

Prognostic and clinical significance of long non-coding RNA HNF1A-AS1 in solid cancers

A systematic review and meta-analysis

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Abstract

Background: LncRNA HNF1A Antisense RNA 1 (HNF1A-AS1) is often dysregulated in cancer. We performed this meta-analysis to clarify the usefulness of HNF1A-AS1 as a prognostic marker in malignant tumors.

Methods: The PubMed, OVID, and Web of Science databases were searched from inception to January 11, 2018. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to explore the relationship between HNF1A-AS1 expression and survival. Odds ratios (OR) were calculated to assess the association between HNF1A-AS1 expression and pathological parameters.

Results: Eight studies with a total of 802 patients were included in the study. The pooled hazard ratio (HR) suggested high HNF1A-AS1 expression correlated with poor overall survival (OS) (HR=4.85, 95% confidence interval (CI): 2.43–9.68), and disease-free survival (DFS) (HR=6.34, 95% CI: 1.03–39.12) in cancer patients. High HNF1A-AS1 expression also correlated with poor histological grade (OR=1.88, 95% CI: 1.27–2.79), high tumor stage (OR=4.04, 95% CI: 2.53–6.47), lymph node metastasis (LNM) (OR=4.53, 95% CI: 2.30–8.92), and distant metastasis (OR=5.99, 95% CI: 2.88–12.48). Begg funnel plot did not show any evidence of obvious asymmetry for high tumor stage ($P > |z| = 0.368$) and LNM ($P > |z| = 1.000$).

Conclusions: Thus high HNF1A-AS1 expression is predictive of poor OS, DFS, lymph node metastasis, distant metastasis, histological grade, and larger tumor stage, which suggests high HNF1A-AS1 expression may serve as a novel biomarker of poor prognosis in cancer.

Abbreviations: BC = bladder cancer, CRC = colorectal cancer, DM = distant metastasis, GAPDH = glyceraldehyde-3-phosphate dehydrogenase, HNF1A-AS1 = HNF1A Antisense RNA 1, HR = hazard ratio, HTS = high tumor stage, LADC = lung adenocarcinoma, LNM = lymph node metastasis, LTS = larger tumor size, NSCLC = non-small cell lung cancer, OS = overall survival, OSC = osteosarcoma, PHG = poor histological grade.

Keywords: HNF1A-AS1, lncRNA, metastasis, neoplasms, prognosis

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XZ and YHF contributed equally as first co-authors to this study.

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1. Introduction

It was recently reported that approximately 1.7 million new cancer cases and 600 thousand cancer deaths are projected to occur in the U.S. in 2017.^[1] However, the 5-year survival rate of most cancers remains still low, and many scientists are looking for new biomarkers useful for diagnosis or determining prognosis in cancer.

Long noncoding RNA (lncRNA) is defined as transcribed RNA molecules greater than 200 nucleotides in length that lack a meaningful open reading frame.^[2] lncRNA has many important functions in disease, including epigenetic regulation, transcriptional and posttranscriptional regulation.^[3] Moreover, it now appears that lncRNA dysregulation may be involved in various types of cancer.^[4–7] For example, some lncRNAs play a key role in cancer cell proliferation, invasion, and metastasis,^[8,9] suggesting lncRNA may be a useful marker of cancer prognosis.^[10]

The lncRNA HNF1A Antisense RNA 1 (HNF1A-AS1) is transcribed as a 2.455 kb lncRNA in the opposite direction of *HNF1A* gene transcription. HNF1A-AS1 is a bidirectional lncRNA located on chromosome 12.^[11] In addition, HNF1A-AS1 is reportedly associated with various tumor biological parameters,^[12–14] including overall survival (OS), lymph node

metastasis, and tumor stage. But although HNF1A-AS1 expression may affect prognosis and metastasis of human cancers, most studies reported so far are limited by discrete outcomes and sample size. We therefore performed this update meta-analysis to determine the prognostic value of HNF1A-AS1 in cancer patients.

2. Materials and methods

2.1. Literature collection

According to the standard guidelines of meta-analyses,^[15,16] a systematic search was performed by 2 authors independently in the electronic databases of Pubmed, OVID, and Web of Science for relevant articles that concerned HNF1A-AS1 as a prognostic biomarker for the survival of cancer patients. The latest search was updated on January 11, 2018. We performed literature search by both text word and MeSH strategy with the terms “HNF1A-AS1”, “HNF1A Antisense RNA 1”, “lncRNA HNF1A-AS1”, “lncRNA” or “noncoding RNA” or “long intergenic noncoding RNA”, “carcinoma” or “neoplasm” or “tumor” or “cancer”, “prognostic” or “prognosis”, “outcome” or “survival” or “recurrence”. The strategy was correspondingly adjusted in the different databases. In the retrieval process, we made a manual search using the reference lists of the relevant articles to include eligible studies. All the analyses were conducted on the basis of the prior published researches. Therefore, it did not require patient consent or ethical approval.

2.2. Study selection

Two researchers evaluated all of the included studies and extracted the data independently. The inclusion criteria were as follows:

1. the relationship between HNF1A-AS1 expression and survival was measured in multiple human tumors;
2. the expression levels of HNF1A-AS1 in human tumor tissue were measured, and the patients were grouped according to the expression levels of HNF1A-AS1;
3. all of the tumors were confirmed by pathological or histological examinations;
4. studies statistically analyzed patient survival or pathological parameters such as lymph node metastasis, tumor size, and tumor stage, with respect to HNF1A-AS1 expression.

The following studies were excluded:

1. reviews, letters, editorials, and expert opinions;
2. non-English language and non-human studies;
3. studies with the molecular structure and functions of HNF1A-AS1 only;
4. database analysis without original data.

2.3. Data extraction

Two reviewers extracted and examined the data from the original articles independently. Disagreements in the literature assessment were resolved through consensus with a third reviewer. The following data were collected: surname of the first author, publication year, country, tumor type, sample size, the number of patients with larger tumor size, poor histological (differentiation) grade, high tumor stage, lymph node metastasis and distant

metastasis, reference gene, HR and 95% CI of elevated HNF1A-AS1 for OS.

2.4. Statistical methods

Statistical analyses were performed using Stata version 12.0 software (StataCorp LLC, College Station, Texas, USA). The heterogeneity among different studies was measured by the Q and I^2 tests. A probability value of $I^2 \geq 50\%$, and $P < .1$ indicated the existence of significant heterogeneity.^[17] A random effects model or fixed effects model was used depending on the results of heterogeneity analysis. If there was a significant heterogeneity among the studies, the random-effects model was adopted, and the fixed-effects model was used if there was no obvious heterogeneity.

Pooled HRs and ORs were extracted from the published data. If the HRs can be obtained directly from the publication, we used crude ones. While the HR and 95% CI were not directly reported in the studies, survival information was extracted from Kaplan–Meier curves and was used to estimate the HR. The log HR and SE were used to summarize the outcome of survival.^[18] An observed HR of >1 indicated poor prognosis in patients with high HNF1A-AS1 expression. OR and their 95% CI were combined to assess the association between HNF1A-AS1 expression and clinicopathological parameters, including tumor size, histological grade (differentiation), tumor stage, lymph node metastasis, and distant metastasis. The sensitivity analysis was also performed to assess the stability of the results. The potential publication bias was assessed by the Begg funnel plot and Egger test. $P < .05$ was considered statistically significant.

3. Results

3.1. Studies characteristics

The detailed screening process is shown in detail in Figure 1. According to the inclusion and exclusion criteria, 8 studies and 802 patients were included in the meta-analysis.^[19–26] Additionally, the characteristics of the 8 studies included in the present meta-analysis are summarized in Table 1. The subject number of 8 studies ranged from 40 to 177, with a mean sample size of 100.25. All studies were conducted in China and were published between 2015 and 2017. Among the 8 studies, 3 focused on colorectal cancer (CRC),^[20,21,25] 2 focused on osteosarcoma (OSC),^[19,26] and 1 each on non-small cell lung cancer (NSCLC),^[22] lung adenocarcinoma (LADC),^[23] bladder cancer (BC).^[24] All of the clinicopathological parameters were all dependent on the pathology. The reference gene of lncRNA HNF1A-AS1 in these studies were found to be inconsistent, including GAPDH,^[19,21–23,26] β -actin.^[20,24,25]

3.2. Association between the HNF1A-AS1 expression level and survival

We performed a cumulative meta-analysis to assess the function of HNF1A-AS1 for overall survival (OS) in patients with cancer. Additionally, 6 included studies with 683 patients reported the relationship between OS and HNF1A-AS1. The random effects model was used for significant heterogeneity ($I^2 = 79.5\%$, $P_Q = .000$). A significant association was observed between HNF1A-AS1 and OS in cancer patients (pooled HR = 4.85, 95% CI: 2.43–9.68; Fig. 2).

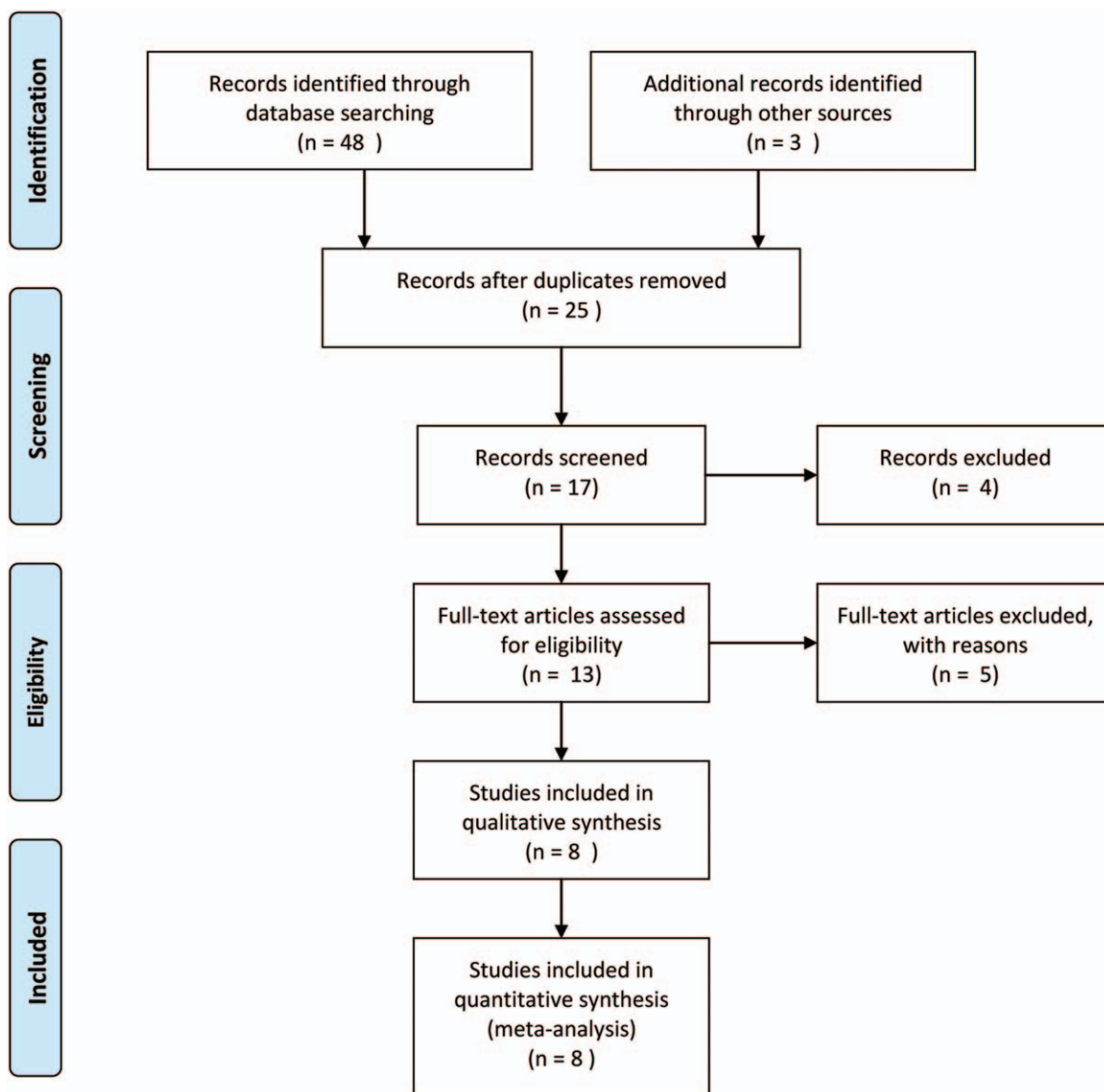


Figure 1. Flowchart presented the steps of study selection in this meta-analysis.

Table 1

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

.Study	Year	Region	Tumor type	Sample size	LncRNA HNF1A-AS1 expression										Reference gene	HR(95% CI) High / Low OS		
					High expression					Low expression								
					Total	LTS	PHG	HTS	LNM	DM	Total	LTS	PHG	HTS			LNM	DM
Cai ^[19]	2016	China	OSC	72	36	20	–	23	–	–	36	18	–	17	–	–	GAPDH	2.634(1.550–5.647)
Fang ^[20]	2017	China	CRC	98	49	21	13	37	37	12	49	26	9	22	20	3	β -actin	25.918 (9.529–70.498)
Gong ^[21]	2017	China	CRC	151	76	34	20	57	57	24	75	17	8	17	17	5	GAPDH	12.247 (5.171–29.008)
Ma ^[22]	2016	China	NSCLC	177	87	–	27	51	52	–	90	–	20	32	35	–	GAPDH	3.166 (1.451–5.332)
Wu ^[23]	2015	China	LADC	40	25	16	8	18	17	–	15	4	7	6	4	–	GAPDH	–
Zhan ^[24]	2017	China	BC	79	51	34	34	42	4	–	28	13	10	15	1	–	β -actin	–
Zhang ^[25]	2017	China	CRC	142	71	–	–	–	–	–	71	–	–	–	–	–	β -actin	2.57 (1.27–5.23)
Zhao ^[26]	2016	China	OSC	43	22	15	–	17	–	9	21	12	–	7	–	2	GAPDH	2.637 (1.391–7.417)

The dashes represent no data.

BC=bladder cancer, CRC=colorectal cancer, DM=distant metastasis, HR=hazard ratio, HTS=high tumor stage, LADC=lung adenocarcinoma, LNM=lymph node metastasis, LTS=lager tumor size, NSCLC=non-small cell lung cancer, OS=overall survival, OSC=osteosarcoma, PHG=poor histological grade.

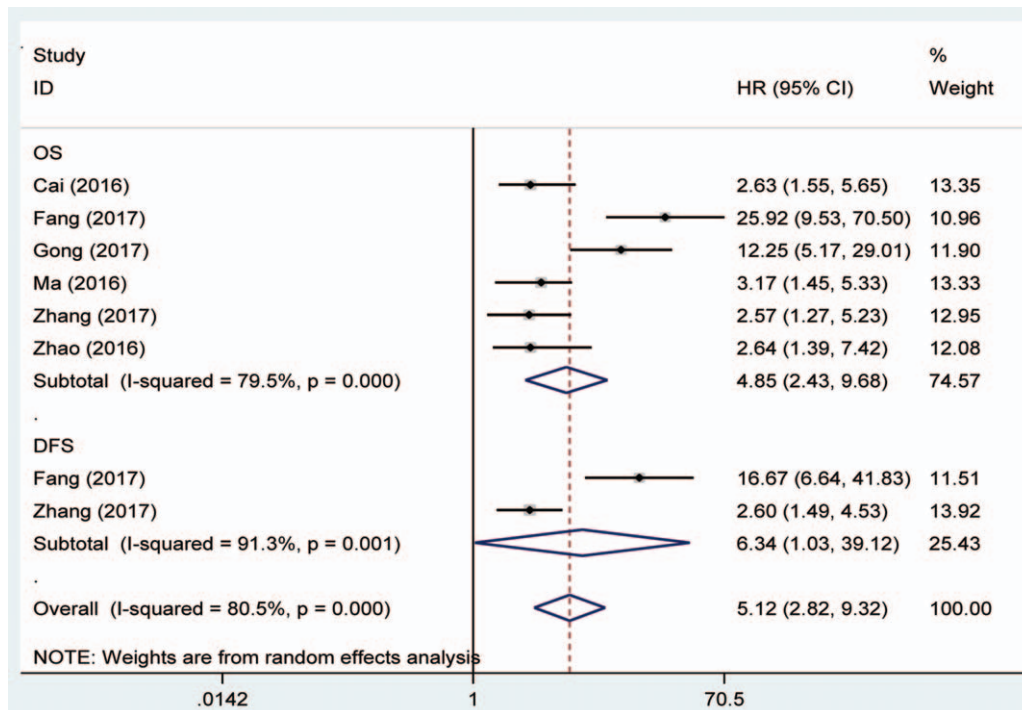


Figure 2. Forest plot showed the association between OS (DFS) and HNF1A-AS1 expression level in cancer.

We performed cumulative meta-analysis to determine the role of HNF1A-AS1 in disease-free survival (DFS) of 240 cancer patients^[20,25] from the eligible studies (Fig. 2). Statistical analyses revealed that HNF1A-AS1 was associated with DFS (pooled HR=6.34, 95% CI: 1.03–39.12) of cancer patients. The random effects model was adopted because of the significant heterogeneity between studies.

This result demonstrated that a high expression of HNF1A-AS1 might be correlated with a shorter OS and DFS in cancer patients. Thus, we found that HNF1A-AS1 was an independent factor of survival among patients with cancer.

3.3. Association between the HNF1A-AS1 expression level and tumor size

The correlations between HNF1A-AS1 expression and tumor size are presented in Figure 3. Six studies with 483 patients declared the association between the HNF1A-AS1 expression levels and number of cancer patients with larger tumor size. There was significant heterogeneity in these studies, and the random-effects model was used ($I^2=50.9%$, $P_Q=0.070$). The analysis showed a pooled OR=1.74 (95% CI: 1.00–3.04; high vs low HNF1A-AS1 expression; Fig. 3). In a sensitivity analysis of all included studies, heterogeneity disappeared after the Cai et al study^[19] were excluded ($I^2=0%$, $P_Q=.51$), and the odds ratio (OR), expressed as high HNF1A-AS1 expression group vs low HNF1A-AS1 expression group, was 2.23 (95% CI: 1.46–3.41).

According to the result, there was not a significant difference in the larger tumor size incidence between the 2 groups, additional more studies will be needed to confirm the relationship between HNF1A-AS1 and histological grade in cancer patients.

3.4. Association between the HNF1A-AS1 expression level and histological grade

A total of 545 patients with cancer from 5 eligible studies were collected and analyzed. The fix effects model was used for limited heterogeneity ($I^2=39.5%$, $P_Q=.158$). The odds ratio (OR), expressed as high HNF1A-AS1 expression group vs low HNF1A-AS1 expression group, was 1.88 (95% CI: 1.27–2.79, Fig. 4). According to the result, there was a significant difference in the poor histological (differentiation) grade incidence between the 2 groups. And the results demonstrated that high expression of HNF1A-AS1 significantly predicted more prone to poor differentiation grade for patients with cancer.

3.5. Association between the HNF1A-AS1 expression level and tumor stage

Six hundred sixty patients in 7 eligible studies were included to detect the relationship between the HNF1A-AS1 expression levels and tumor stage in this meta-analysis. The random effects model was used for significant heterogeneity ($I^2=44.6%$, $P_Q=.094$). A significant connection was found between a high HNF1A-AS1 expression level and high tumor stage in cancer patients (pooled OR=4.04, 95% CI: 2.53–6.47, Fig. 5).

From the analysis results, the tumor stage was significantly increased in the high HNF1A-AS1 expression group compared with that in the low HNF1A-AS1 expression group, and the results demonstrated that a high expression of HNF1A-AS1 significantly increased the risk of high tumor stage.

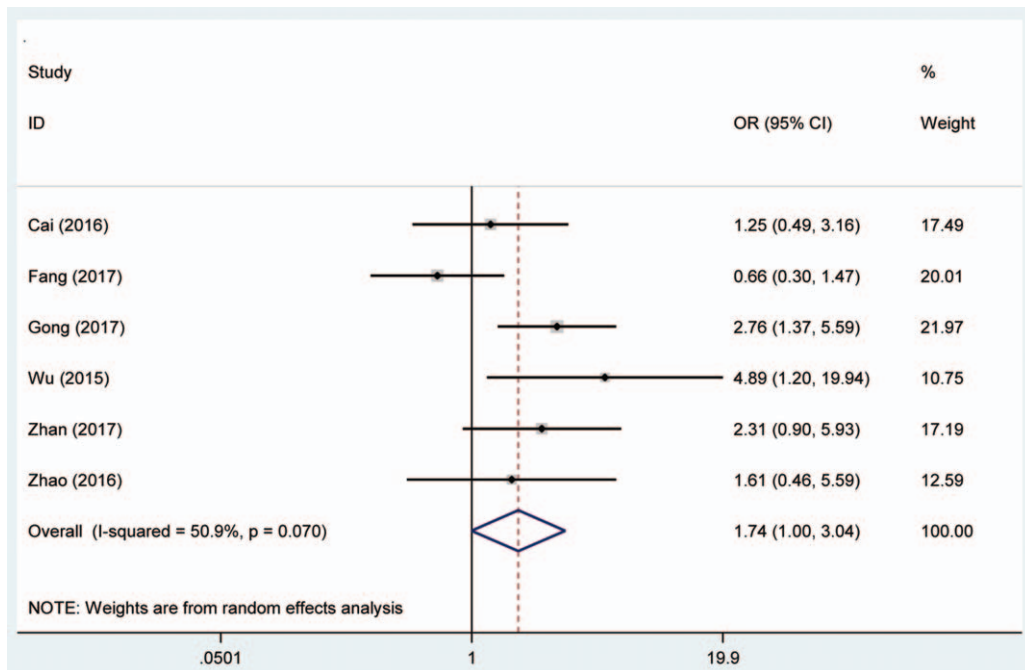


Figure 3. Forest plot showed the association between tumor size and HNF1A-AS1 expression level in cancer.

3.6. Association between the HNF1A-AS1 expression level and lymph node metastasis

A total of 545 patients with cancer from 5 eligible studies were collected and analyzed. The random effects model was used for significant heterogeneity ($I^2 = 58.2\%$, $P_Q = .048$). The odds ratio (OR), expressed as high HNF1A-AS1 expression group vs low

HNF1A-AS1 expression group, was 4.53 (95% CI: 2.30–8.92, Fig. 6). According to the result, there was a significant difference in the lymph node metastasis incidence between the 2 groups. And the results demonstrated that high expression of HNF1A-AS1 significantly predicted more prone to developing lymph node metastasis for patients with cancer.

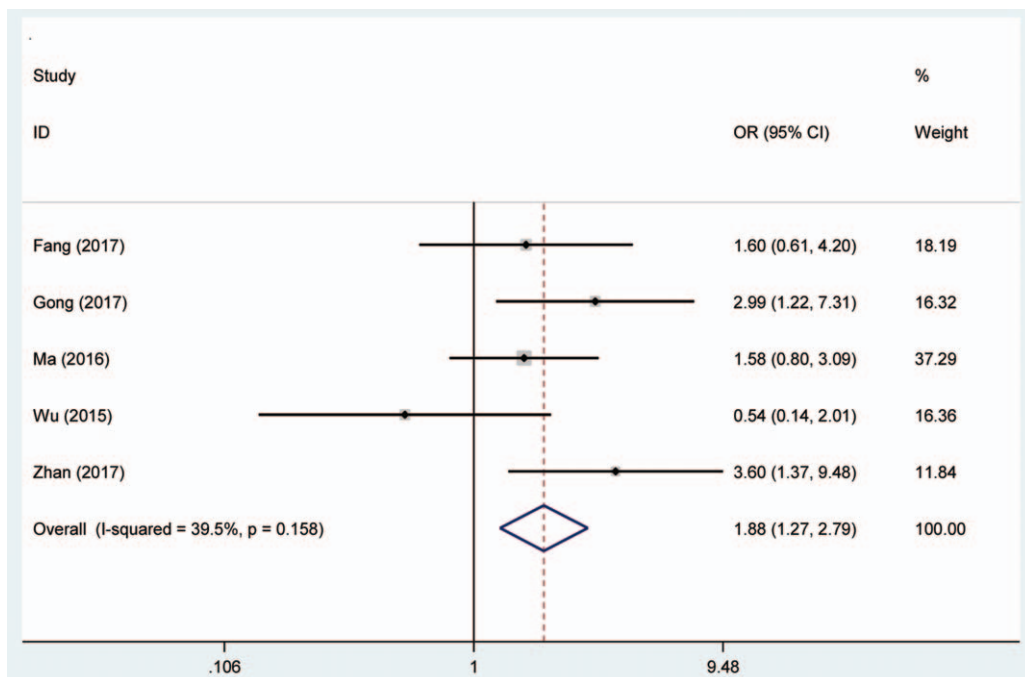


Figure 4. Forest plot of studies evaluated the correlation between histological grade and HNF1A-AS1 expression level in cancer.

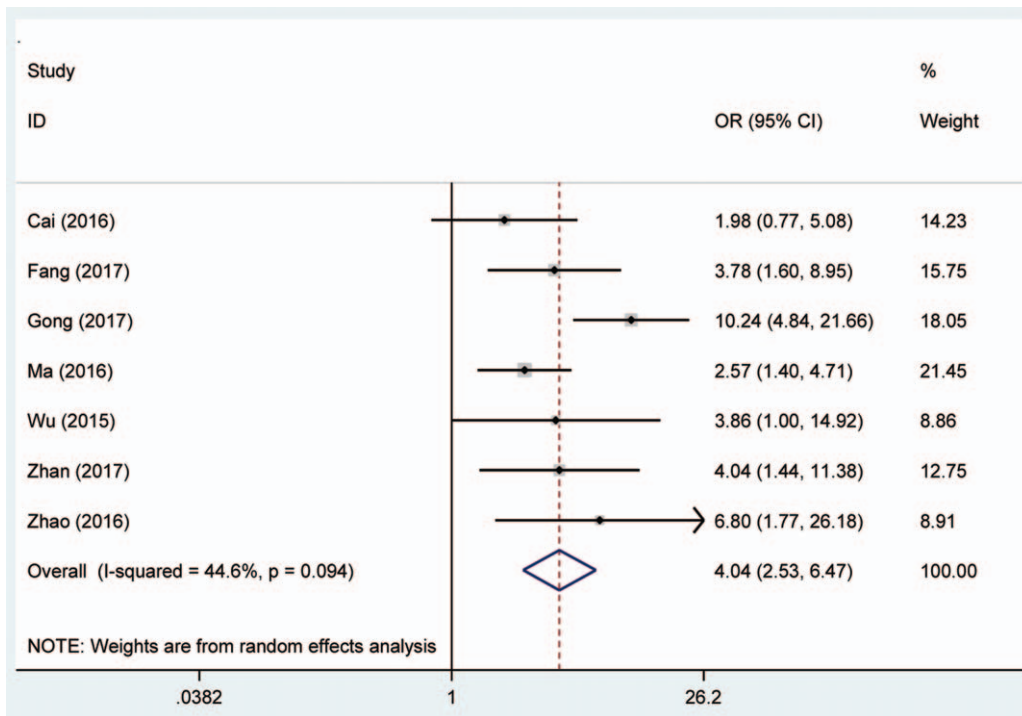


Figure 5. Forest plot showed the correlation between tumor stage and HNF1A-AS1 expression level in cancer.

3.7. Association between the HNF1A-AS1 expression level and distant metastasis

Two hundred ninety two patients with cancer from 3 eligible studies were collected and analyzed. The fix effects model was used for limited heterogeneity ($I^2=0.0\%$, $P_Q=.948$). The odds

ratio (OR), expressed as the high HNF1A-AS1 expression group vs low HNF1A-AS1 expression group was 5.99 (95% CI: 2.88–12.48, Fig. 7). According to the result, there was a significant difference between the 2 groups in the distant metastasis incidence. Additionally, the results demonstrated that a high

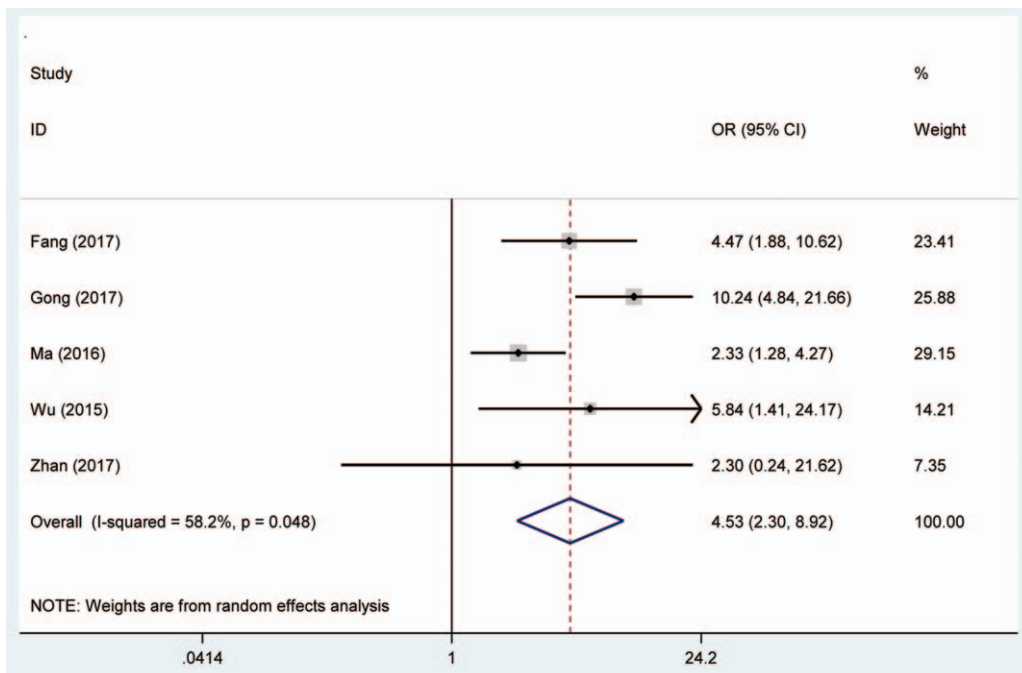


Figure 6. Forest plot of studies evaluated the correlation between lymph node metastasis and HNF1A-AS1 expression level in cancer.

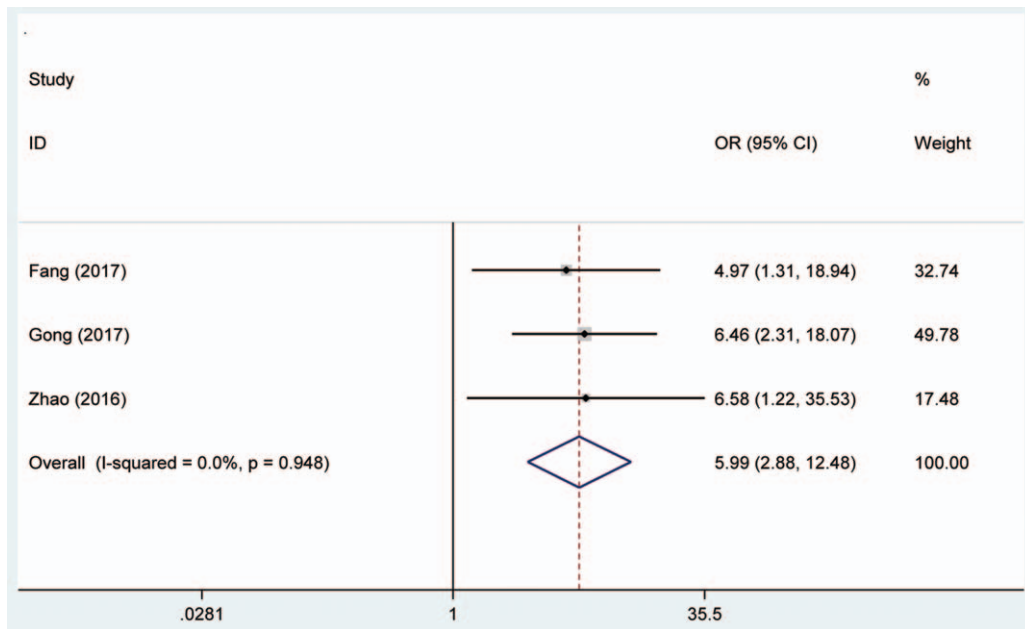


Figure 7. Forest plot of studies evaluated the relationship between distant metastasis and HNF1A-AS1 expression level in cancer.

expression of HNF1A-AS1 significantly predicted a higher tendency to develop distant metastasis in patients with cancer.

3.8. Publication bias

Next, a Begg funnel plot was conducted to evaluate publication bias. The figure of the Begg funnel plot (Fig. 8) did not show any evidence of obvious asymmetry for high tumor stage ($Pr > |z| = 0.368$). Similarly, there were no evidences for significant publication bias in terms of LNM ($Pr > |z| = 1.000$, Fig. 9).

4. Discussion

Cancer remains a serious threat to human health, and the incidence of cancer has increased gradually in recent years.^[1] The occurrence of metastasis is an important indicator of a poor prognosis,^[27,28] but the precise mechanism on metastasis remains uncertain in cancer patients. At present, cancer research hotspot-molecular biomarkers play a critical role in the prediction and treatment of cancer.^[29,30] It therefore continues to be necessary to identify new molecular markers predictive of tumor metastasis.

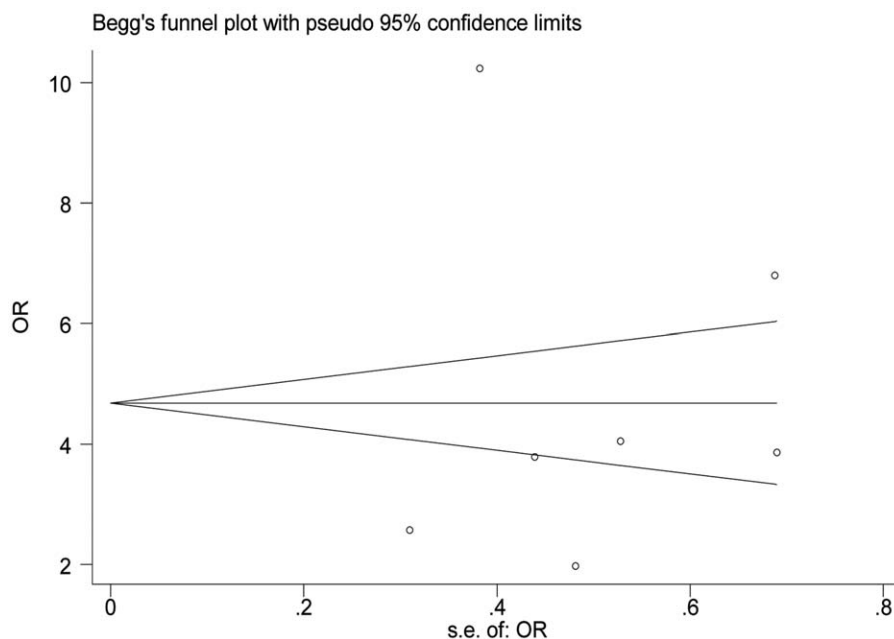


Figure 8. Begg funnel plot for all eligible studies provided OR for HNF1A-AS1 expression and high tumor stage.

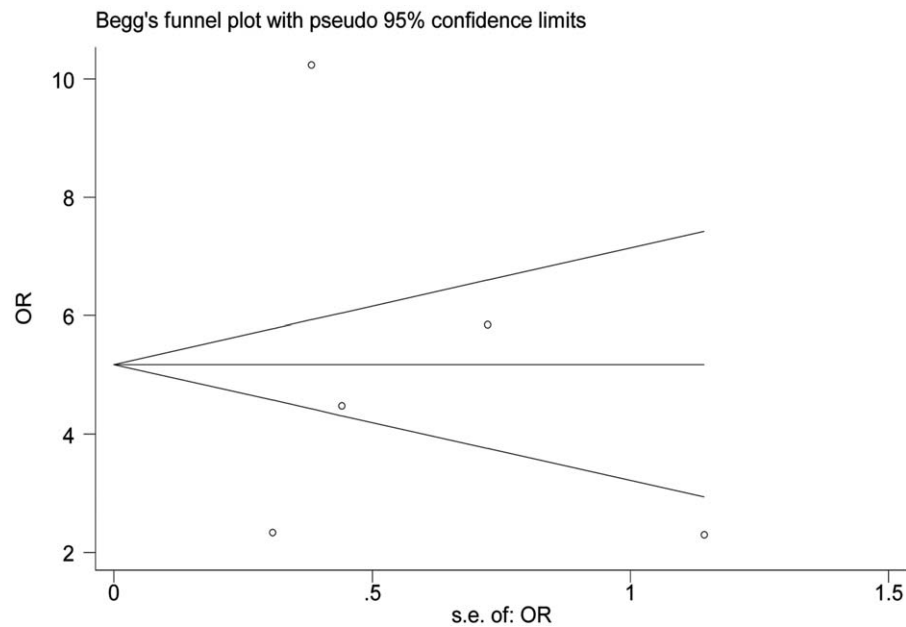


Figure 9. Begg funnel plot for all eligible studies provided OR for HNF1A-AS1 expression and LNM.

Among these molecular markers are lncRNAs, which can impact both the occurrence and development of tumors, and have shown potential to serve as easily collected biomarkers useful for diagnosing and monitoring tumors.^[31]

Previous studies have shown that HNF1A-AS1 is a critical oncogene in a variety human cancer types, including osteosarcoma, colorectal cancer, non-small cell lung cancer, bladder cancer, and lung adenocarcinoma.^[19–26] Recent advances have confirmed that HNF1A-AS1 is associated with poor survival in osteosarcoma patients, and increased expression of HNF1A-AS1 was observed in local recurrences compared with paired primary osteosarcoma.^[19] And Fang et al demonstrated that patients with high HNF1A-AS1 expression had an increased risk of tumor recurrence and shorter survival.^[20] In addition, Zhan et al^[24] found that HNF1A-AS1 promotes proliferation and suppresses apoptosis of bladder cancer cells through upregulating Bcl-2. And Zhang et al^[32] reported that HNF1A-AS1 promoted cell proliferation and invasion via regulating miR-17–5p in non-small cell lung cancer. These studies suggest that lncRNA HNF1A-AS1 may serve as an important prognostic factor in cancer patients. Until now, the underlying mechanisms by which HNF1A-AS1 affected human cancers and its utility as a biomarker remained largely unclear. Through this meta-analysis, we explored the clinicopathologic significance and prognostic value of HNF1A-AS1 in cancer patients.

A total of 802 patients with cancer from 8 eligible studies were collected and analyzed in this study. A random effects model or fixed effects model was used depending on the results of heterogeneity analysis. We found that high HNF1A-AS1 expression may indicate a poor prognosis in cancer patients. By combining HRs from Cox multivariate analyses, we detected a significant difference in OS between high and low HNF1A-AS1 expression groups. We found that high HNF1A-AS1 expression was significantly associated with DFS in different types of cancer. Furthermore, high HNF1A-AS1 expression correlated significantly with high tumor stage, poor histological grade, lymph

node metastasis, and distant metastasis in cancer patients. Taken together, these findings suggest HNF1A-AS1 may be a useful prognostic biomarker of poor outcome in most cancers.

5. Limitations

There were several limitations that must be taken into account while interpreting the conclusions of the present meta-analysis. First, all included studies were from China. Therefore our data may not be globally applicable. Second, the included types and numbers of cancers were small. Third, 4 articles did not mention the criterion used to define high expression, and the cut-off value for high expression in the remaining 4 articles was the median. Third, since there is no literature to study the role of HNF1A-AS1 in non-solid tumors, we mainly studied the effect of HNF1A-AS1 expression level on solid tumors. Therefore, additional well-designed, high-quality studies are needed to confirm the function of HNF1A-AS1 in cancer.

6. Conclusion

In sum, high levels of HNF1A-AS1 expression in multiple cancers is significantly correlated with poor OS, DFS, lymph node metastasis, distant metastasis, histological grade, larger tumor stage. Therefore, HNF1A-AS1 expression may serve as a promising biomarker for predicting prognosis and metastasis in cancer patients.

Author contributions

Data curation: Xi Zhou, Yang-Hua Fan, Yan Wang.

Funding acquisition: Xi Zhou.

Investigation: Xi Zhou, Yang-Hua Fan, Yan Wang, Yong Liu.

Methodology: Yang-Hua Fan.

Supervision: Yong Liu.

Validation: Xi Zhou.

Writing – original draft: Xi Zhou.

Writing – review & editing: Yong Liu.

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