Review Article
Prognostic significance of long non-coding RNA AFAP1-AS1 in human gastrointestinal cancers: a meta-analysis

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Abstract: Background: AFAP1-AS1, as a newly discovered lncRNA, is aberrantly expressed in gastrointestinal cancer tissues and is related with clinical progression and prognosis. This meta-analysis was performed to systematically assess the clinical value of AFAP1-AS1 in gastrointestinal cancers. Methods: A systematic search was performed in Pubmed, Web of Science, Springer together with Wanfang database, and Chinese National Knowledge Infrastructure (CNKI) until August 15, 2017. We collected relevant publications to explore the prognostic significance of AFAP1-AS1 in gastrointestinal cancers. Results: A total of 831 patients from 10 studies were included in the meta-analysis. The pooled results showed that there was a significant association between high AFAP1-AS1 expression and worse overall survival (OS) (HR = 1.82, 95% CI = 1.44-2.19, $p < 0.001$), shorter disease-free survival (DFS) (HR = 2.21; 95% CI = 1.08-3.34; $p < 0.001$), and poorer progression-free survival (PFS) (HR = 1.73; 95% CI = 1.11-2.35; $p < 0.001$) in gastrointestinal cancers. For OS, subgroup analyses were also conducted to confirm the prognostic value of AFAP1-AS1. Additionally, high AFAP1-AS1 expression was correlated with unfavorable features regarding lymph node metastasis, distant metastasis, and clinical stage in gastrointestinal cancers. Conclusions: AFAP1-AS1 might serve as a novel prognostic biomarker for patients with gastrointestinal cancers.

Keywords: AFAP1-AS1, gastrointestinal cancer, prognosis, meta-analysis

Introduction

Gastrointestinal (GI) cancers are major malignancies, which seriously threaten human health and make a huge burden on society [1, 2]. Recently, increasing interests have focused on searching for promising prognostic tumor-biomarkers for these cancers [3-5]. Novel prognostic markers are in urgent need and significant for clinical practices.

With revolutions in the development of new technologies, long noncoding RNAs, which once were perceived as transcriptions of "noise", have now aroused mounting interests for their vital roles in diverse biological processes [6, 7]. Accumulating evidence shows that lncRNAs are frequently aberrantly expressed in cancers and involved in tumorigenesis and progression [8-10]. Furthermore, they might be

act as prognostic biomarkers and therapeutic targets in human cancers [11-13].

LncRNA-actin filament associated protein 1 antisense RNA1 (AFAP1-AS1) is a newly identified lncRNA found to be up-regulated in cancer tissues and function as an oncogene in the occurrence and development of various cancers [14-17]. Recently, the potential prognostic value of AFAP1-AS1 as a biomarker in gastrointestinal cancers has drawn much attention. Numerous studies indicate that AFAP1-AS1 is implicated in tumor invasion and metastasis, and shows prognostic power for predicting survival of patients with gastrointestinal cancers [18-20]. However, no specific meta-analysis was performed to systematically elucidate the prognostic value of AFAP1-AS1 in gastrointestinal cancers until now. Therefore, this present analysis aimed to give a comprehensive assess-
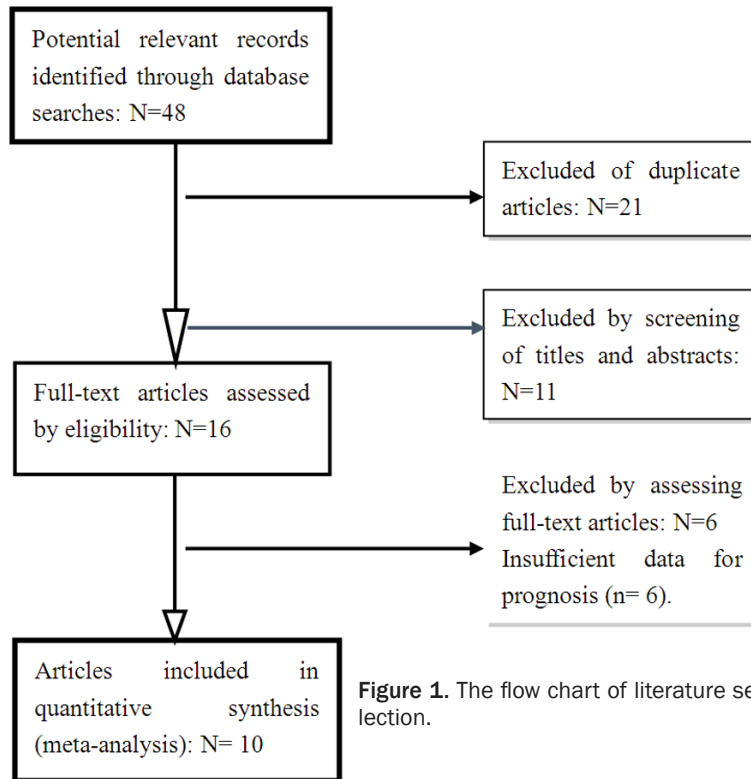
Figure 1. The flow chart of literature selection.

ment of the prognostic value of AFAP1-AS1 in gastrointestinal cancers.

Materials and methods

Search strategy

We conducted a systematic search for AFAP1-AS1-related articles in several online databases: Pubmed, Web of Science, Springer, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) datasets. The last update of searching time was August 15, 2017. The following search keywords were used in the search: AFAP1-AS1, AFAP1 antisense RNA, or lncRNA-AFAP1-AS1.

Selection criteria

Inclusion criteria: (1) Studies investigated the relationships between AFAP1-AS1 and gastrointestinal cancers; (2) Correlation of AFAP1-AS1 with prognosis was reported; (3) Patients were divided into two groups according to the level of AFAP1-AS1 in tissue samples.

Exclusion criteria: (1) Case reports, letters, reviews and abstracts; (2) Duplicate publica-

tions, (3) Studies without usable data.

Data extraction

The following information were extracted: first author's name, publication year, country, cancer type, sample size, clinical stage, preoperative treatment, follow-up time, outcome measures, expression pattern, cut-off value, determination method, and analysis type.

Additionally, the relevant clinicopathological features (tumor differentiation, lymph node metastasis, distant metastasis, clinical staging) were also extracted from eligible studies.

We extracted survival data from Kaplan-Meier survival curves via Engauge Digitizer V4.1 if a study only provided graphical survival plots. If a study provided multivariate cox regression analysis, then the data was used directly.

Quality assessment

The Newcastle-Ottawa assessment scale (NOS) was used for quality control since all included studies were non-randomized studies. The NOS comprised three parameters of quality: selection (score: 0-4), comparability (score: 0-2) and outcome assessment (score: 0-3). There was a score ranging from 0 to 9 in the method. In this meta-analysis, a study with equal or great than 6 was considered as high-quality.

Statistical analysis

We calculated the pooled HRs for OS/DFS/PFS by Stata SE12.0, and the RevMan5.3 software was used to calculate the pooled ORs for clinicopathological factors.

The Cochran's Q test and Higgins I-squared statistic were used to assess heterogeneity among studies, with a *P* value < 0.1 or I^2 value > 50%

Table 1. Main characteristics of all included studies

First author, Year	Country	Cancer type	Sample Size	Tumor stage	Therapy before surgery	Follow-up	High expression (N, %)	Cut-off value	Detection method	Outcome measures	Analysis type	NOS
Ye Y, 2015	China	PDAC	90	24/66 (I/II)	None	< 5 years	45 (50%)	Median	qRT-PCR	OS, PFS	Univariate	7
Fu XL, 2016	China	PDAC	80	12/52/8/8 (I/II/III/IV)	None	< 5 years	40 (50%)	Median	qRT-PCR	OS	Multivariate	7
Li Q, 2016	China	CRC	30	20/10 (II-III)	None	< 5 years	15 (50%)	2 folds	qRT-PCR	OS	Univariate	6
Wang F, 2016	China	CRC	52	21/31 (I-II/III-IV)	None	< 5 years	26 (50%)	Median ratio	qRT-PCR	OS, DFS	Multivariate	6
Lu X, 2016	China	HCC	156	40/116 (I/II-III)	None	≥ 5 years	78 (50%)	Median	qRT-PCR	OS, DFS	Univariate	9
Zhang JY, 2016	China	HCC	78	32/46 (I-II/III-IV)	N/A	≥ 5 years	57 (73.1%)	cancerous/adjacent > 1	qRT-PCR	OS	Multivariate	7
Zhou XL, 2016	China	ESCC	162	26/53/52/31 (I/II/III/IV)	None	≥ 5 years	81 (50%)	Median	qRT-PCR	OS, PFS	Multivariate	8
Ma F, 2016	China	GBC	40	18/22 (I-II/III-IV)	None	< 5 years	19 (47.5%)	Median ratio	qRT-PCR	OS	Univariate	6
Qiao CF, 2017	China	GC	87	35/52 (I-II/III-IV)	N/A	≥ 5 years	44 (50.6%)	Median	qRT-PCR	OS	Univariate	8
Lu X, 2017	China	CCA	56	34/22 (I-II/III)	None	≥ 5 years	28 (50%)	Median	qRT-PCR	OS	Univariate	7

PDAC: pancreatic ductal adenocarcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; GBC: gallbladder cancer; CCA: cholangiocarcinoma; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; qRT-PCR: quantitative real-time-polymerase chain reaction; N/A, not available.
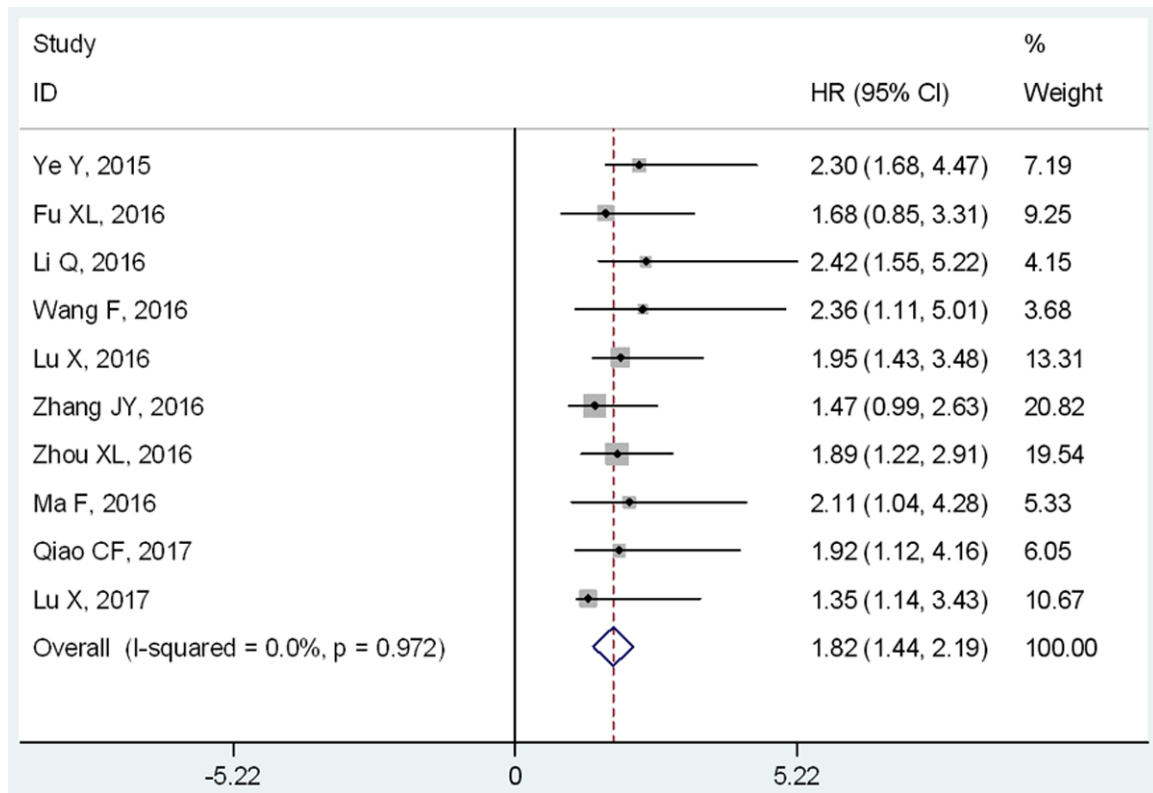
Figure 2. Forest plot of HR for the relationship between AFAP1-AS1 and OS.

being considered significant. The random effects model was used for significant heterogeneity; otherwise, the fixed effects model was applied.

We used the funnel plot and Begg's test/Egger's test to assess potential publication bias, and sensitivity analysis was also conducted to assess the stability of results. A *p*-value < 0.05 was considered statistically significant.

Results

Literature search analysis

According to the selection criteria mentioned above, there were 10 articles enrolled in this meta-analysis [18-27]. The detailed selection steps are shown in **Figure 1**. All studies investigated the prognostic significance of AFAP1-AS1 in gastrointestinal cancers. Ten studies reported the OS of cancer patients, while four were concerned with the PFS/DFS. All included studies were high-quality.

There were a total of 831 patients with survival data in this meta-analysis and those articles were published from 2015 to 2017. All articles were written in English, and those studies all came from China. Among those studies, the mean sample size was 83.1 with a minimum sample size of 30 and a maximum number of 162. A total of 7 different types of gastrointestinal cancers were evaluated in this meta-analysis, including one for esophageal squamous cell carcinoma (ESCC), one for gastric cancer (GC), two for colorectal cancer (CRC), two for hepatocellular carcinoma (HCC), two for pancreatic ductal adenocarcinoma (PDAC), one for gallbladder cancer (GBC), and one for cholangiocarcinoma (CCA). All recruited patients had pathologically or histologically confirmed gastrointestinal cancers. Expression of AFAP1-AS1 in tissue samples was all measured by qRT-PCR. Among those studies, there were four studies directly reporting the HRs and 95% CIs in multivariate analyses, and other six studies provided univariate analyses. The main information is summarized in **Table 1**.

Association between AFAP1-AS1 expression and prognosis

AFAP1-AS1 and OS: All included studies with 831 cases explored the relationship between AFAP1-AS1 and OS in gastrointestinal cancers. As seen in **Figure 2**, the combined re-
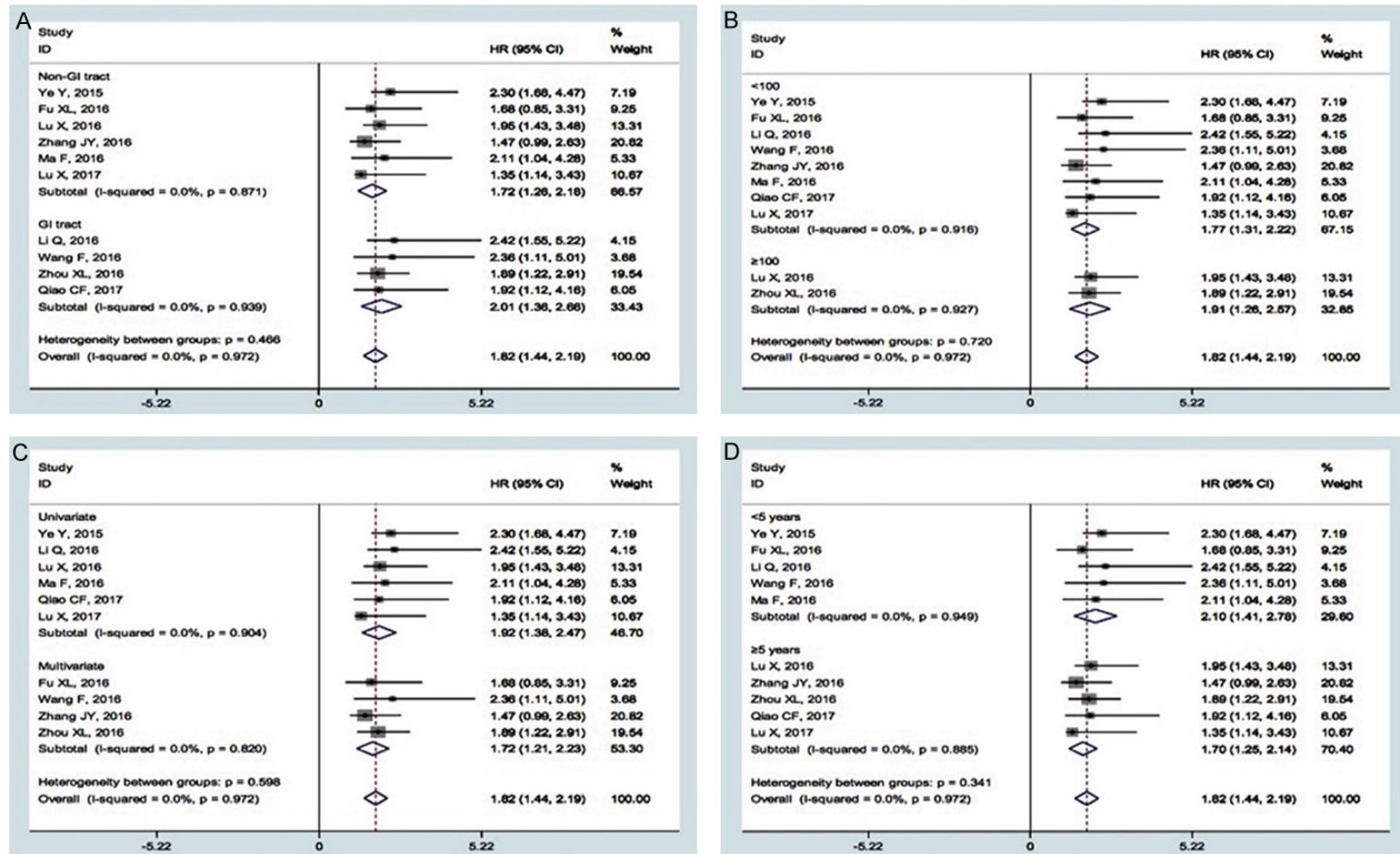
Figure 3. Subgroup analysis for OS stratified by the cancer type (A), sample size (B), analysis type (C) and follow-up time (D).

Table 2. Summary of the meta-analysis results of pooled HRs of OS of patients with high AFAP1-AS1

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	p-value	Heterogeneity	
					I^2 (%)	P_h
[1] Cancer type						
GI tract	4	331	2.01 (1.36-2.66)	< 0.001	0.0	0.939
Non-GI tract	6	500	1.72 (1.26-2.18)	< 0.001	0.0	0.871
[2] Sample size						
≥ 100	2	318	1.91 (1.26-2.57)	< 0.001	0.0	0.927
< 100	8	513	1.77 (1.31-2.22)	< 0.001	0.0	0.916
[3] Analysis type						
Multivariate	4	372	1.72 (1.21-2.23)	< 0.001	0.0	0.820
Non-multivariate	6	459	1.92 (1.38-2.47)	< 0.001	0.0	0.904
[4] Follow-up time						
≥ 5 years	5	539	1.70 (1.25-2.14)	< 0.001	0.0	0.885
< 5 years	5	292	2.10 (1.41-2.78)	< 0.001	0.0	0.949
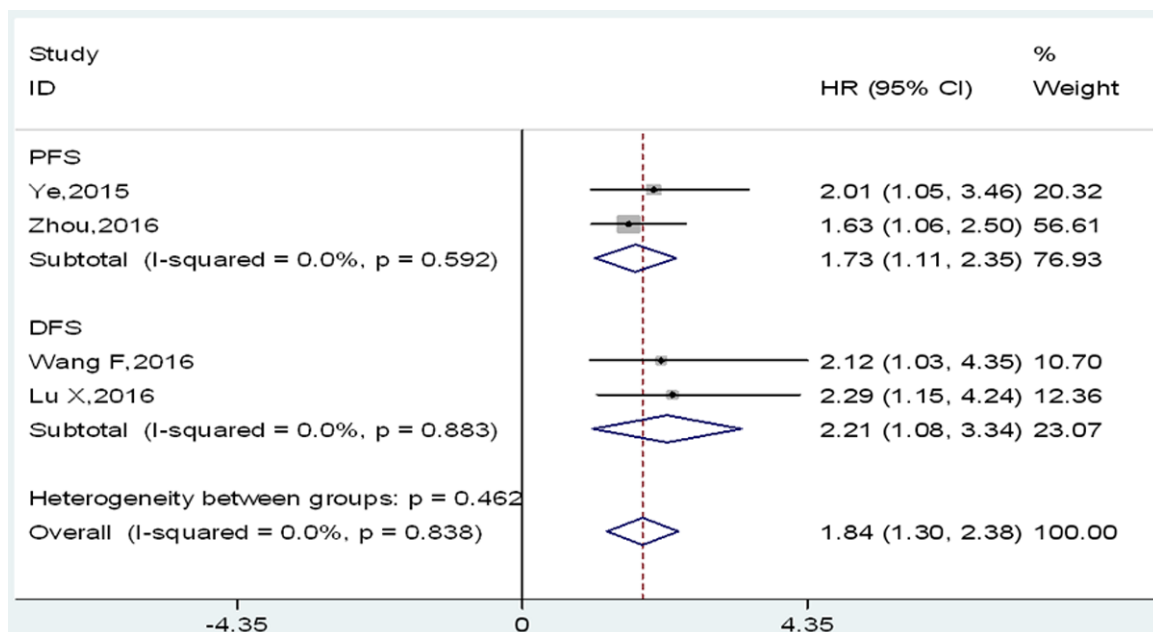
Figure 4. Forest plot of HR for the relationship between AFAP1-AS1 and DFS/PFS.

sults showed a significant association between AFAP1-AS1 expression and OS (HR = 1.82, 95% CI = 1.44-2.19, p < 0.001) with no significant heterogeneity across-studies (I^2 = 0.0%, P = 0.972). The patients with high AFAP1-AS1 expression had a shorter overall survival time than those with low AFAP1-AS1 expression.

Subgroup analysis for OS: We performed subgroup meta-analysis to further investigate the prognostic significance of AFAP1-AS1 in gastrointestinal cancers. As shown in **Figure 3** and **Table 2**. The overall results showed a nega-

tive effect of high AFAP1-AS1 expression on OS in patients with GI tract cancers (HR = 2.01; 95% CI = 1.36-2.66; p < 0.001) or non-GI tract cancers (HR = 1.72; 95% CI = 1.26-2.18; p < 0.001) (**Figure 2A**). Furthermore, the pooled HR values > 1 for OS were consistently calculated in subgroup meta-analysis stratified by the sample size (**Figure 2B**), analysis type (**Figure 2C**) and follow-up time (**Figure 2D**).

AFAP1-AS1 and DFS/PFS: Four studies, comprising a total of 460 patients, reported an association between the expression of AFAP1-AS1 and DFS/PFS. The overall results showed
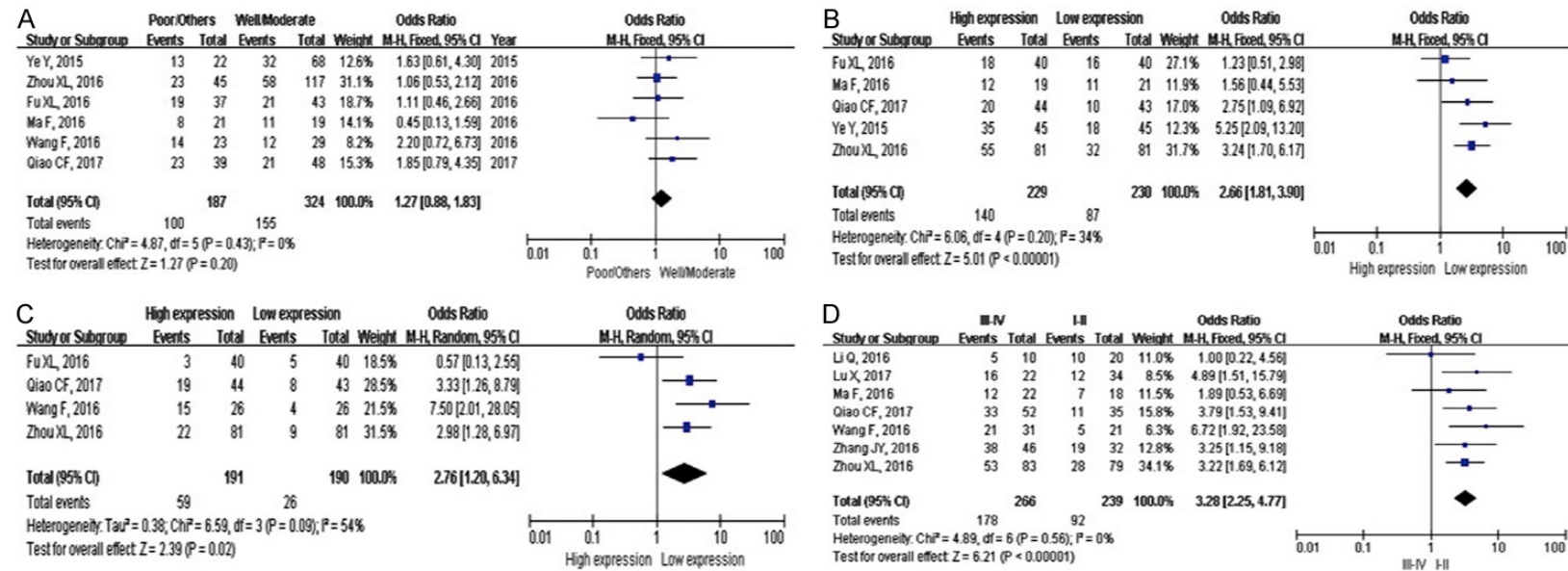
Figure 5. Meta-analysis for the association between up-regulation of AFAP1-AS1 and tumor differentiation (A), lymph node metastasis (B), distant metastasis (C) and clinical stages (D).

Table 3. Meta-analysis of the association between AFAP1-AS1 and clinicopathologic parameters

Variable	Studies (n)	Number of patients	OR (95% CI)	p-value	Heterogeneity		
					I^2 (%)	P-value	Model
Tumor differentiation (Poorly/others vs. Well/moderately)	6	511	1.27 (0.88-1.83)	0.20	0	0.43	Fixed
Lymph node metastasis (Yes vs. No)	5	459	2.66 (1.81-3.90)	< 0.00001	34	0.20	Fixed
Distant metastasis (Yes vs. No)	4	381	2.76 (1.20-6.34)	0.02	54	0.09	Random
TNM stage (III-IV vs. I-II)	7	505	3.28 (2.25-4.77)	< 0.00001	0	0.56	Fixed
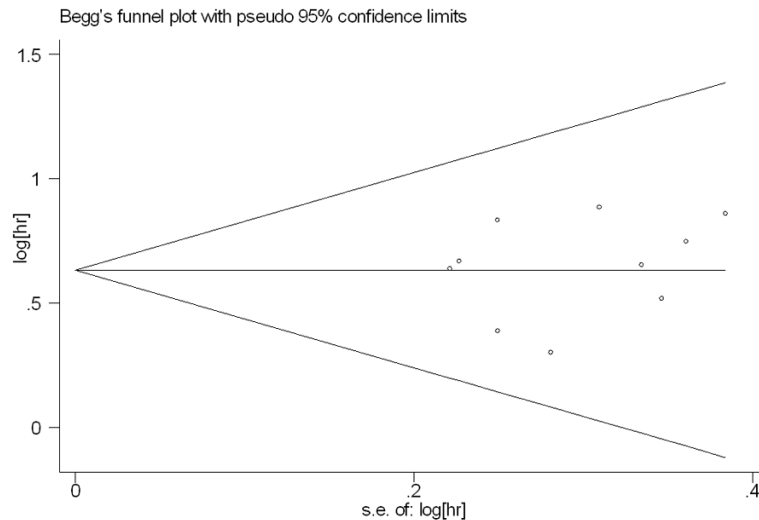
Figure 6. Funnel plot analysis of potential publication bias.

Figure 7. Sensitivity analysis of the pooled HRs of AFAP1-AS1 and OS.

intestinal cancers. As seen in **Figure 5** and **Table 3**, the pooled results showed that increased AFAP1-AS1 was significantly associated with positive lymph node metastasis (OR = 2.66, 95% CI: 1.81-3.90) (**Figure 5B**), distant metastasis (OR = 2.76, 95% CI: 1.20-6.34) (**Figure 5C**) and higher TNM stage (OR = 3.28, 95% CI: 2.25-4.77) (**Figure 5D**). However, no significant correlation was observed between AFAP1-AS1 expression with tumor differentiation from present results (**Figure 5A**).

Publication bias

For meta-analysis of the relationship between AFAP1-AS1 and OS, Begg's funnel plot was displayed in **Figure 6**. The results also revealed that no significant publication bias was observed among studies (for Begg's test: Pr > |z| = 0.592; for Egger's test, P > |t| = 0.598).
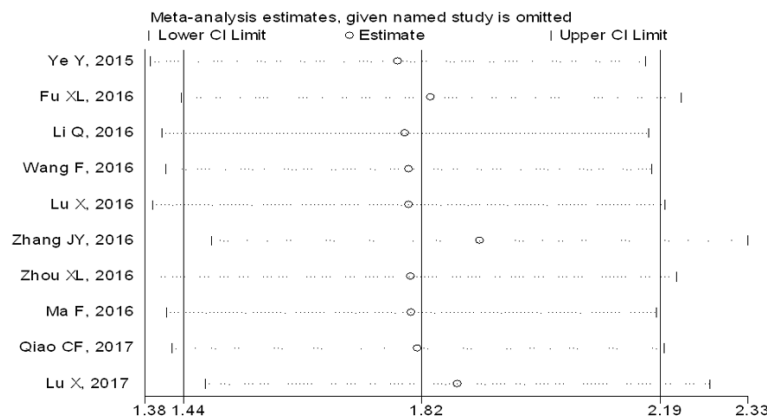
Sensitivity analysis

Sensitivity analysis was conducted to assess the effect of any individual study on OS. It revealed that the overall result was not significantly altered after the exclusion of any studies (**Figure 7**).

that the patients with lower AFAP1-AS1 expression had better DFS (HR = 2.21; 95% CI = 1.08-3.34; *p* < 0.001) or PFS (HR = 1.73; 95% CI = 1.11-2.35; *p* < 0.001) (**Figure 4**).

Association between AFAP1-AS1 expression and clinicopathological features

Additionally, we also assessed the clinicopathological significance of AFAP1-AS1 in gastro-

Discussion

AFAP1-AS1 was reported to be implicated in various human tumors, including gastrointestinal cancers. As a well-known oncogenic lncRNA, many studies have found that abnor-

mal expression of AFAP1-AS1 was related with tumorigenesis and progression and played a pivotal part in gastrointestinal cancers. The role of AFAP1-AS1 as a tumor promoter was initially confirmed in Barrett's esophagus and esophageal adenocarcinoma [28, 29]. In gastric cancer, AFAP1-AS1 was up-regulated, and it could regulate the gastric cancer cell proliferation and apoptosis via PTEN/p-AKT pathway [30]. A study by Han et al. [31] also revealed AFAP1-AS1 was obviously elevated in CRC tissues and cells, and its knock-down exhibited antitumor effect by suppression of tumor formation and hepatic metastasis of CRC cells in nude mice. For hepatocellular carcinoma [23], pancreatic cancer[19] and cholangiocarcinoma [27, 32], its oncogenic functions was also confirmed. Expression of AFAP1-AS1 was found to be up-regulated and functional analysis showed that AFAP1-AS1 knock-down could significantly inhibit proliferation and reduce cell migration and invasion, whereas elevated expression of AFAP1-AS1 could promote cell growth and migration, enhance colony-forming ability *in vivo* and *in vitro* for those cancers.

To the best of our knowledge, this is the first meta-analysis providing integrity evaluations of prognostic value of AFAP1-AS1 in gastrointestinal cancers. In order to give an insight into the relationship of AFAP1-AS1 and cancer prognosis, we combined the results of all relevant studies about AFAP1-AS1 and gastrointestinal cancer. Finally, a total of ten studies with 831 cases were considered eligible and included, along with seven different types of gastrointestinal cancers. Pooled data of eligible studies showed that the AFAP1-AS1 expression was negatively associated with OS and DFS/PFS in gastrointestinal cancers, with the patients having higher AFAP1-AS1 expression associated with poorer prognosis than those with lower expression. Furthermore, the subgroup analysis results for OS also confirmed the prognostic significance of AFAP1-AS1 in gastrointestinal cancers. Regarding the clinical relevance of AFAP1-AS1 in gastrointestinal cancers, from the present results, we found that high expression of AFAP1-AS1 predicted more prone to LNM and DM. Additionally, the patients with elevated expression tended to have higher clinical stage. Taken together, AFAP1-AS1 might be closely associated with progression and prognosis of gastrointestinal cancers, which indi-

cated its potential promising predictive values in gastrointestinal cancers.

However, there are some limitations in our meta-analysis that should be mentioned. First of all, the eligible studies in this analysis were relatively small, only 10 studies with 831 patients were included, and we failed to evaluate the prognostic value of AFAP1-AS1 in some certain type of gastrointestinal cancer. Secondly, all included studies were conducted with Chinese sample populations, consequently, our results may result in potential ethnic bias and are only applicable in this group. Additionally, clinicopathological data provided in different studies were not the same and limited, and positive results were easier to be published than negative results. Furthermore, the cut-off value of AFAP1-AS1 expression varied in different studies. Lastly, many factors, such as treatment, and duration of follow-up, may also affect patient survival.

In conclusion, our meta-analysis provides strong evidence that elevated AFAP1-AS1 expression is associated with an unfavorable prognosis and advanced clinical progression in gastrointestinal cancers. AFAP1-AS1 might serve as a novel prognostic biomarker for patients with gastrointestinal cancers. Nevertheless, considering the limitations described above, well-designed studies with large-volume and other ethnic groups are warranted to further confirm and update the findings of this analysis.

Disclosure of conflict of interest

None.

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