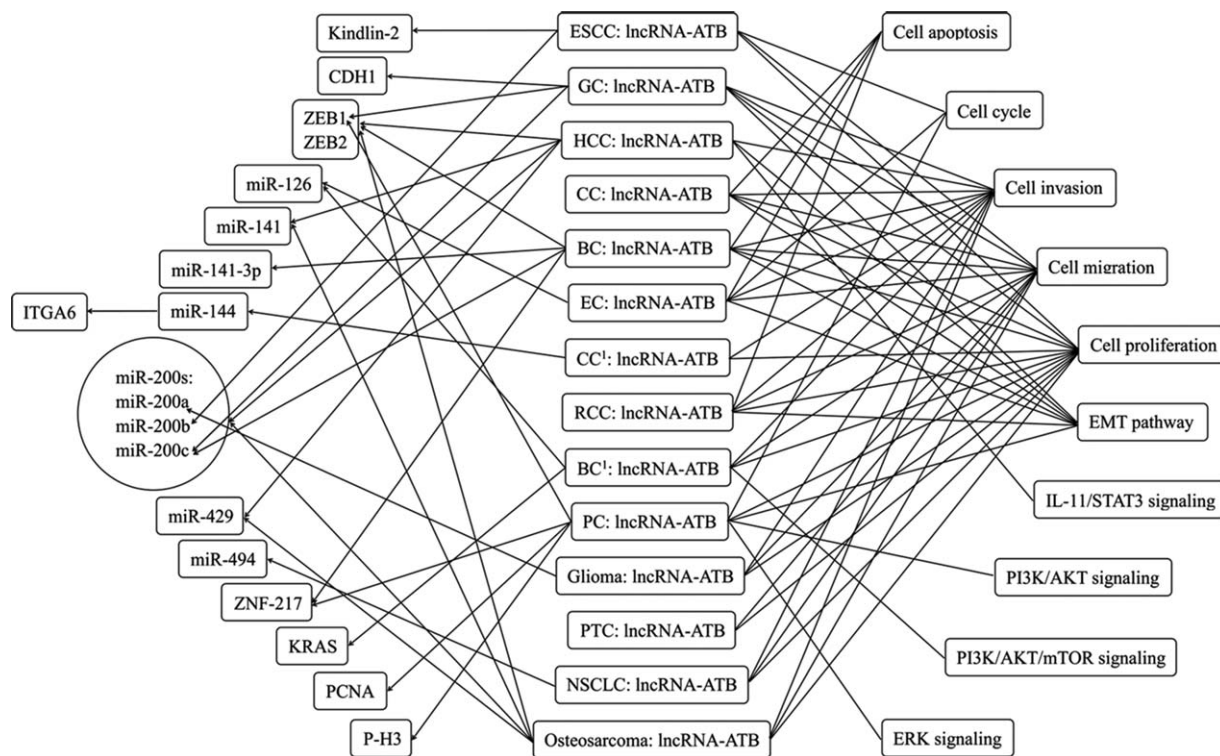


Figure 7. Summary of potential targets and signaling pathways of lncRNA-ATB in cancers from different systems. AKT=protein kinase B, BC=breast cancer, BC¹=bladder Cancer, CC=colon cancer, CC¹=cervical cancer, CDH1=cadherin 1, EC=endometrial cancer, EMT=epithelial-mesenchymal transition, ERK=extracellular regulated protein kinases, ESCC=esophageal squamous cell carcinoma, GC=gastric cancer, HCC=hepatocellular carcinoma, IL-11=interleukin-11, ITGA6=integrin α 6, KRAS=Kirsten rat sarcoma viral oncogene homolog, mTOR=mammalian target of rapamycin, NSCLC=Non-small cell lung cancer, PC=prostate carcinoma, PCNA=proliferating cell nuclear antigen, P-H3=phosphorylated histone H3, PI3K=phosphoinositide 3 kinase, PTC=papillary thyroid cancer, RCC=renal cell carcinoma, STAT3=signal transducer and activator of transcription 3, ZEB1=zinc-finger E-box binding homeobox 1, ZEB2=zinc-finger E-box binding homeobox 2, ZNF-217=zinc finger protein 217.

lncRNA-ATB in EMT to facilitate the invasion and migration of cancer cells via the miR-200s/ZEB axis, leading to the acceleration of disease progression to malignancy. Moreover, lncRNA-ATB was also confirmed to exhibit tumor-promoting effects by interacting with other microRNAs, such as miR-126,^[36] miR-141-3p,^[34] miR-144,^[35] and miR-494,^[37] which further contribute to the progression and metastasis of malignant tumors. Therefore, the underlying relationship between lncRNA-ATB and microRNAs may be attractive research targets in anti-cancer therapy in order to provide a better understanding of the functional roles of lncRNA-ATB in DSCs.

In the present comprehensive meta-analysis, the clinicopathological features of 1227 patients were studied. The results showed that high expression of lncRNA-ATB was significantly associated with an increased risk of earlier lymph node metastasis and more advanced clinical staging compared with low expression in all DSCs excluding PRC. Our results also showed that except for PRC, increased lncRNA-ATB expression indicated poor OS and RFS in DSCs compared with low lncRNA-ATB expression, which was further verified by subgroup analysis. The outcomes of sensitivity analysis confirmed that the results of this study were relatively stable and credible. Though there was publication bias for OS, the adjusted pooled HR (HR: 1.725, 95%CI: 0.95–3.12) (Fig. 6) confirmed that lncRNA-ATB could serve as an independent prognostic predictor for DSCs. Therefore, the aggregated results showed that lncRNA-ATB could be considered an influential molecular biomarker for the prognosis of patients with DSCs.

Although similar meta-analyses regarding the prognostic value of lncRNA-ATB in human cancers were conducted by Fan et al and Shen et al, several critical assessments with important parameters were performed in this study as compared with previous studies. First, as the most common malignancies in human cancers, several frequently used diagnostic biomarkers are available for DSCs such as AFP, CEA, CA19-9, and CA724. However, there are hardly any prognostic biomarkers with sufficient sensitivity or specificity to be applied in clinical practice. Though Fan et al and Shen et al evaluated the prognostic role of lncRNA-ATB in various cancers, the predictive ability of lncRNA-ATB in the prognosis of DSCs may be limited by the combination of data from other system cancers in their meta-analyses. Our literature search was performed with more comprehensive selection and screening using different databases (PubMed, Embase, Cochrane Library, Web of Science, Springerlink, Nature, and Karger) and included a few additional publications^[17,19–21] in comparison with previous studies. With regard to the sample size, 11 studies with 1227 DSC patients in the current meta-analysis provided more convincing evidence and accurate estimations compared with 603 DSC patients in Fan et al’s study and 755 DSC patients in Shen et al’s study. Furthermore, in terms of tracing heterogeneous sources of pooled results for OS, we assessed several new factors used for the subgroup stratification such as country, data extraction, NOS score, and weight, and identified novel risk factors associated with increased lncRNA-ATB expression for DSCs compared with the previous meta-analyses in human cancers. Of note, the high

expression of lncRNA-ATB was further found to exhibit an independent prognostic value for the OS of patients with GC, CC, and HCC, but not ESCC, which was the specific prognostic impact of lncRNA-ATB in DSCs revealed in this study in comparison with that in human cancers reported by the former studies. Additionally, meta-regression analysis for OS was performed in our research, which was not performed in the other 2 studies, and the data further supported the results of heterogeneous analysis. Finally, the mechanisms by which lncRNA-ATB mediated the progression of cancers in different systems were first systematically summarized in the present study (Fig. 7). We also uncovered the significant impact of lncRNA-ATB expression on cancer cell proliferation, invasion, and migration, which was further confirmed by the important roles of lncRNA-ATB in EMT via the miR-200s/ZEB axis.^[12,26,28] Therefore, the interaction between lncRNA-ATB and the miR-200s/ZEB axis in EMT warrants more attention to prevent the progression or metastasis of cancers in future studies. To our knowledge, the present study is the first meta-analysis to assess the prognostic significance of lncRNA-ATB in DSCs. All of the studies included in this meta-analysis had sample sizes greater than 30 and publication dates after 2014, further confirming the feasibility and utility of the consequences for DSC patients. The results of this meta-analysis confirmed the correlation between high expression of lncRNA-ATB and aggressive clinicopathological features or poor prognosis for patients with DSCs. To a certain extent, investigation of the lncRNA-ATB expression level may be sufficiently beneficial to prompt clinical treatment decisions, thus potentially enabling the improvement of life expectancy for patients diagnosed with DSCs and the reduction of the mortality rate associated with DSCs.

Limitations: (1) All the included studies were conducted with Asian populations; therefore, the conclusions of this study may not be applicable to populations outside Asia. (2) Only manuscripts published in the English language were used, thus some studies in other languages related to the prognostic value of lncRNA-ATB in DSCs may have been ignored. (3) The meta-analysis included 4 studies whose HR and 95%CI extracted from Kaplan-Meier survival curves were not available. (4) Since it is difficult to obtain a consensus regarding the cut-off value to determine the over-expression of lncRNA-ATB in different DSCs, the criterion for the lncRNA-ATB expression level varied in the included studies.

5. Conclusions

A high expression of lncRNA-ATB was significantly correlated with lymph node metastasis, advanced clinical staging, poor OS, and RFS in DSCs. The expression level of lncRNA-ATB can be recommended as a promising biomarker for evaluating the clinicopathological features and predicting the prognosis for DSC patients. Ultimately, larger-size, multi-center, and higher-quality studies are required to validate the clinical utility of lncRNA-ATB in DSCs.

Author contributions

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Investigation: Houyu Duan, Xiang Ding.

Methodology: Houyu Duan.

Writing – original draft: Houyu Duan.

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