

Prognostic role of long non-coding RNA HNF1A-AS1 in Chinese cancer patients: a meta-analysis

Chunbo Zhuang¹Lei Zheng¹Pei Wang²

¹Department of Clinical Laboratory Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China;

²Department of Gastroenterology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China

Background: Long non-coding RNAs (LncRNAs) play important roles in tumorigenesis and progression. Recent studies have demonstrated that LncRNA HNF1A antisense RNA 1 (*HNF1A-AS1*) is aberrantly expressed in several types of cancers and is associated with poor outcomes. This meta-analysis was conducted to investigate the relationship between HNF1A-AS1 expression and clinical outcomes in cancer patients.

Methods: We searched PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wan Fang databases (updated until December 31, 2017) for literature. A total of eight studies with 789 cancer patients were finally included in the present meta-analysis.

Results: The results showed that high expression of HNF1A-AS1 significantly predicted poor overall survival (HR=3.10, 95% CI: 1.58–6.11, $P=0.001$), which was further validated using The Cancer Genome Atlas (TCGA) dataset. Moreover, high HNF1A-AS1 expression was also associated with advanced TNM stage (OR=3.32, 95% CI: 2.28–4.83, $P<0.001$), lymph node metastasis (OR=3.08, 95% CI: 1.95–4.85, $P<0.001$), and distant metastasis (OR=5.53, 95% CI: 1.94–15.77, $P=0.001$).

Conclusion: Our results suggested that elevated HNF1A-AS1 was associated with poor clinical outcomes and might serve as a potential prognostic biomarker of cancer.

Keywords: cancer, overall survival, TCGA, long non-coding RNA, HNF1A-AS1, meta-analysis

Introduction

Cancer is a major public health problem with increasing incidence and mortality.¹ In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States.² Although the evolving treatment strategies such as targeted therapy and biotherapy improved the outcomes of cancer patients, the applicable patients were limited.³ In addition, the 5-year survival rates for most cancers are still very low, which is mainly because of the late-stage diagnosis and insufficient understanding of the molecular mechanisms underlying cancer development. Therefore, it is critical to identify useful prognostic biomarkers and novel potential therapeutic targets for cancer therapy.

Long non-coding RNAs (LncRNAs) are a group of RNAs that are larger than 200 nucleotides in length and lack the protein-coding capability.⁴ In the last decade, numerous studies have reported the critical roles of these kinds of transcripts in biological processes, such as cell differentiation, proliferation, and apoptosis.⁵ Moreover, accumulating evidence has shown the dysregulated expression of numerous LncRNAs in human cancers and that LncRNAs may act as oncogenes or tumor suppressors participating in tumorigenesis and metastasis.⁶ A number of LncRNAs have been shown to be novel promising prognostic biomarkers in human cancers.⁷

HNF1A antisense RNA 1 (HNF1A-AS1), a natural antisense transcript of HNF1A, is a newly identified LncRNA located at chromosomal band 12q24.31 with 2,455

Correspondence: Pei Wang
Department of Gastroenterology,
The First Affiliated Hospital of
Zhengzhou University, No 1 Jian She
East Road, Zhengzhou, Henan 450052,
People's Republic of China
Tel/fax +86 371 6691 3230
Email pennypaul@126.com

nucleotides in length.⁸ HNF1A-AS1 has been reported to be upregulated and act as an oncogene in many types of cancers.^{8–19} Moreover, the expression of HNF1A-AS1 is associated with poor prognosis and high risk of metastasis in several cancers, such as osteosarcoma, colon cancer, lung cancer, and hepatocellular carcinoma (HCC).^{9,10,12,17,20} However, individual study may be inaccurate or insufficient due to the limitations of sample sizes or research programs. Therefore, we collected all relevant publications and conducted this meta-analysis to explore the association of HNF1A-AS1 with clinical outcomes and to investigate whether HNF1A-AS1 could serve as a potential biomarker for prognosis in cancer patients.

Materials and methods

Literature search

We conducted a comprehensive literature search in the following databases: PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wan Fang (updated until December 31, 2017). The key words for search included the following: “HNF1A antisense RNA 1”, “HNF1A-AS1”, “HNF1AAS1”, “Long non-coding RNA HNF1A-AS1”, “LncRNA HNF1A-AS1”, “tumor”, “cancer”, “carcinoma”, “neoplas*”, and “malignan*”. A manual review of the reference lists of relevant articles was also performed to identify potentially eligible papers.

Inclusion and exclusion criteria

The inclusion criteria of this meta-analysis were the studies in which: 1) the expression of HNF1A-AS1 in tumor tissues was measured, 2) patients were divided into two groups based on high and low expression levels of HNF1A-AS1, 3) the associations of HNF1A-AS1 expression levels with prognosis or clinicopathological features were described, and 4) HRs or ORs with 95% CIs were reported or sufficient data were available for the computation.

Exclusion criteria were as follows: 1) duplicated articles, 2) editorials, letters, expert opinions, case reports, and reviews, and 3) studies without available data. Two authors screened the studies independently, and the disagreement was resolved by consensus.

Data collection

Two investigators (Chunbo Zhuang and Lei Zheng) extracted the data independently from the eligible studies, and disagreements were resolved by a third investigator (Pei Wang). The following information were extracted: the name of first author, year of publication, country, cancer type, sample

size, detection method of HNF1A-AS1, internal control, cutoff values, tumor stage, outcome, follow-up time, HR and its corresponding 95% CI, and the clinicopathological parameters from each eligible study. If both the univariate and multivariate analyses were provided by the eligible studies, the multivariate values were selected as they had higher precision on interpreting confounding factors. For the studies only reporting Kaplan–Meier curves, the Engauge Digitizer (Version 4.1) software was used to extract the survival data, as previously described.²¹

Public data and tools

The Gene Expression Profiling Interactive Analysis (GEPIA) is an online database for analyzing the RNA sequencing expression data of tumors and normal samples from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects, using a standard processing pipeline (<http://gepia.cancer-pku.cn/>). In this study, we used the GEPIA database to analyze the tumor/normal differential expression of HNF1A-AS1 and its correlation with overall survival (OS) in TCGA dataset. One-way ANOVA was used for differential expression analysis, and the Kaplan–Meier method was used for survival analysis. The HR and 95% CI were also shown in the survival plot.

Statistical analyses

The Stata SE12.0 and Revman 5.3 software were used to perform all statistical analyses. HRs and 95% CIs were calculated to assess the association between HNF1A-AS1 and OS. An observed HR of >1 indicated poor prognosis in patients with high HNF1A-AS1 expression. In addition, ORs and 95% CIs were used to assess the correlation between HNF1A-AS1 expression and the clinicopathological features. The heterogeneity between the included studies was determined by I^2 value derived from the Q test and a P -value from the Chi square test. The fixed-effects model was used if there was no obvious heterogeneity ($I^2 \leq 50\%$ or $P \geq 0.05$); otherwise, a random-effects model was applied. Begg’s test with a funnel plot and Egger’s test were used to estimate the publication bias. The sensitivity analysis was also performed to assess the stability of the results. $P < 0.05$ was considered statistically significant.

Results

Study characteristics

The details of literature screening procedure are presented in Figure 1. Our initial search retrieved 94 papers from PubMed, Embase, Web of Science, CNKI, and Chinese Wan

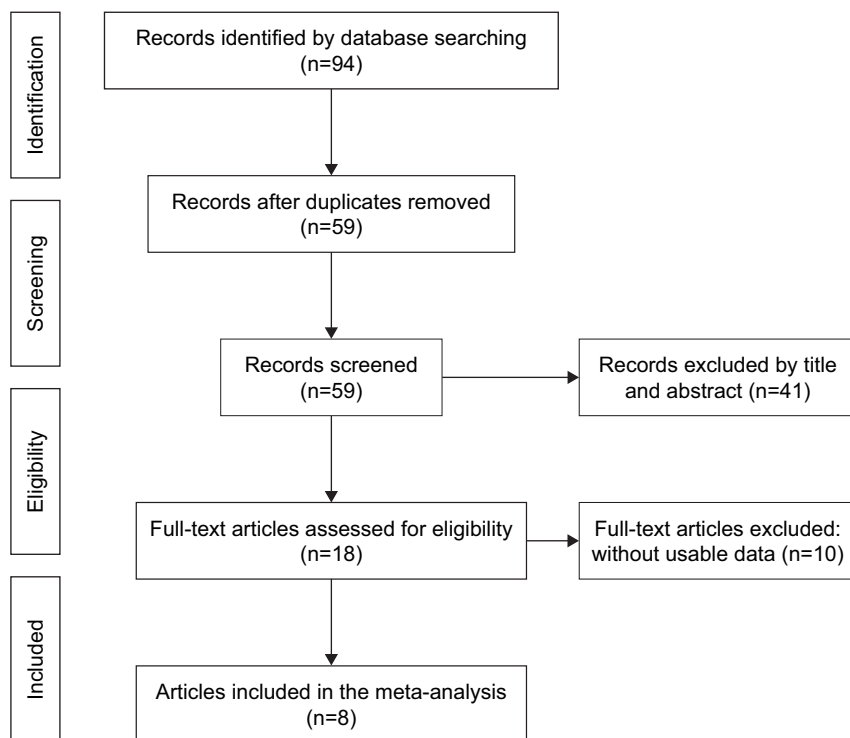


Figure 1 Flow diagram of the literature search and selection.

Fang databases. After the removal of duplicates, 59 articles remained. After carefully screening the titles and abstracts, we excluded 41 articles including letters, reviews, conference abstracts, and unrelated studies. The remaining 18 full-text articles were further reviewed and assessed, and 10 of them were excluded because of incomplete data. Ultimately, eight articles were included in this meta-analysis.

All the eight studies were from China and related to six types of cancers, including osteosarcoma, colon cancer, non-small cell lung cancer, HCC, bladder cancer, and lung adenocarcinoma. A total number of 789 patients were included in this study. The expression of HNF1A-AS1 was detected by quantitative reverse transcription PCR (qRT-PCR) in all the included studies, while the cutoff values were different. HRs and 95% CIs were directly extracted from four studies and were calculated by survival curve in two studies. The characteristics of the included studies are summarized in Table 1.

Association between HNF1A-AS1 expression and OS

Six studies reported the association between HNF1A-AS1 expression and OS. A random-effects model was applied to calculate the pooled HR and 95% CI due to the existence of significant heterogeneity across these six studies ($P < 0.001$,

$I^2 = 80\%$). The result suggested that high level of HNF1A-AS1 expression was associated with poor OS (HR=3.10, 95% CI: 1.58–6.11, $P = 0.001$) (Figure 2).

Subsequently, we performed subgroup analyses according to internal control and cutoff values to evaluate the prognostic role of HNF1A-AS1 in cancers. As shown in Table 2, high expression of HNF1A-AS1 was significantly associated with poor OS when detected using GAPDH as an internal control or using median value as a cutoff.

Association between HNF1A-AS1 expression and clinicopathological parameters

In order to comprehensively analyze the potential role of HNF1A-AS1 in various cancers as a prognostic biomarker, we investigated the association between HNF1A-AS1 expression and clinicopathological characteristics. As shown in Table 3, high HNF1A-AS1 expression was significantly associated with advanced TNM stage (OR=3.32, 95% CI: 2.28–4.83, $P < 0.001$; Figure 3A), lymph node metastasis (OR=3.08, 95% CI: 1.95–4.85, $P < 0.001$; Figure 3B), and distant metastasis (OR=5.53, 95% CI: 1.94–15.77, $P = 0.001$; Figure 3C). However, no significant association was observed between HNF1A-AS1 expression and age, gender, tumor size, or tumor differentiation.

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

Study	Country	Cancer type	Sample size	Detection method	Internal control	Cutoff	Tumor stage	Metastasis analysis	Outcome	Analysis	HR estimation	Follow-up months
Cai et al (2017) ⁹	China	Osteosarcoma	72	qRT-PCR	GAPDH	Median	IIA–III	IM	OS	M/U	Reported	36
Fang et al (2017) ¹⁰	China	Colon cancer	98	qRT-PCR	β-Actin	Median	I–IV	LN/DM	OS/DFS	M/U	Reported	60
Ma et al (2016) ¹²	China	NSCLC	177	qRT-PCR	GAPDH	Median	I–IV	LNM	OS	M/U	Reported	60
Zhao et al (2016) ¹⁷	China	Osteosarcoma	43	qRT-PCR	GAPDH	Median	I–III	DM	OS	M/U	Reported	60
Zhang (2017) ²⁰	China	HCC	138	qRT-PCR	GAPDH	Fold change	I–IV	NA	OS	U	SC	80
Zhang et al (2017) ²¹	China	Colorectal cancer	142	qRT-PCR	β-Actin	Median	I–IV	NA	OS/DFS	U	SC	60
Zhan et al (2017) ¹⁶	China	Bladder cancer	79	qRT-PCR	β-Actin	Fold change	Ta–T4	LNM	NA	NA	NA	NA
Wu et al (2015) ¹⁵	China	Lung adenocarcinoma	40	qRT-PCR	GAPDH	Fold change	I–IV	LNM	NA	NA	NA	NA

Abbreviations: DFS, disease-free survival; DM, distant metastasis; HCC, hepatocellular carcinoma; HR, hazard ratio; IM, initial metastasis; LNM, lymph node metastasis; M, multivariate; NA, not available; NSCLC, non-small cell lung cancer; OS, overall survival; qRT-PCR, quantitative reverse transcription PCR; SC, survival curve; U, univariate.

Sensitivity analysis and publication bias

Given that significant heterogeneity was observed in the meta-analysis of OS ($P < 0.001$, $I^2 = 80\%$), we performed sensitivity analysis to assess the influence of individual study on the synthetic results. As shown in Figure 4, the pooled HR was not significantly affected after removing any single study. However, the result also showed that the study by Fang et al¹⁰ was responsible for the heterogeneity.

We performed Begg's funnel plot and Egger's test to evaluate the publication bias of the included studies for OS. The Begg's funnel plot is shown in Figure 5, and the P -value of Egger's test was 0.399. These results suggested that there was no significant publication bias in this meta-analysis.

Validation of the results in TCGA dataset

To validate the abovementioned results, we first evaluated the expression of HNF1A-AS1 in five kinds of cancers using the data from TCGA. As shown in Figure 6A, HNF1A-AS1 was overexpressed in four of them, including colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), liver hepatocellular carcinoma (LIHC), and rectum adenocarcinoma (READ) ($|\text{Log}_2\text{FC}|$ cutoff > 0.6 and $P < 0.01$). Then, we accessed the association of HNF1A-AS1 expression with OS in all the cancers from TCGA dataset. A total of 8,787 patients were divided into high or low expression group based on median expression of HNF1A-AS1. As shown in Figure 6B, patients in the high expression group showed a worse OS than those in the low expression group. These results confirmed that HNF1A-AS1 was upregulated and significantly associated with poor prognosis in various cancers.

Discussion

Recently, a growing number of studies have reported the association between lncRNAs and cancer, and the functional roles of these tumor-associated lncRNAs in tumorigenesis and progression were gradually characterized.⁶ In addition, lncRNAs exhibit genome-wide expression patterns in various tissues and tissue-specific expression characteristics, making them novel promising biomarkers and therapeutic targets for cancer. Accumulating studies have suggested that lncRNAs could serve as potential prognostic biomarkers of different cancers.^{22–25} HNF1A-AS1 is one of these hot lncRNAs.

HNF1A-AS1 has been reported to be upregulated in various types of cancers. Recent studies demonstrated that HNF1A-AS1 promoted tumorigenesis and progression by regulating various cellular processes, including proliferation, migration, invasion, apoptosis, and autophagy.¹⁸ However, the

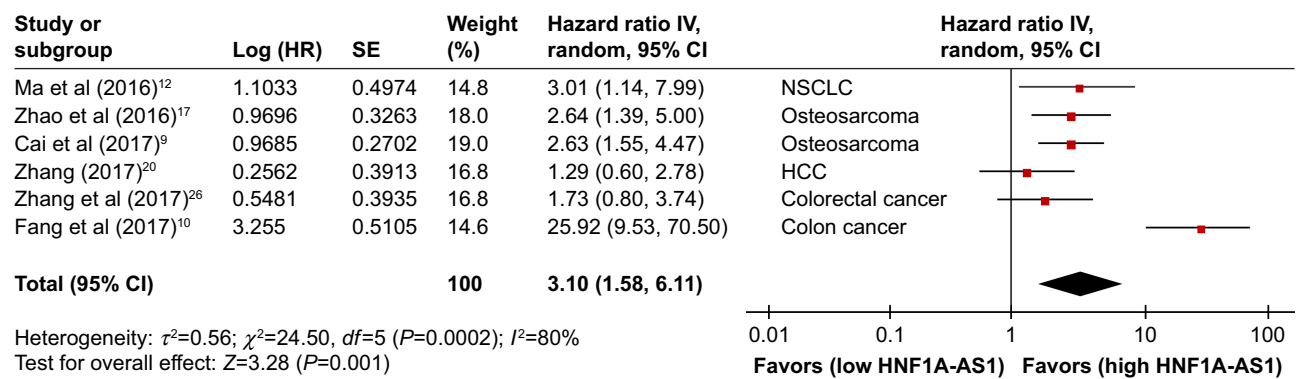


Figure 2 Forest plot for the association between HNF1A-AS1 expression and OS.

Abbreviations: HNF1A-AS1, HNF1A antisense RNA 1; OS, overall survival; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

underlying mechanisms have not been fully elucidated. It was reported that knockdown of HNF1A-AS1 could inhibit the expression of H19, a well-known cancer-related LncRNA.⁸ Knockdown of HNF1A-AS1 suppressed tumor cell invasion and migration by reducing the epithelial–mesenchymal transition program in osteosarcoma, lung adenocarcinoma, and nasopharyngeal carcinoma.^{9,15,19} In line with these findings, Wang et al¹³ demonstrated that HNF1A-AS1 promoted HCC cell proliferation through repressing *NKDI* and *p21* expression by interacting with *EZH2*. Moreover, as an oncogene in osteosarcoma and colorectal cancer, LncRNA HNF1A-AS1 promoted tumor cell proliferation and metastasis by activating the Wnt/ β -catenin signaling pathway.^{17,26} In addition, HNF1A-AS1 has been demonstrated to function as a competing endogenous RNA (ceRNA) that binds to and inhibits the expression of miRNAs such as miR-30b and miR-34a. In HCC, HNF1A-AS1 inhibited apoptosis by the miR-30b/Bcl-2 pathway and promoted autophagy by the miR-30b/AGT5 pathway.¹¹ In another study by Fang et al,¹⁰ HNF1A-AS1 facilitated colon cancer cell proliferation and metastasis in an miR-34a/p53-dependent manner. These studies suggested that HNF1A-AS1 might serve as an oncogene and predict poor outcomes in cancer patients.

In the present meta-analysis, a total of eight studies including 789 patients were included, and the result suggested that enforced HNF1A-AS1 expression was

significantly associated with poor prognosis in patients with various types of cancers. The increased HNF1A-AS1 expression was associated with shorter OS. The pooled HR for OS was 3.10 (95% CI: 1.58–6.11, $P=0.001$). The association between HNF1A-AS1 expression and clinicopathological characteristics was also analyzed in this meta-analysis. Our results showed that increased HNF1A-AS1 expression was associated with advanced TNM stage, lymph node metastasis, and distant metastasis. The pooled ORs were 3.32 (95% CI: 2.28–4.83, $P<0.001$), 3.08 (95% CI: 1.95–4.85, $P<0.001$), and 5.53 (95% CI: 1.94–15.77, $P=0.001$), respectively.

However, there are still some limitations that should be noted in this meta-analysis. First, the total sample size was relatively small, and all the included patients were from China. Second, statistical heterogeneity was observed, which may be due to the differences in cancer types, internal control, cutoff value, clinical characteristics, and sample sizes. Third, although no obvious publication bias was observed, the selection bias may exist in the present meta-analysis. For example, Dang et al²⁷ reported that HNF1A-AS1 was significantly downregulated in gastric cancer, and low HNF1A-AS1 expression was associated with tumor size and levels of serum CEA and CA199. Using high-throughput next-generation sequencing (NGS)-based technologies, Müller et al²⁸ reported that HNF1A-AS1 was downregulated

Table 2 Subgroup analysis of the association between HNF1A-AS1 expression and OS by internal control and cutoff value

Subgroup factor	Divided standard	Study number	Pooled HR (95% CI)	P-value	Heterogeneity		Model
					I^2 (%)	P_h	
Internal control	GAPDH	4	2.33 (1.66–3.27)	<0.0001	0	0.41	Fixed
	β -Actin	2	6.57 (0.46–93.17)	0.16	94	<0.0001	Random
Cutoff value	Median	5	3.52 (1.58–7.82)	0.002	83	0.0001	Random
	Fold change	1	1.73 (0.80–3.74)	0.16	–	–	–

Notes: Bold figures indicate statistically significant $P<0.05$. “–” indicates data not available.

Abbreviations: HNF1A-AS1, HNF1A antisense RNA 1; OS, overall survival.

Table 3 The association between HNF1A-AS1 expression and clinical features

Clinicopathological parameters	Studies (n)	Patients (n)	OR (95% CI)	P-value	Heterogeneity		
					I ² (%)	P _h	Model
Age	7	647	0.93 (0.68–1.28)	0.67	0	0.60	Fixed
Gender	7	647	0.86 (0.60–1.23)	0.40	0	0.64	Fixed
Tumor size	6	470	1.40 (0.95–2.08)	0.09	34	0.18	Fixed
Tumor differentiation	5	517	0.76 (0.34–1.73)	0.51	68	0.01	Random
TNM stage	6	569	3.32 (2.28–4.83)	<0.0001	5	0.56	Fixed
LNM	4	394	3.08 (1.95–4.85)	<0.0001	0	0.50	Fixed
DM	2	141	5.53 (1.94–15.77)	0.001	0	0.80	Fixed

Note: Bold figures indicate statistically significant $P < 0.05$.

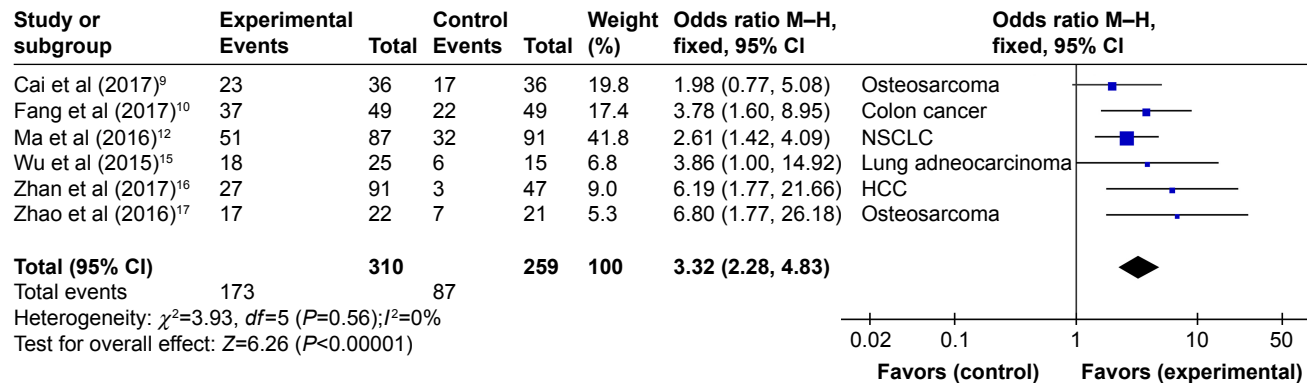
Abbreviations: DM, distant metastasis; HNF1A-AS1, HNF1A antisense RNA I; LNM, lymph node metastasis.

in pancreatic cancer. These two studies suggested a possible role of HNF1A-AS1 as a tumor suppressor. However, the lack of relevant data precluded them from the present meta-analysis. Finally, some HRs were extracted from the survival curves, which may lead to small statistical errors.

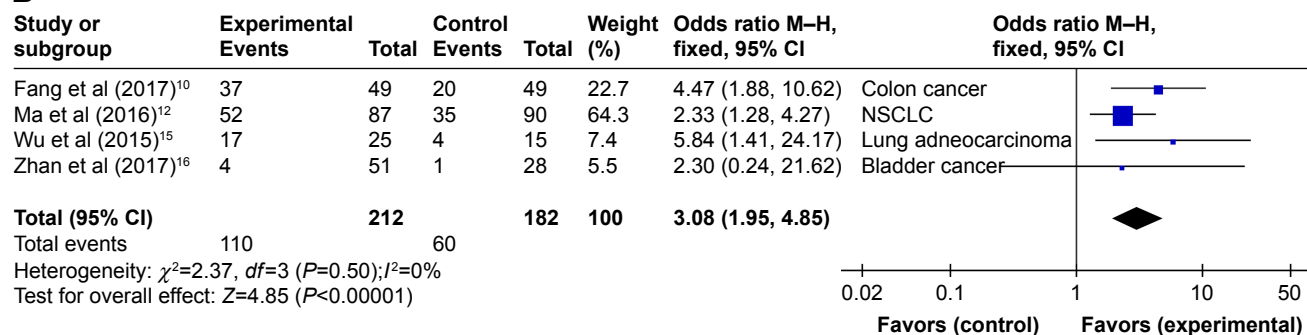
Conclusion

Our meta-analysis suggested that high expression of HNF1A-AS1 was significantly associated with poor outcomes in various cancers and could serve as a potential prognostic biomarker. However, considering the limitations of the

A



B



C

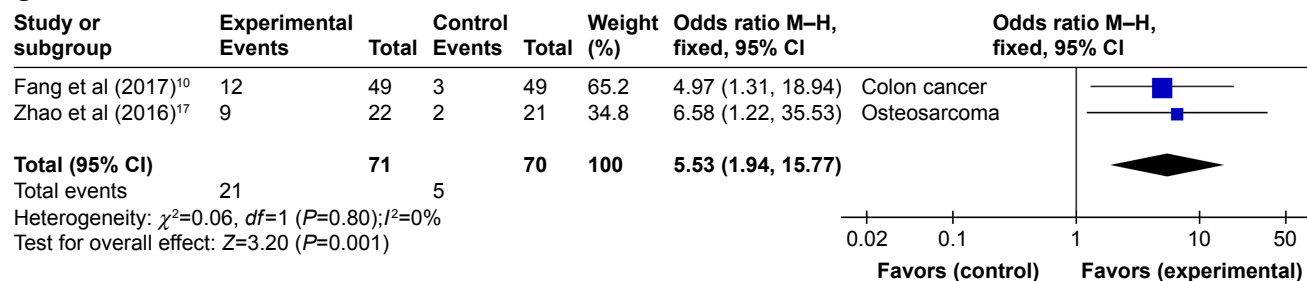


Figure 3 Forest plots for the association between HNF1A-AS1 expression and (A) TNM stage (III/IV vs I/II), (B) lymph node metastasis (yes vs no), and (C) distant metastasis (yes vs no).

Abbreviations: HNF1A-AS1, HNF1A antisense RNA I; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer.

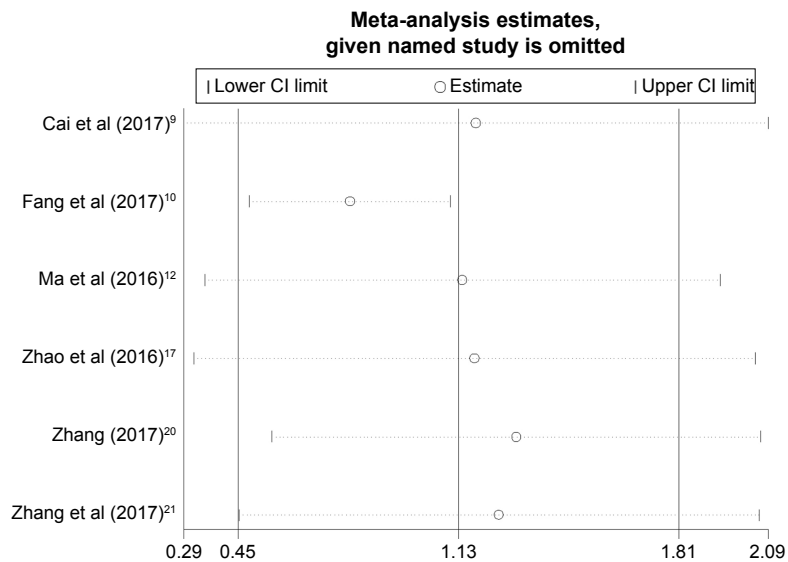


Figure 4 Sensitivity analysis on the association between HNF1A-AS1 expression and OS.
Abbreviations: HNF1A-AS1, HNF1A antisense RNA I; OS, overall survival.

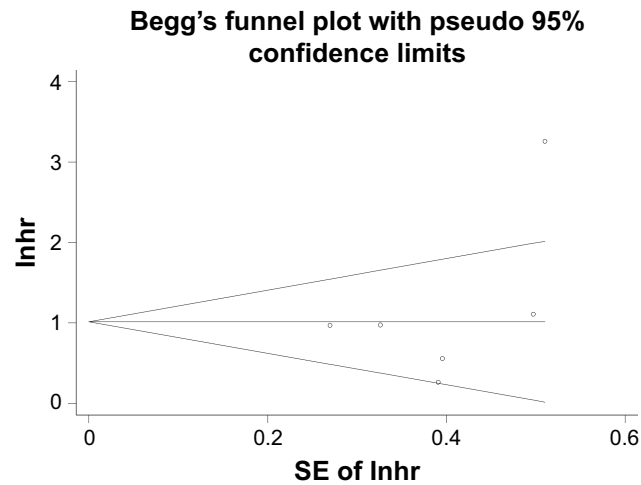


Figure 5 Begg's funnel plot of publication bias for OS.
Abbreviations: OS, overall survival; SE, standard error.

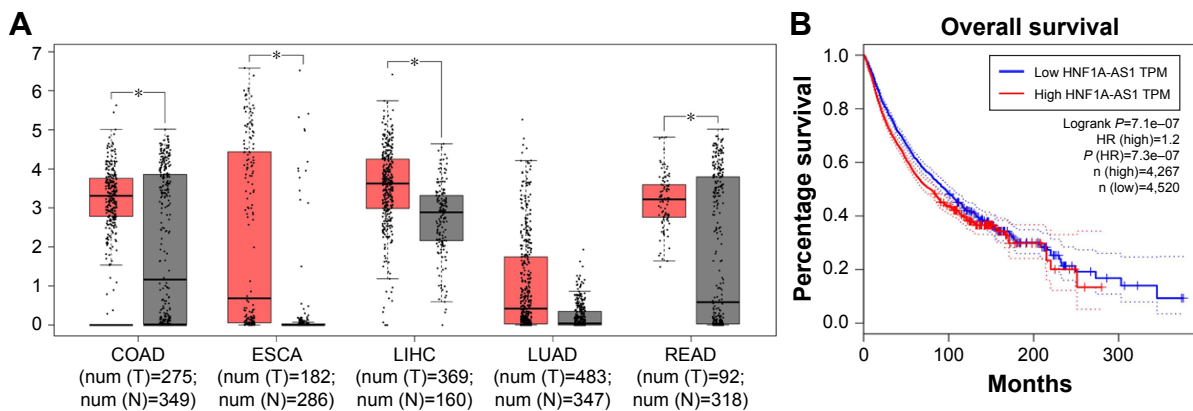


Figure 6 Validation of HNF1A-AS1 in TCGA dataset.
Notes: (A) The expression levels of HNF1A-AS1 in five kinds of cancer tissues and normal tissues. ****** $|\text{Log}_2\text{FC}| > 0.6$ and $P < 0.01$. (B) Survival curves of HNF1A-AS1 are plotted for all kinds of cancers from TCGA dataset ($n=8,787$).
Abbreviations: COAD, colon adenocarcinoma; ESCA, esophageal carcinoma; HNF1A-AS1, HNF1A antisense RNA I; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; READ, rectum adenocarcinoma; TCGA, The Cancer Genome Atlas.

present analysis, more studies with high quality and large sample size are needed to further confirm the prognostic role of HNF1A-AS1 in cancers.

Acknowledgment

This study was supported by the National Natural Science Foundation of China (No 81700514).

Disclosure

The authors report no conflicts of interest in this work.

References

- Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132.
- Siegel RL, Miller KD, Jemal A. Statistics C. *CA Cancer J Clin*. 2017; 2017;67(1):7–30.
- Neal JW, Sledge GW. Decade in review-targeted therapy: successes, toxicities and challenges in solid tumours. *Nat Rev Clin Oncol*. 2014; 11(11):627–628.
- Mercer TR, Dinger ME, Mattick JS. Long non-coding RNAs: insights into functions. *Nat Rev Genet*. 2009;10(3):155–159.
- Jandura A, Krause HM. The New RNA World: Growing Evidence for Long Noncoding RNA Functionality. *Trends in Genetics*. 2017; 33(10):665–676.
- Bhan A, Soleimani M, Mandal SS. Long Noncoding RNA. and Cancer: A New Paradigm. *Cancer Res*. 2017;77(15):3965–3981.
- Serghiou S, Kyriakopoulou A, Ioannidis JPA. Long noncoding RNAs as novel predictors of survival in human cancer: a systematic review and meta-analysis. *Mol Cancer*. 2016;15(1):50.
- Yang X, Song JH, Cheng Y, et al. Long non-coding RNA *HNF1A-AS1* regulates proliferation and migration in oesophageal adenocarcinoma cells. *Gut*. 2014;63(6):881–890.
- Cai L, Lv J, Zhang Y, Li J, Wang Y, Yang H. The lncRNA *HNF1A-AS1* is a negative prognostic factor and promotes tumorigenesis in osteosarcoma. *J Cell Mol Med*. 2017;21(11):2654–2662.
- Fang C, Qiu S, Sun F, et al. Long non-coding RNA *HNF1A-AS1* mediated repression of miR-34a/SIRT1/p53 feedback loop promotes the metastatic progression of colon cancer by functioning as a competing endogenous RNA. *Cancer Lett*. 2017;410:50–62.
- Liu Z, Wei X, Zhang A, Li C, Bai J, Dong J. Long non-coding RNA *HNF1A-AS1* functioned as an oncogene and autophagy promoter in hepatocellular carcinoma through sponging hsa-miR-30b-5p. *Biochem Biophys Res Commun*. 2016;473(4):1268–1275.
- Ma YF, Liang T, Li CR, Li YJ, Jin S, Liu Y. Long non-coding RNA *HNF1A-AS1* up-regulation in non-small cell lung cancer correlates to poor survival. *Eur Rev Med Pharmacol Sci*. 2016;20(23):4858–4863.
- Wang C, Mou L, Chai H-X, Wang F, Yin Y-Z, Zhang X-Y. Long non-coding RNA *HNF1A-AS1* promotes hepatocellular carcinoma cell proliferation by repressing *NKD1* and *P21* expression. *Biomed Pharmacother*. 2017;89:926–932.
- Wang G, Zhao W, Gao X, et al. *HNF1A-AS1* promotes growth and metastasis of esophageal squamous cell carcinoma by sponging miR-214 to upregulate the expression of *SOX-4*. *Int J Oncol*. 2017; 51(2):657–667.
- Wu Y, Liu H, Shi X, Yao Y, Yang W, Song Y. The long non-coding RNA *HNF1A-AS1* regulates proliferation and metastasis in lung adenocarcinoma. *Oncotarget*. 2015;6(11):9160–9172.
- Zhan Y, Li Y, Guan B, et al. Long non-coding RNA *HNF1A-AS1* promotes proliferation and suppresses apoptosis of bladder cancer cells through upregulating *Bcl-2*. *Oncotarget*. 2017;8(44):76656–76665.
- Zhao H, Hou W, Tao J, et al. Upregulation of lncRNA *HNF1A-AS1* promotes cell proliferation and metastasis in osteosarcoma through activation of the Wnt/beta-catenin signaling pathway. *Am J Transl Res*. 2016;8(8):3503–3512.
- Zhu W, Zhuang P, Song W, et al. Knockdown of lncRNA *HNF1A-AS1* inhibits oncogenic phenotypes in colorectal carcinoma. *Mol Med Rep*. 2017;16(4):4694–4700.
- Zhuang K, Wu Q, Jin C-S, Yuan H-J, Cheng J-Z. Long non-coding RNA *HNF1A-AS* is upregulated and promotes cell proliferation and metastasis in nasopharyngeal carcinoma. *Cancer Biomarkers*. 2016;16(2):291–300.
- Zhang LF. *Screening and Function Study of Aberrantly Expressed LncRNAs in Hepatocellular Carcinoma* [Doctoral dissertation, in Chinese]. Hangzhou: Zhejiang University; 2017.
- Zhang Y, Cai P, Liang T, Wang L, Hu L. *TIM-3* is a potential prognostic marker for patients with solid tumors: A systematic review and meta-analysis. *Oncotarget*. 2017;8(19):31705–31713.
- Wang Y, Huang Y, Xiang P, Tian W. LncRNA expression and implication in osteosarcoma: a systematic review and meta-analysis. *Oncotargets Ther*. 2017;10:5355–5361.
- Zhu J, Kong F, Xing L, Jin Z, Li Z. Prognostic and clinicopathological value of long noncoding RNA *XIST* in cancer. *Clinica Chimica Acta*. 2018;479:43–47.
- Chen T, Wang H, Yang P, He Z-Y, Zy H. Prognostic role of long noncoding RNA *NEAT1* in various carcinomas: a meta-analysis. *Oncotargets Ther*. 2017;10:993–1000.
- Chen X, Lun L, Hou H, Tian R, Zhang H, Zhang Y. The Value of lncRNA *HULC* as a Prognostic Factor for Survival of Cancer Outcome: A Meta-Analysis. *Cellular Physiology and Biochemistry*. 2017; 41(4):1424–1434.
- Zhang X, Xiong Y, Tang F, Bian Y, Chen Y, Zhang F. Long noncoding RNA *HNF1A-AS1* indicates a poor prognosis of colorectal cancer and promotes carcinogenesis via activation of the Wnt/ β -catenin signaling pathway. *Biomed Pharmacother*. 2017;96:877–883.
- Dang Y, Lan F, Ouyang X, et al. Expression and clinical significance of long non-coding RNA *HNF1A-AS1* in human gastric cancer. *World J Surg Oncol*. 2015;13(1):302.
- Müller S, Raulefs S, Bruns P, et al. Next-generation sequencing reveals novel differentially regulated mRNAs, lncRNAs, miRNAs, sdRNAs and a piRNA in pancreatic cancer. *Mol Cancer*. 2015;14(1):94.

OncoTargets and Therapy

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress