

Long noncoding RNA AFAP1-AS1, a potential novel biomarker to predict the clinical outcome of cancer patients: a meta-analysis

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Abstract: A number of studies have demonstrated that the expression level of actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1) was upregulated in various cancers. High expression of AFAP1-AS1 is associated with an increased risk of metastasis and a poor prognosis in cancer patients. The electronic search was conducted in PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang database. We collected relevant articles to explore the association between the expression levels of AFAP1-AS1 and lymph node metastasis, distant metastasis, overall survival, relapse-free survival, and progression-free survival. A total of 1,017 patients from eight studies were finally included. The results showed that cancer patients with high AFAP1-AS1 expression suffered an increased risk of developing lymph node metastasis (odds ratio =3.19, 95% confidence interval [CI]: 2.11–4.83, $P<0.00001$) and distant metastasis (odds ratio =3.05, 95% CI: 1.84–5.04, $P<0.0001$). Moreover, we found that patients with high AFAP1-AS1 expression also had a poorer overall survival (hazard ratio [HR]: 1.98, 95% CI: 1.57–2.38, $P=0.000$), a worse progression-free survival (HR: 1.73, 95% CI: 1.11–2.35, $P=0.000$), and a shorter recurrence-free survival (HR: 1.96, 95% CI: 1.02–2.90, $P=0.000$) than those with low AFAP1-AS1 expression. High expression of AFAP1-AS1 was associated with poor clinical outcome. AFAP1-AS1 might serve as a potential novel biomarker for indicating the clinical outcomes in human cancers.

Keywords: lncRNA, AFAP1-AS1, carcinoma, clinical outcome, meta-analysis

Introduction

Long noncoding RNAs (lncRNAs) are nonprotein-coding transcripts with length >200 nucleotides.^{1,2} They have been dismissed as transcriptional “noise” in the past decades, but nowadays they are regarded as rising stars in the field of cancer therapy and prediction.^{3–5} Much more attention has been paid to lncRNAs. Accumulating evidence has shown that lncRNAs can participate in a wide range of physiological processes, and they could regulate gene transcription at the transcriptional, posttranscriptional, and epigenetic levels.^{6–8} The dysregulation of lncRNAs has been reported to play a vital role in diverse human diseases, especially in cancers,^{9–12} the dysregulation of lncRNAs are associated with tumor initiation, progression, and metastasis.

Among all lncRNAs, actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1) is a newly identified lncRNA, which has attracted widespread attention recently. Dysregulated expression of AFAP1-AS1 has been reported in various human cancers, including esophageal adenocarcinoma,¹³ pancreatic carcinoma,¹⁴ and lung cancer.¹⁵ Abnormal expression of AFAP1-AS1 was involved in human carcinogenesis. AFAP1-AS1 expressed at high levels in cancerous tissue was reported to be associated

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with metastasis and prognosis in various kinds of cancer. Therefore, AFAP1-AS1 might be feasible as a diagnostic biomarker and prognostic factor. This current meta-analysis was performed to explore the correlation of AFAP1-AS1 with clinical outcome of cancer patients, to further determine whether AFAP1-AS1 could serve as an effective biomarker for metastasis and prognosis.

Methods

Literature search strategies

We conducted a comprehensive search in PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure, and Wanfang database. We based our dates for literature retrieval from January 1, 1988 to February 10, 2016. There was no language restriction. The keywords for the search were as follows: “long non-coding RNA AFAP1-AS1” or “lncRNA AFAP1-AS1” or “AFAP1-AS1” or “AFAP1 antisense RNA 1” or “actin filament associated protein 1 antisense RNA1”. Besides, in order to get potentially eligible papers, we got additional relevant articles by manually viewing the reference lists.

Inclusion and exclusion criteria

Inclusion criteria were the following: 1) articles investigating the role of AFAP1-AS1 in the development of human cancer, 2) the expression levels of AFAP1-AS1 in primary cancerous tissue were measured, and 3) patients were divided into high and low groups based on the expression levels of AFAP1-AS1.

Exclusion criteria were the following: 1) studies without usable data, 2) duplicate publications, and 3) reviews, letters, case reports, and expert opinions.

Date extraction and quality assessment

The information was individually extracted from each included studies by two investigators (YZ and TFH). The information and data are listed as following: name of first author, year of publication, country, ethnicity, cancer type, total number of patients, number of high AFAP1-AS1 expression group and low AFAP1-AS1 expression group, number of patients with lymph node metastasis (LNM) and distant metastasis (DM) in each group, outcome measures, the assessment methods, the criteria of high expression. If there were disagreements, a consensus was reached by the third investigator (QZX). The Newcastle–Ottawa Scale (NOS) was applied to assess the quality of all included studies. The NOS score ranged between 0 and 9, and a study with an NOS score ≥ 6 was considered to be of high quality.

Statistical methods

This meta-analysis was conducted by using Review Manager 5.3 software (Cochrane network) and Stata SE12.0 (StataCorp, College Station, TX, USA). The heterogeneity among studies was determined by using the chi-square-based Q test and I^2 statistics,¹⁶ a P -value for Q test < 0.05 , and I^2 value $> 50\%$ were all considered as significant heterogeneity. If there was a significant heterogeneity across studies ($P_Q \leq 0.05$, $I^2 \geq 50\%$), we chose the random-effects model,¹⁷ if no severe heterogeneity was observed between studies ($P_Q > 0.05$, $I^2 < 50\%$), the fixed-effects model was adopted.¹⁸ The P -value < 0.05 was considered to be statistically significant.

For the statistical analysis of hazard ratios (HRs), the steps of analysis were as follows: first, the data were directly extracted from article if available. If not, the data were extracted with Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>, a free downloaded software) from Kaplan–Meier curves. Second, the data pending analysis was input in Stata SE12.0. For the data with severe heterogeneity ($P_Q \leq 0.05$, $I^2 \geq 50\%$), the combination result was obtained with “metan hr lci uci, label (namevar = study) random effect (“HR”) textsize (180)”. For the data without severe heterogeneity ($P_Q > 0.05$, $I^2 < 50\%$), combination result was obtained with “metan hr lci uci, label (namevar = study) fixed effect (“HR”) textsize (180)”. Hereinto, hr = hazard ratio, lci = lower confidence intervals; uci = upper confidence intervals; textsize (180) indicated an adjustable text size in the input image. Third, the result and image was extracted.

Results

Studies characteristics

Figure 1 shows the detailed process of literature retrieval. Finally, a total of seven articles (eight studies) were included in this meta-analysis.^{14,15,19–23} There were a total of 1,017 cancer patients, the mean patient sample size was 127.1 (range 78–226). All included studies came from People’s Republic of China. Five different types of cancer were evaluated in the meta-analysis, with three cases of lung cancer, one case of pancreatic ductal adenocarcinoma, one case of esophageal squamous cell carcinoma, one case of nasopharyngeal carcinoma, and two cases of hepatocellular carcinoma. In these included studies, the level of AFAP1-AS1 expression was determined in collected tumor tissues. The negative control was adjacent noncancerous tissues and healthy tissues. The main characteristics are summarized in Table 1. And these studies were evaluated to be of high quality.

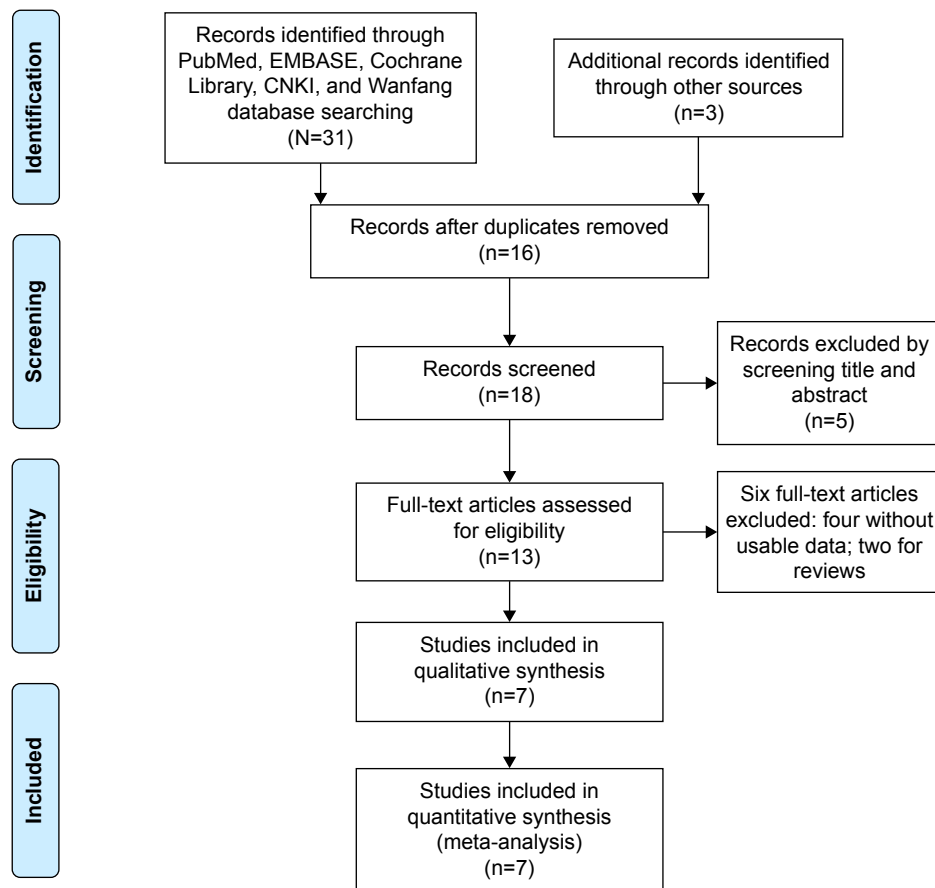


Figure 1 Flowchart presenting the steps of literature search and selection.

Abbreviation: CNKI, China National Knowledge Infrastructure.

The association between lncRNA AFAP1-AS1 and metastasis

Association between lncRNA AFAP1-AS1 and LNM

Four studies reported the number of patients according to AFAP1-AS1 expression levels in a total of 451 cancer patients. There was no severe heterogeneity among studies ($I^2=0\%$, $P_Q=0.50$), then the fixed-effects model was applied to calculate the data. The odds ratio (OR) expressed as high AFAP1-AS1 expression group versus low expression group, was 3.19 (95% confidence interval [CI]: 2.11–4.83, $P<0.00001$) (Figure 2). From the analysis results, we found that compared with low AFAP1-AS1 expression group, a significant elevated LNM rate was observed in high AFAP1-AS1 expression group.

Association between lncRNA AFAP1-AS1 and DM

Three studies reported the number of patients with DM. There was no severe heterogeneity across studies ($I^2=7\%$, $P_Q=0.34$), and the fixed-effects model was adopted. The result showed that patients with high AFAP1-AS1 expression in

tumor tissues may have an increased risk of developing DM (OR: 3.05, 95% CI: 1.84–5.04, $P<0.0001$) (Figure 3).

The association between lncRNA AFAP1-AS1 and prognosis

Association between lncRNA AFAP1-AS1 and overall survival

All included studies reported the overall survival (OS) according to AFAP1-AS1 expression levels in a total of 1,017 patients. Due to no significant heterogeneity ($I^2=0\%$, $P_Q=0.853$), the fixed-effects model was chosen to estimate the pooled HRs with corresponding 95% CIs. The HR, expressed as high AFAP1-AS1 expression group versus low expression group, was 1.98 (95% CI: 1.57–2.38, $P=0.000$) (Figure 4). When comparing the OS of cancer patients between the two groups, we found that there was a significant difference in the OS. Compared with low AFAP1-AS1 expression group, high AFAP1-AS1 expression group had a statistically significant reduced OS. The cancer patients with high AFAP1-AS1 expression might be correlated with shorter OS.

Table 1 The basic information and data of the all included studies in the meta-analysis

Author (Year)	Country	Ethnicity	Cancer type	Total number	AFAP1-AS1 expression				Outcome measures	Detection method	High expression		
					High with LNM	High with DM	Low with LNM	Low with DM					
Bo et al ¹⁹ (2015)	People's Republic of China	Asian	NPC	78	20	20	23	45	27	55	OS, RFS	qRT-PCR	≥ Cutoff value
Deng et al ²⁰ (2015)	People's Republic of China	Asian	LC	121	37	43	66	17	25	55	OS	qRT-PCR	N/A
Ye et al ¹⁴ (2015)	People's Republic of China	Asian	PDAC	90	35	-	45	18	-	45	OS, PFS	qRT-PCR	Above the median
Zeng et al ¹⁵ (2016)	People's Republic of China	Asian	LC	226	-	-	34	-	-	192	OS, RFS	qRT-PCR	N/A
Zeng et al ¹⁵ (2016)	People's Republic of China	Asian	LC	106	-	-	6	-	-	100	OS	qRT-PCR	N/A
Zhou et al ²¹ (2016)	People's Republic of China	Asian	ESCC	162	55	22	81	32	9	81	OS, PFS	qRT-PCR	≥ Median value
Lu et al ²² (2016)	People's Republic of China	Asian	HCC	156	-	-	78	-	-	78	OS	qRT-PCR	Above the median
Zhang et al ²³ (2016)	People's Republic of China	Asian	HCC	78	-	-	57	-	-	21	OS	qRT-PCR	N/A

Abbreviations: AFAP1-AS1, actin filament-associated protein 1 antisense RNA 1; DM, distant metastasis; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; LNM, lymph node metastasis; LC, lung cancer; NPC, nasopharyngeal carcinoma; N/A, not available; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; qRT-PCR, quantitative reverse-transcriptase polymerase chain reaction; RFS, relapse-free survival.

Association between lncRNA AFAP1-AS1 and recurrence-free survival

Two studies reported the recurrence-free survival (RFS) according to AFAP1-AS1 expression levels. No significant heterogeneity was observed between studies ($I^2=0\%$, $P_Q=0.875$), the fixed-effects model was applied to estimate the pooled HRs with corresponding 95% CIs. Overall, we found a shorter RFS in the cancer patients with elevated AFAP1-AS1 expression (HR: 1.96, 95% CI: 1.02–2.90, $P=0.000$) (Figure 5).

Association between lncRNA AFAP1-AS1 and progression-free survival

Two studies reported the progression-free survival (PFS) according to AFAP1-AS1 expression levels. Because of no significant heterogeneity across studies ($I^2=0\%$, $P_Q=0.592$), the fixed-effects model was applied to calculate the pooled HRs and the associated 95% CIs. Overall, the analysis result indicated that PFS was significantly worse in patients with high AFAP1-AS1 expression in tumor tissues (HR: 1.73, 95% CI: 1.11–2.35, $P=0.000$) (Figure 6).

Sensitivity analysis

For meta-analysis of the association between AFAP1-AS1 and OS, sensitivity analysis was conducted by deleting each study in turn from the pooled analysis to examine the influence of the removed data set to the overall HRs. Exclusion of each study did not influence the result, suggesting that the result of synthetic analysis was robust.

Publication bias

For meta-analysis of the association between AFAP1-AS1 and OS, Begg's funnel plot with pseudo 95% CIs was provided (Figure 7). There was no significant publication bias observed across studies. Publication bias was assessed statistically using the Begg's test and Egger's test. Still, the results of Begg's test ($Pr>|z|=0.083$) revealed no publication bias ($P>0.05$), and the results of Egger's test ($P>|t|=0.235$, 95% CI: -1.266 to 4.240) also showed no publication bias.

Discussion

In recent years, lncRNA has become a rising star in the noncoding RNA. More than thousands of lncRNAs have been detected and reported, such as HOTAIR,²⁴ MALAT1,²⁵ and PCAT-1.²⁶ Aberrant expressions of lncRNAs have been found in tumor tissues, and are involved in the onset and progression of cancer. lncRNAs could act as oncogenic and tumor suppressor roles in tumorigenesis. For example, lncRNA-UCA1 was reported to function as an oncogene

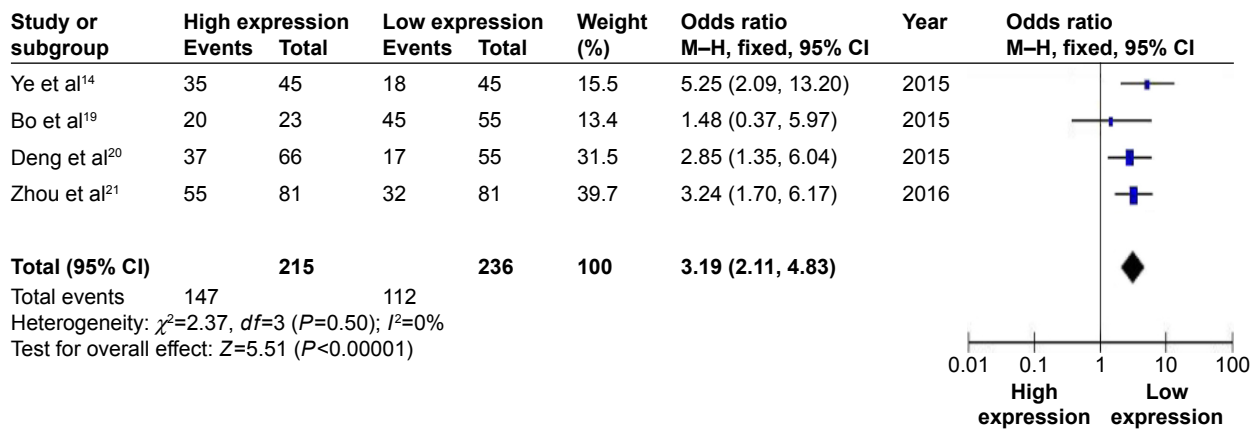


Figure 2 Forest plot for the association between AFAP1-AS1 expression levels with LNM.

Abbreviations: AFAP1-AS1, actin filament-associated protein 1 antisense RNA 1; CI, confidence interval; LNM, lymph node metastasis; M-H, Mantel-Haenszel test.

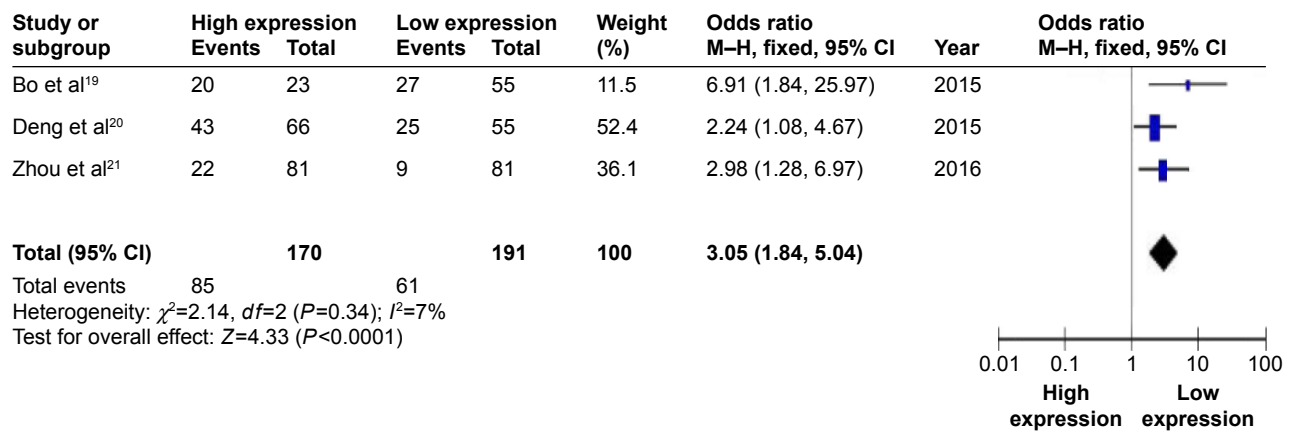


Figure 3 Forest plot for the association between AFAP1-AS1 expression levels with DM.

Abbreviations: AFAP1-AS1, actin filament-associated protein 1 antisense RNA 1; CI, confidence interval; DM, distant metastasis; M-H, Mantel-Haenszel test.

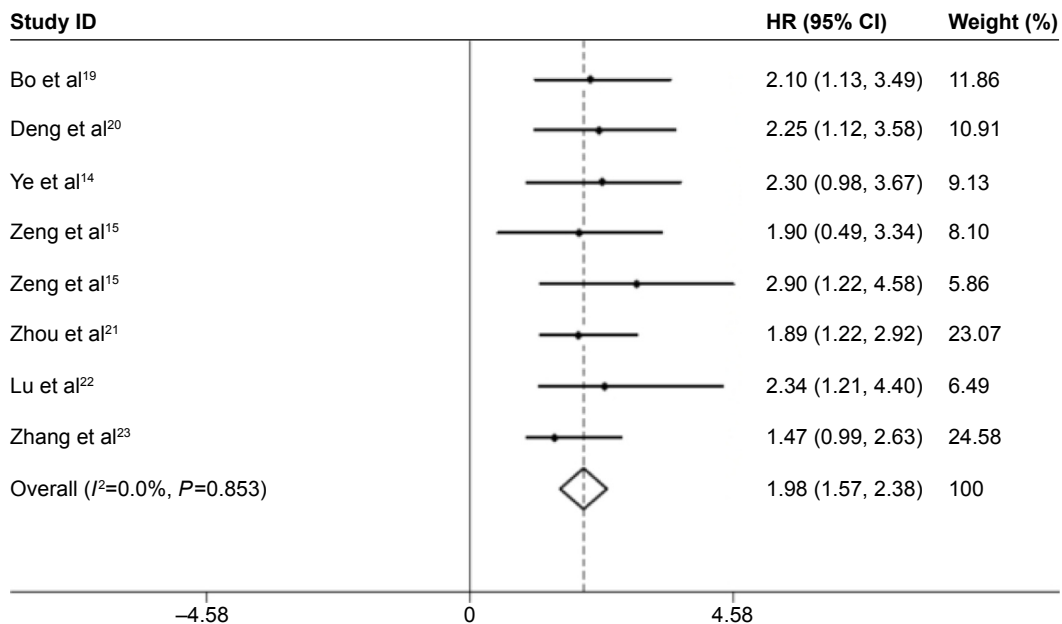


Figure 4 Meta-analysis of the pooled HRs of OS.

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.

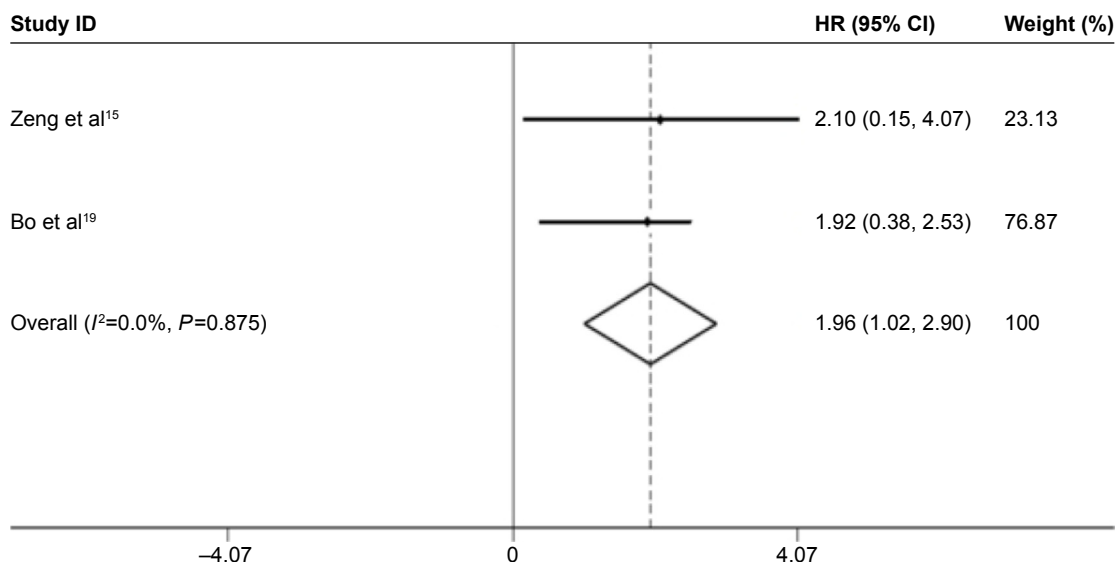


Figure 5 Meta-analysis of the pooled HRs of RFS.

Abbreviations: CI, confidence interval; HR, hazard ratio; RFS, relapse-free survival.

in non-small cell lung cancer²⁷ and breast cancer,²⁸ and plasmacytoma variant translocation 1 (PVT1) has also been brought under the spotlight as the important oncogenes in cancer recently.²⁹ For GAS5,³⁰ TUSC7,³¹ and ANRIL,³² they are all identified as pivotal tumor suppressor lncRNAs in human cancers. Growing number of studies have focused on relationship between lncRNAs and tumors, but the related mechanisms remain to be unclear.

AFAP1-AS1 is one of the lncRNAs located on the anti-sense strand of protein-coding gene AFAP1. AFAP1 is a kind

of motor fiber-related protein, which acts as an adapter molecule to link to other proteins, such as SRC and PKC, to modulate changes in actin filament integrity, and to influence the cytophagy, cell movement, tumor invasion, and metastasis³³⁻³⁶ and the AFAP1-AS1 exon 2 and AFAP1 exons 14, 15, and 16 are just overlapping and complementary regions.¹⁹

Many researchers have reported that expression levels of AFAP1-AS1 in tumor tissues were significantly higher than in paired noncancerous tissues. AFAP1-AS1 might play the role of oncogenic lncRNA in cancer. Knocking

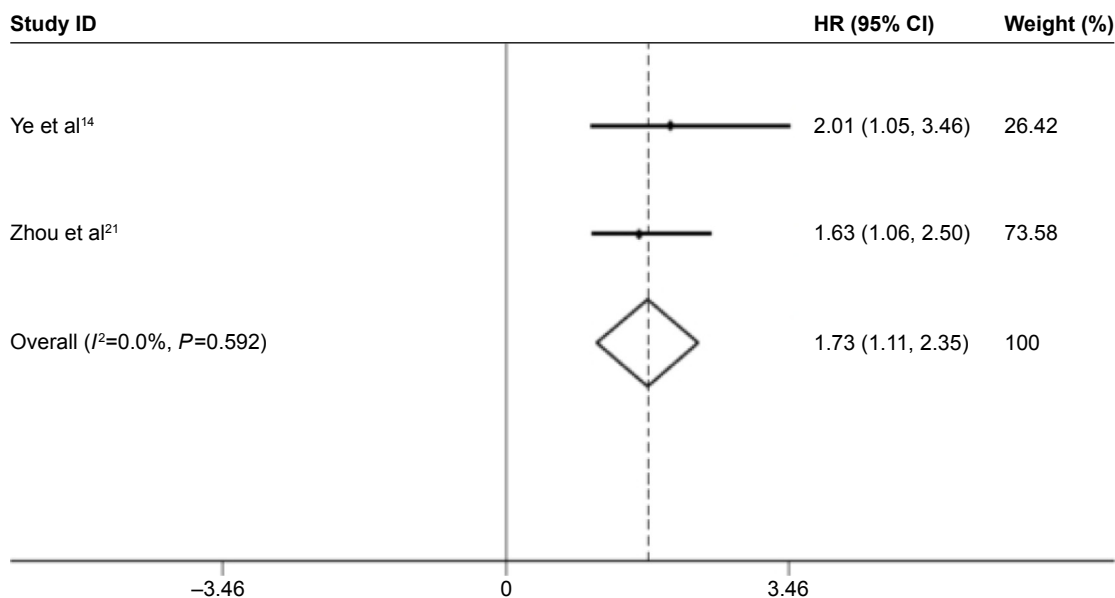


Figure 6 Meta-analysis of the pooled HRs of PFS.

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

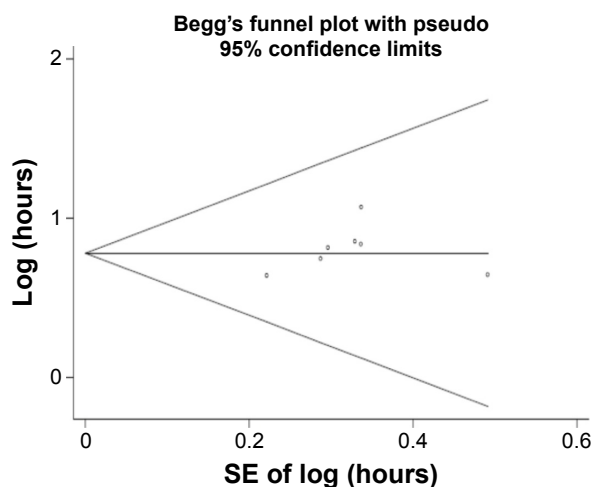


Figure 7 Funnel plot analysis of potential publication bias for OS.
Abbreviations: OS, overall survival; SE, standard error.

down of AFAP1-AS1 could significantly inhibit the tumor cells, migration and invasive capability in vitro. On the contrary, cell proliferation, migration, and invasion could be enhanced by the expression of AFAP1-AS1. There was a close association between AFAP1-AS1 expression and tumor development and progression. Preliminary studies have suggested that AFAP1-AS1 could regulate the expression of AFAP1 gene, further affecting the Rho/Rac signaling pathway, inducing the regulation of cytoskeleton remodeling, thereby promoting tumor cell invasion and metastasis in lung cancer,¹⁵ nasopharyngeal carcinoma,¹⁹ and hepatocellular carcinoma.²³ However, the specific molecular mechanism needs to be further investigated. Another study by Lu et al²² showed that cell proliferation and invasion in hepatocellular carcinoma would be promoted by AFAP1-AS1 through mediating related gene expression, such as *BCL-2* and *Bax*, which were well-known genes involved in cancer.³⁷ In addition, AFAP1-AS1 was reported to be involved in chemoradiotherapy resistance, which might have predictive significance of definitive chemoradiotherapy response in esophageal squamous cell carcinoma.²¹ AFAP1-AS1 is one of the most intensely and frequently overexpressed lncRNAs in pancreatic ductal adenocarcinoma,¹⁴ and it has also been revealed that its overexpression was correlated with perineural invasion¹⁴ and poor disease-free survival.²²

This meta-analysis we performed investigated the association of lncRNA-AFAP1-AS1 with metastasis (LNM, DM) and prognosis outcomes (OS, RFS, and PFS) in patients with cancer. From the available evidence, we found that there was a significant association between the expression levels of AFAP1-AS1 and metastasis and prognosis in various tumors. The patients with high AFAP1-AS1 expression might

suffer higher probability of occurrence of LNM and DM. Furthermore, high expression was significantly correlated with a shorter OS and a poorer RFS and a worse PFS may be observed in the patients with high expression. And because there was no severe heterogeneity among studies and the limited number of studies included, sensitivity analysis and assessment of publication bias was not performed for LNM, DM, RFS, and PFS. The meta-analysis results indicated that lncRNA AFAP1-AS1 may act as a novel biomarker in predicting the clinical outcome of cancer patients.

Study limitations

First, the number of patients and types of cancers included was small. Second, studies included in the meta-analysis came from People's Republic of China, for this reason, the results we found may just represent the cases of Chinese patients with cancer. Third, because positive results could be published more easily than negative results, this may lead to larvaceous publication bias. Finally, there was a lack of a unified criterion for high expression. Therefore, more larger-scale, multicenter, and high-quality studies are required to confirm our findings in the future.

Disclosure

The authors report no conflicts of interest in this work.

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