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Prognostic value of lncRNA FEZF1 antisense RNA 1 over-expression in oncologic outcomes of patients with solid tumors

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Abstract

Background: FEZ family zinc finger 1 antisense RNA 1 (FEZF1-AS1), as a novel lncRNA, was reported to be up-regulated in various cancers and involved in tumor progression. This study systematically assessed the prognostic value of FEZF1-AS1 in solid tumors.

Methods: Web of Science, PubMed, EMBASE, Chinese National Knowledge Infrastructure, and Wanfang databases were searched for eligible studies that evaluated the prognostic role of FEZF1-AS1 expression in cancer patients. Pooled hazard ratios (HRs) and combined odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated. The meta-analysis was conducted using Stata/SE 14.1.

Results: Fifteen original studies involving 1378 patients were enrolled. Pooled results showed that increased expression of FEZF1-AS1 significantly correlated with shorter overall survival (OS) in cancer patients (HR 2.04, 95% CI 1.60–2.47), and also shorter disease-free survival (DFS) (HR 2.08, 95% CI 1.27–2.89). Additionally, the combined ORs indicated that increased FEZF1-AS1 expression was significantly associated with lymph node metastasis (OR 3.35, 95% CI 1.98–5.67), distant metastasis (OR 3.10, 95% CI 1.86–5.15), poor tumor differentiation (OR 2.90, 95% CI 1.45–5.80), high depth of tumor invasion (OR 2.72, 95% CI 1.36–5.43), and advanced clinical stage (OR 2.76, 95% CI 1.75–4.35). Expression analysis using the Gene Expression Profiling Interactive Analysis database indicated that the expression of FEZF1-AS1 was higher in tumor tissues than that in the corresponding normal tissues. The results of survival analysis revealed that increased FEZF1-AS1 expression was correlated with poor OS and DFS in cancer patients.

Conclusions: LncRNA FEZF1-AS1 may serve as a valuable prognostic biomarker for clinical outcomes in various solid tumors.

Abbreviations: 95% CI = 95% confidence interval, CRC = colorectal cancer, DFS = disease-free survival, EMT = epithelial–mesenchymal transition, FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1, GC = gastric cancer, GEPIA = Gene Expression Profiling Interactive Analysis, GTEx = genotype-tissue expression, HCC = hepatocellular carcinoma, HR = hazard ratio, LAD = lung adenocarcinoma, lncRNA = long noncoding RNA, LSD1 = lysine-specific demethylase 1, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratio, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma, TCGA = The Cancer Genome Atlas.

Keywords: FEZF1-AS1, LncRNA, meta-analysis, prognosis

1. Introduction

Malignant tumors can lead to death. Due to poor therapeutic effects, they have heavy burdens on families and countries.[1,2] Despite great advancements in diagnosis and treatment, the prognosis, especially the 5-year survival rate, for most malignant tumors, is still low.[3–5] Gene or targeted therapies for cancer have received much attention recently, and they may be important approaches to cure cancer in the future. Therefore, it is important to identify the mechanism and therapeutic targets of cancer.

In recent years, numerous potential biomarkers for the diagnosis, prognosis, and treatment of cancer have been identified, such as microRNAs, long noncoding RNAs (lncRNAs), and circular RNA.[6–9] As a result, the mechanisms of cancer development and progression have been gradually revealed. Among these biomarkers, lncRNAs—a group of ncRNAs greater than 200 nt in length and with limited or no protein-coding capacity—have gained momentum for their vital roles in diverse biological processes.[10,11] Furthermore, many studies have demonstrated that lncRNAs may be potential therapeutic targets or prognostic biomarkers for various tumors.[12–15]

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FEZ family zinc finger 1 antisense RNA 1 (FEZF1-AS1)—a lncRNA that produces a 2564-bp transcript in chromosome 7q31.32 and localizes to the opposite strand of the FEZF1 gene—has been recently identified, and its dysregulation has been reported in many cancers.[16–18] lncRNA FEZF1-AS1 has been reported to have oncogenic functions in various biological processes. Increased FEZF1-AS1 expression was found in cancer tissues and cell lines, and is associated with poor prognosis and advanced clinicopathological parameters.

However, there is no specific meta-analysis to evaluate the association between the FEZF1-AS1 level and the clinical outcomes in diverse cancers. Consequently, we conducted this study to provide a systematic evaluation of the clinical value of FEZF1-AS1 as a promising biomarker based on previously published data.

2. Material and methods

2.1. Search strategy

Ethical approval was not required for this meta-analysis. A comprehensive strategy was employed to search several electronic databases, namely, PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure, and Wanfang databases. The latest search was conducted on 14 November 2018. The following keywords were used in accordance with the search strategy: "FEZF1 antisense RNA 1," "FEZF1-AS1," or "AK057037" or "LOC154860."

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: FEZF1-AS1 expression was measured in tissue samples from primary solid cancers; correlation between FEZF1-AS1 expression and prognosis (overall survival [OS]/disease-free survival [DFS]) was reported; sufficient data were available for calculating the hazard ratio (HR) with 95% confidence interval (CI); and patients were classified into high-FEZF1-AS1 expression and low-FEZF1-AS1 expression groups. The exclusion criteria were as follows: duplications; reviews, case reports, conference abstracts, case reports; those on hematologic tumors, or animal experiments; those only investigating the molecular functions of FEZF1-AS1.

2.3. Data extraction

Two investigators collected data independently in accordance with predesigned tables, which included the name of the first author, publication year, country, cancer type, sample size, expression pattern, tumor stage, criterion of high expression, detection method, follow-up time, outcome measures, and analysis type. Additionally, relevant information, as it pertained to the clinicopathological features, was also collected, including the sex, histological grade, depth of tumor invasion, lymph node metastasis, metastasis, and TNM stage.

For the extraction of survival data, the HRs and 95% CIs were retrieved with Engauge Digitizer (version 4.1). If a study only provided Kaplan–Meier curves and reported the data of univariate and multivariate analyses, the latter was directly applied. The data of clinicopathological features were directly extracted from identified studies. The quality of each included study was assessed independently by 2 researchers using the Newcastle–Ottawa Quality Assessment Scale (NOS). This method was composed of 3 parameters of quality: selection (score: 0–4), comparability (score: 0–2), and outcome assessment (score: 0–3), with the total score ranging from 0 to 9. An NOS score >6 was considered as a high-quality study.

2.4. Public data and tools

In this study, Gene Expression Profiling Interactive Analysis (GEPIA)—a free online database (http://gepia.cancer-pku.cn/index.html)—was utilized. This database contains a large amount of RNA sequencing expression data of tumors and normal specimens from The Cancer Genome Atlas (TCGA) and the genotype-tissue expression (GTEx) projects. The GEPIA database was used to display the expression level of FEZF1-AS1 in other types of human cancer and to further validate its prognostic values regarding OS/DFS in TCGA dataset. In all, 9190 patients with solid tumors were divided into the high or low group according to the median expression. One-way analysis of variance was applied for differential expression analysis, and Kaplan–Meier plots were utilized for survival analysis.

2.5. Statistical analysis

Stata statistical software (version 14.1) was used to analyze the relationship between lncRNA FEZF1-AS1 expression and OS/DFS, and also to determine the clinicopathological significance of FEZF1-AS1 expression in human cancers.

The heterogeneity among the included studies was assessed using I^2 statistics and chi-square Q test, with $I^2 \geq 50\%$ or a $P_h < .10$, indicating a significant difference. The random-effects model was used in cases of heterogeneity, and the fixed-effects model was adopted if no significant heterogeneity was observed. Publication bias was evaluated by the funnel plot and Begg/Egger test. Sensitivity analysis was used to evaluate the stability of the results. P values $<.05$ were considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

The literature retrieval procedure is shown in Fig. 1. After further discussion and consideration of the retrieved articles, 14 publications (including 15 cohort studies)[16–29] published between 2016 and 2018 were selected for this meta-analysis. The 15 studies included 1378 patients with a mean sample size of 91.9 (range 30–153). Fourteen studies presented data on the association between FEZF1-AS1 expression and OS, and 5 of the selected eligible studies discussed the correlation between FEZF1-AS1 expression and DFS. Among these studies, 10 different kinds of solid tumors were analyzed in this meta-analysis, including gastric cancer (GC), colorectal cancer (CRC), lung adenocarcinoma (LAD), pancreatic ductal adenocarcinoma (PDAC), cervical cancer, breast cancer, osteosarcoma, hepatocellular carcinoma (HCC), nasopharyngeal carcinoma, and ovarian cancer (OVC). All primary cancer tissues and adjacent nontumor tissue samples were collected from patients in P.R. China. The expression of lncRNA FEZF1-AS1 in the tissue samples was measured by quantitative real-time polymerase chain reaction (14 studies) and in situ hybridization (1 study). All articles were written in English. The main characteristics of all cohort studies are summarized in Table 1.

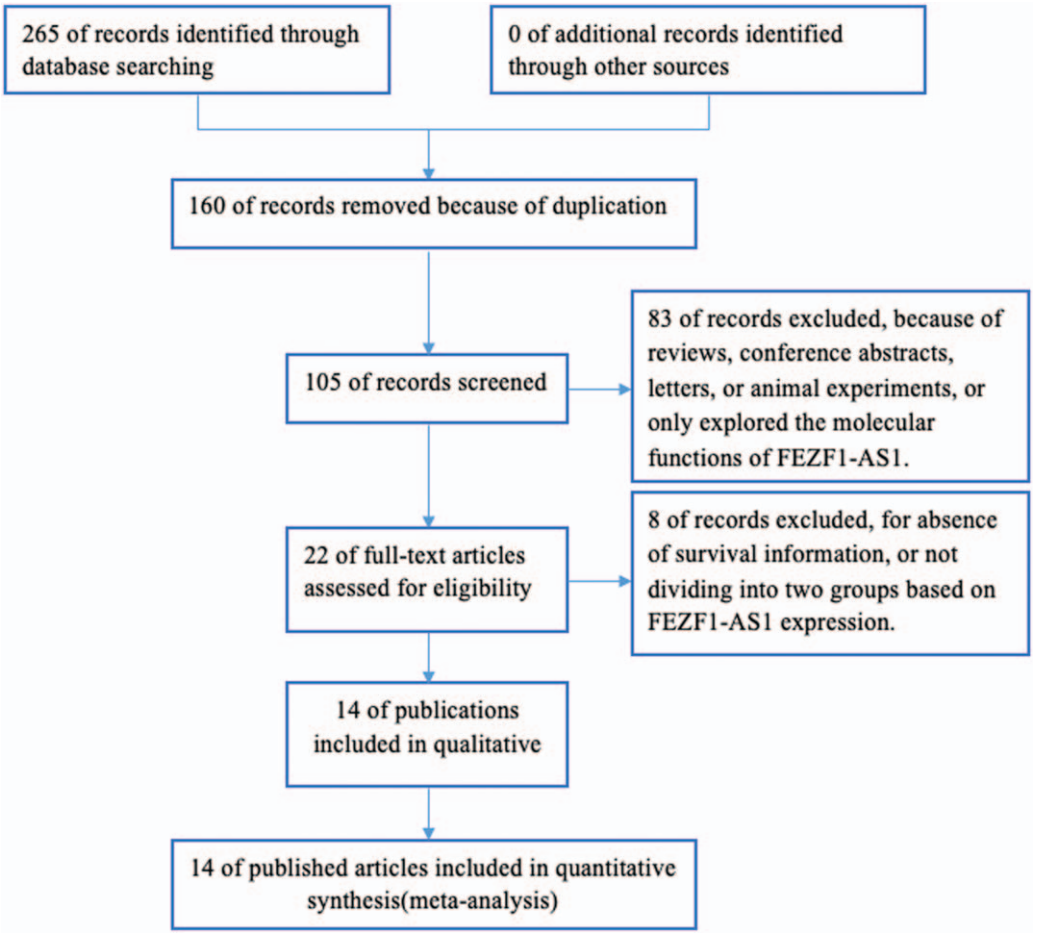

Figure 1. Flow diagram of included studies.

3.2. Association between increased FEZF1-AS1 expression and overall survival

Fourteen cohort studies with 1296 cases reported the HRs for OS. The pooled results of the analysis of these studies are displayed in Fig. 2. The results revealed that high expression of FEZF1-AS1 in cancer tissues was strongly associated with poor long-term OS (HR 2.04, 95% CI 1.60–2.47, $P < .001$), and the heterogeneity test revealed mild heterogeneity ($I^2 = 11.7\%$, $P_h = .325$) (Fig. 2).

Table 1

Characteristics of included studies.

First author	Year	Disease type	Sample size	Clinical stage	Cut-off value	Detection method	Endpoints	Follow-up, y	HR statistics	NOS
Chen	2016	CRC	153	NA	A final staining score of ≥3	ISH	OS, DFS	≥5	Reported	8
Jin	2017	LAD	80	I-IIIa	Mean expression	qRT-PCR	OS	≥5	Survival curve	7
Liu	2017	GC	82	I-III	Fold change (tumor/normal) ≥2	qRT-PCR	DFS	<5	Reported	7
Wu	2017	GC	104	I-IV	Median expression	qRT-PCR	OS, DFS	≥5	Survival curve	8
Ye	2017	PDAC	94	I-IV	Median expression	qRT-PCR	OS	≥5	Reported	7
Bian (a)	2018	CRC	108	I-IV	NA	qRT-PCR	OS, DFS	≥5	Reported (OS); Survival curve (DFS)	8
Bian (b)	2018	CRC	97	I-IV	NA	qRT-PCR	OS	≥5	Survival curve	7
Wang	2018	HCC	139	I-IV	Median expression	qRT-PCR	OS	≥5	Survival curve	7
Zhang	2018	CC	196	I-IV	Median expression	qRT-PCR	OS	≥5	Reported	8
Zhang	2018	BC	30	I-III	Median expression	qRT-PCR	OS	≥5	Survival curve	6
Liu	2018	LAD	63	NA	Mean value	qRT-PCR	OS	≥5	Survival curve	6
Zhou	2018	Osteosarcoma	58	I-III	Median expression	qRT-PCR	OS	≥5	Survival curve	6
Cheng	2018	NPC	71	I-IV	Median expression	qRT-PCR	OS, DFS	≥5	Survival curve	7
Gong	2018	HCC	58	NA	NA	qRT-PCR	OS	≥5	Survival curve	6
Zhao	2018	OVC	45	NA	NA	qRT-PCR	OS	≥5	Survival curve	7

BC = breast cancer, CC = cervical cancer, CRC = colorectal cancer, DFS = disease-free survival, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, ISH = in situ hybridization, LAD = lung adenocarcinoma, NOS = Newcastle–Ottawa Quality Assessment Scale, NPC = nasopharyngeal carcinoma, OS = overall survival, OVC = ovarian cancer, PDAC = pancreatic ductal adenocarcinoma, qRT-PCR = quantitative real-time polymerase chain reaction.

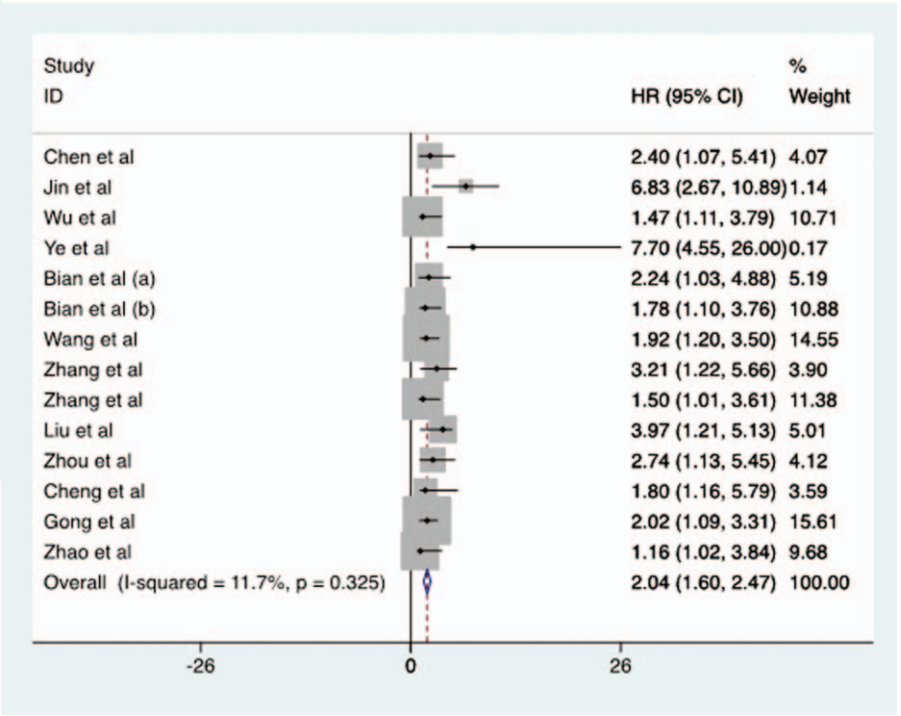

Figure 2. Meta-analysis of the pooled HRs of OS from patients with high FEZF1-AS1 expression. FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1, HR = hazard ratio, OS = overall survival.

The high expression level of FEZF1-AS1 serves as an unfavorable prognostic factor in human solid cancers.

3.3. Association between increased FEZF1-AS1 expression and disease-free survival

Five cohort studies with 518 cases investigated the association between FEZF1-AS1 expression and DFS. Increased FEZF1-AS1 expression indicated an poor DFS outcome, with a combined HR of 2.08 (95% CI 1.27–2.89, $P < .001$) (Fig. 3), revealing that patients with higher FEZF1-AS1 expression had a lower DFS rate compared with patients with lower FEZF1-AS1 expression. No significant heterogeneity was found among the 4 studies ($I^2 = 0.0\%$, $P_h = .871$).

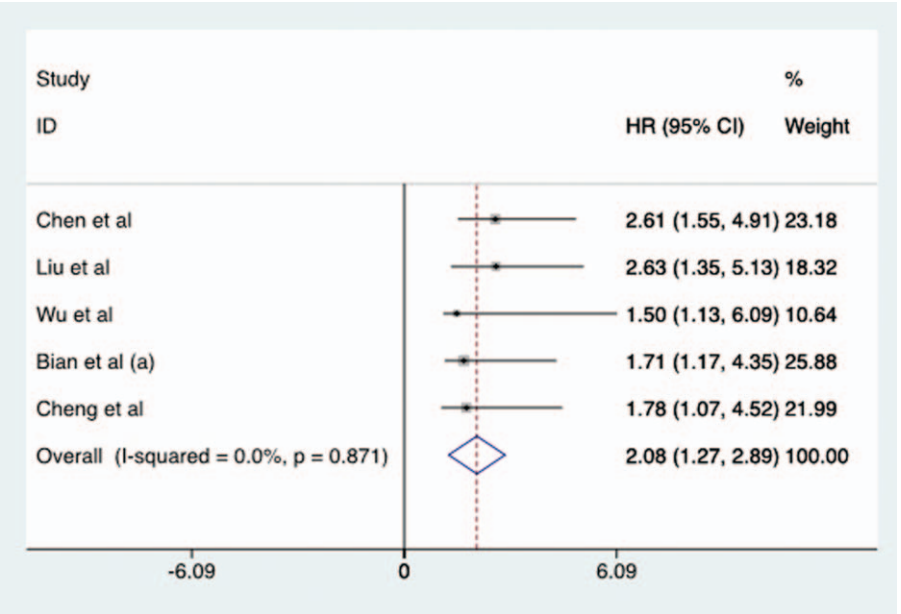

Figure 3. Meta-analysis of the pooled HRs of DFS from patients with high FEZF1-AS1 expression. DFS = disease-free survival, FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1, HR = hazard ratio.

Table 2

Results of the meta-analysis of high FEZF1-AS1 and clinicopathological parameters.

Clinicopathological parameter	Studies (n)	OR (95% CI)	*P*	Heterogeneity		
				I^2 (%)	P_h	Model
Sex (male vs female)	8	1.22 (0.91–1.62)	.182	0.0	.938	Fixed
Histological grade (G3/G2 vs G1)	7	1.50 (0.76–2.96)	.248	77.7	.000	Random
Tumor depth (T3–T4 vs T1–T2)	2	2.72 (1.36–5.43)	.005	48.4	.164	Fixed
Lymph node metastasis (pos. vs neg.)	3	3.35 (1.98–5.67)	.000	0.0	.495	Fixed
Distant metastasis (pos. vs neg.)	4	3.10 (1.86–5.15)	.000	0.0	.729	Fixed
Clinical stage (III-IV vs I-II)	10	2.76 (1.75–4.35)	.000	60.7	.006	Random

CI = confidence interval, OR = odds ratio.

3.4. Association between increased FEZF1-AS1 expression and the clinicopathological parameters

The pooled ORs were calculated to investigate the association between increased **FEZF1-AS1** expression and the clinicopathological features (Table 2). Increased FEZF1-AS1 expression was associated with various clinicopathological parameters, including lymph node metastasis (OR 3.35, 95% CI 1.98–5.67), distant metastasis (OR 3.10, 95% CI 1.86–5.15), poor tumor differentiation (OR 2.90, 95% CI 1.45–5.80), deeper tumor invasion (OR 2.72, 95% CI 1.36–5.43), and poor clinical stage (OR 2.76, 95% CI 1.75–4.35). However, no clear correlation was found between increased **FEZF1-AS1** expression and sex (OR 1.22, 95% CI 0.91–1.62, $P = .182$) or histological grade (OR 1.50, 95% CI 0.76–2.96, $P = .248$) in cancer patients.

3.5. FEZF1-AS1 expression in different cancer types

The results from the GEPIA—a newly developed interactive web server for analyzing the RNA sequencing expression data from the TCGA and the GTEx projects—indicated that the expression of FEZF1-AS1 was significantly higher in the tumor tissues than the corresponding normal tissues (Fig. 4).

3.6. Validation of the prognostic value of FEZF1-AS1 expression in human solid tumors

The results of survival analysis through the GEPIA database revealed that increased FEZF1-AS1 was associated with a worse OS and DFS in various solid cancers (Fig. 5).

3.7. Publication bias

The Begg visible plots are shown in Fig. 6, and the *P* values of Begg were .155 for OS and .221 for DFS, indicating that there was no publication bias in the present meta-analysis.

3.8. Sensitivity analysis

Sensitivity analysis was performed by omitting 1 study at a time to examine the influence of the removed data set on the pooled HR. The overall results were not significantly influenced by the

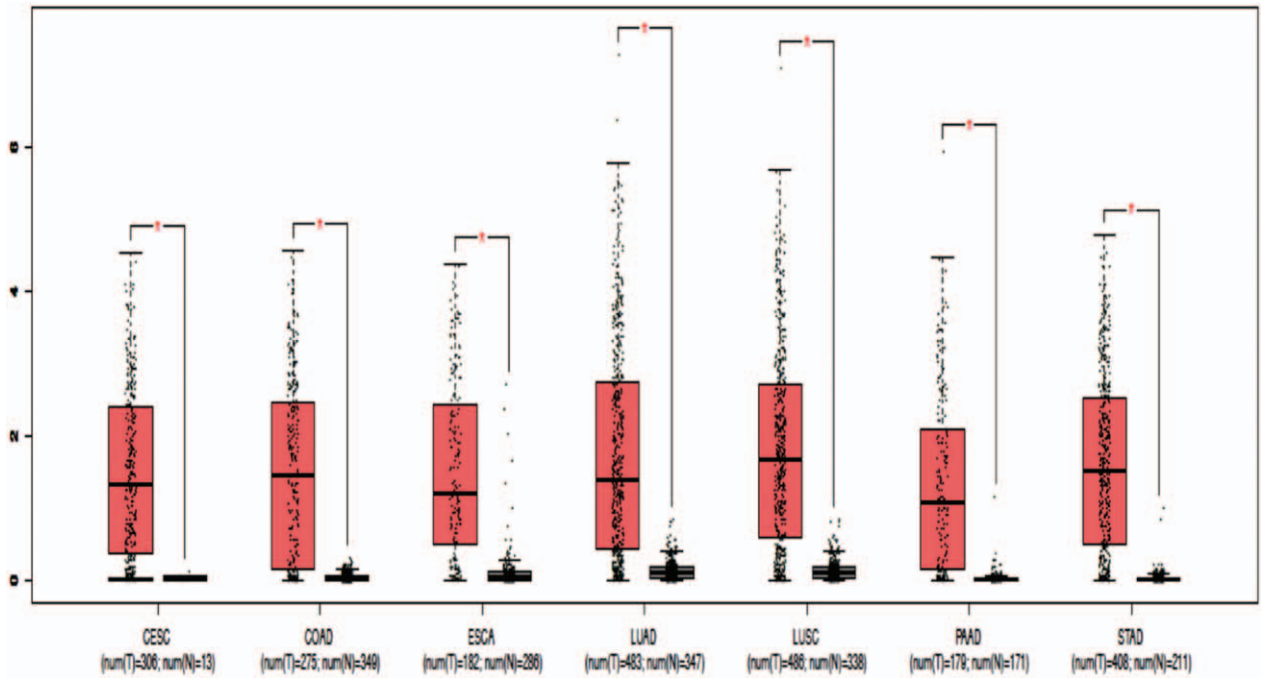

Figure 4. FEZF1-AS1 expression in different types of human cancers. FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1.

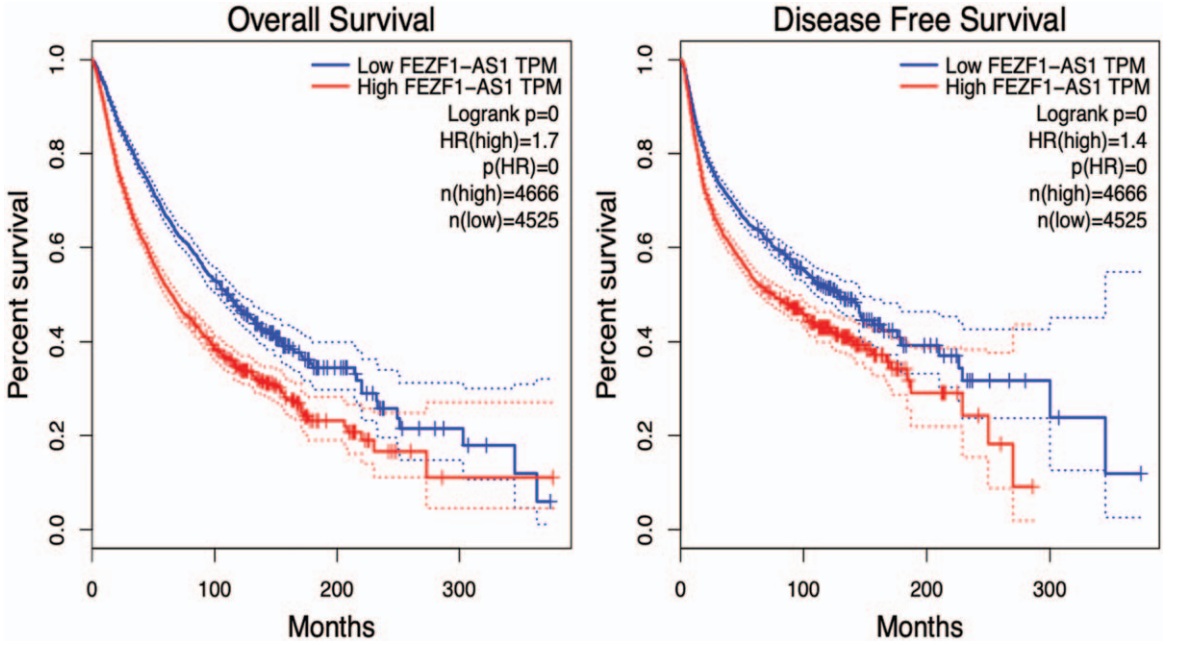

Figure 5. Validation of the prognostic value of FEZF1-AS1 in various solid tumors. FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1.

exclusion of individual studies, indicating that the current results were robust (Fig. 7).

4. Discussion

FEZF1-AS1 is an antisense lncRNA derived from the promoter region of FEZF1. As a novel identified cancer-related lncRNA, it is significantly upregulated in cancer tissues compared with para-cancerous or normal samples. High FEZF1-AS1 expression is correlated with poor prognosis of malignancies, such as CRC, LAD, and GC.[17,20,22] FEZF1-AS1 is considered an oncogenic lncRNA, playing a critical role in tumor occurrence and development. The upregulation of FEZF1-AS1 expresison can promote cell proliferation, invasion, and metastasis, whereas the knockdown of FEZF1-AS1 can significantly inhibit these processes.

FEZF1-AS1 has been reported to promote LAD cell proliferation by influencing the cell cycle and apoptosis.[17] Silencing of

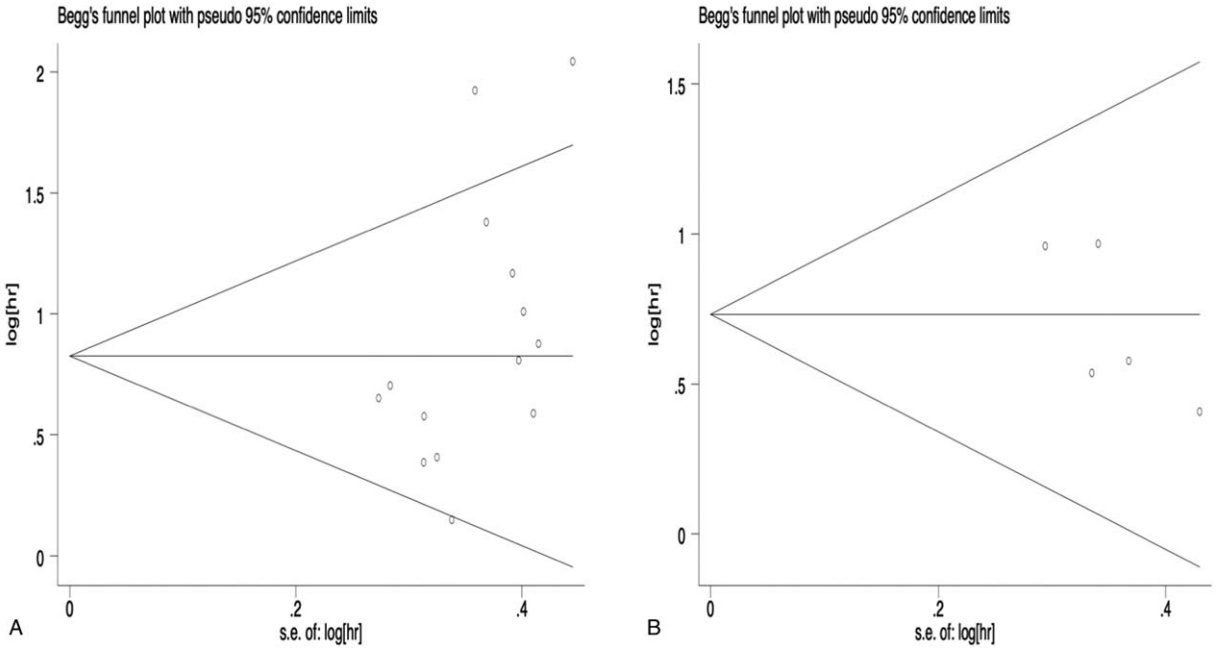

Figure 6. Publication bias assessment of FEZF1-AS1 expression and OS (A) or DFS (B). DFS = disease-free survival, FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1, OS = overall survival.

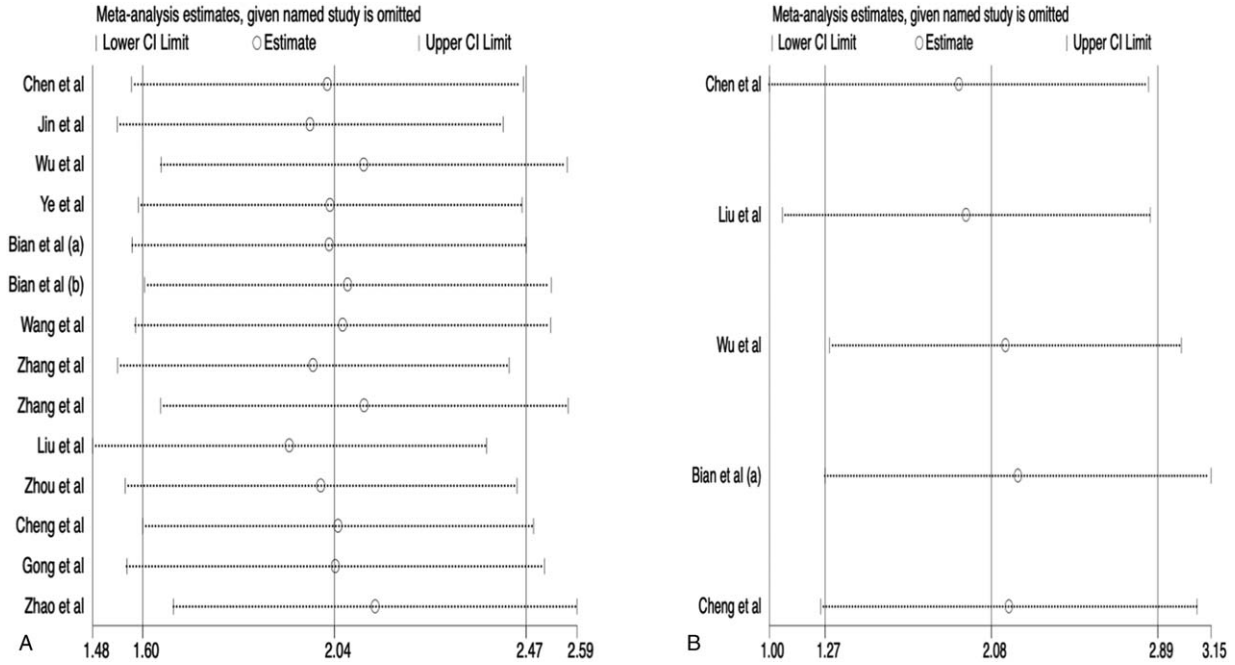

Figure 7. Sensitivity analysis of FEZF1-AS1 expression and OS (A) or DFS (B). DFS = disease-free survival, FEZF1-AS1 = FEZ family zinc finger 1 antisense RNA 1, OS = overall survival.

FEZF1-AS1 can suppress LAD cell proliferation, cause apoptosis, and arrest the cell cycle. FEZF1-AS1 can synchronously recruit RNA-binding proteins EZH2 and lysine-specific demethylase 1 (LSD1) to p57 promoter regions and repress their transcription, thereby promoting the progression of LAD.[16] p57 is a tumor suppressor, and its low expression can lead to tumor development.[30–33] Meanwhile, He et al revealed that FEZF1-AS1·LSD1–EZH2 complex could repress the expression of E-cadherin epigenetically in NSCLC cells. The downregulation of FEZF1-AS1 increases E-cadherin expression, which inhibits the epithelial–mesenchymal transition (EMT). EMT has been confirmed to play a key role in the invasion and metastasis of tumor cells.[34,35]

As a vital transcription factor, SP1 can bind to the FEZF1-AS1 promoter to control FEZF1-AS1 expression. The overexpression of SP1 has been detected in various cancers, including GC.[36,37] p21, one of the most cyclin dependent kinase inhibitors, which inhibits the activity of kinases, such as cyclinD/CDK4, cyclinD/CDK6, and cyclinE/CDK2, play an important role in the p53 signaling pathway for the G1/S transition.[38,39] FEZF1-AS1, together with LSD1, can suppress p21 expression to induce GC cell proliferation.[18] Another study reported that FEZF1-AS1 was found to stimulate the activation of Wnt/β-catenin signaling in GC cells,[22] which can promote cancer progression.[40]

LncRNA FEZF1-AS1 and its sense-cognate gene ZNF312B are overexpressed in tissues and cell lines of human PDAC, which is associated with disease progression and poor prognosis.[19] The FEZF1-AS1/miR-107/ZNF312B axis-induced promotion of PDAC cell proliferation is mediated by apoptosis and the G1-S checkpoint. In HCC cells, FEZF1-AS1 knockdown suppressed cell invasion and migration by downregulating JAK2/STAT3 signaling-mediated EMT.

Our study is the first meta-analysis of the prognostic value of lncRNA FEZF1-AS1 in cancer. We found that high FEZF1-AS1 expression correlated with a significantly shorter OS and lower DFS rate compared with low FEZF1-AS1 expression. Furthermore, the correlation between FEZF1-AS1 expression and the clinicopathological features was also assessed. Interestingly, high FEZF1-AS1 expression in cancer tissues was significantly correlated with lymph node metastasis, tumor metastasis, advanced tumor stage, and high depth of tumor invasion. However, there was no association between FEZF1-AS1 expression and sex or histological grade. The results of our comprehensive analysis indicated a vital role of FEZF1-AS1 in the development of cancer and suggested that FEZF1-AS1 might be a useful biomarker of the progression and prognosis of cancer.

Nevertheless, several limitations must be considered to interpret the results of this present meta-analysis. First, the number of studies and the sample size were relatively small. Thus, additional studies with greater sample sizes are required. Second, all participants were recruited from China, and studies that include individuals of other races are needed, as this may limit the application of our conclusions. Third, some HRs and their corresponding 95% CIs were extracted from the survival curves and may be less accurate than those directly obtained from the studies that carried out multivariate analysis. In addition, significant heterogeneity was observed in some clinicopathological features.

5. Conclusions

In conclusion, this study shows that increased lncRNA FEZF1-AS1 expression is significantly associated with unfavorable clinical outcomes in patients with solid tumors. As a vital node in the gene expression pathway, lncRNA FEZF1-AS1 is regulated by upstream molecules, and it also regulates the occurrence and progression of cancer cells in multiple ways. Therefore, we believe that FEZF1-AS1 is a promising therapeutic target for cancer.

Author contributions

Conceptualization: Guoliang Xiao, Shubin Tang
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Formal analysis: Yi Zhang, Tingting Peng
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Methodology: Qiuxi Yang, Lijuan Wang
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Supervision: Shubin Tang
Writing – original draft: Yi Zhang, Tingting Peng, Guoliang Xiao
Writing – review & editing: Yi Zhang, Qiu-xi Yang.
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