LncRNA HOXA-AS2 is a prognostic and clinicopathological predictor in patients with cancer: A meta-analysis

TIJUN XIAO[1], AN YAN[2], LIFANG TAN[1], HONGWEI ZHU[2] and WENZHE GAO[2]

[1]Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Shaoyang University, Shaoyang, Hunan 422000; [2]Department of Hepatopancreatobiliary Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, P.R. China

Received November 21, 2023; Accepted February 23, 2024

DOI: 10.3892/ol.2024.14359

Abstract. Elevated expression of long non-coding RNA homeobox A cluster antisense RNA 2 (lncRNA HOXA-AS2) is known to have prognostic value in various solid tumors. The present meta-analysis aimed to comprehensively quantify its prognostic significance across a wider spectrum of malignancies and to provide an updated synthesis of evidence that could refine prognostic models. To achieve this aim, multiple databases were carefully searched for lncRNA HOXA-AS2-related articles published in the past 10 years. Hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to demonstrate the prognostic value of lncRNA HOXA-AS2 using Stata 15.0 software. The function of lncRNA HOXA-AS2 was inferred from its associations with key clinical outcomes such as lymph node metastasis, distant metastasis, tumor stage and tumor size, which may reflect its role in tumor biology. In the present systematic review and meta-analysis of 454 patients across 7 studies, it was found that high lncRNA HOXA-AS2 expression was significantly associated with a shorter overall survival (OS) time in patients with cancer (HR=2.14; 95% CI, 1.40-3.27; P<0.001). High lncRNA HOXA-AS2 expression was also associated with lymph node metastasis [odds ratio (OR)=2.06; 95% CI, 1.07-3.99; P=0.032], distant metastasis (OR=2.11; 95% CI, 1.15-3.88; P=0.016), advanced tumor stage (OR=2.71; 95% CI, 1.50-4.89; P=0.001) and larger tumor size (OR=2.02; 95% CI, 0.86-4.78; P=0.006). However, no significant association was observed with age (OR=1.00; 95% CI, 0.63-1.59; P=0.991) or sex (OR=1.55; 95% CI, 0.72-3.34; P=0.258). In conclusion, elevated expression of lncRNA HOXA-AS2 was significantly related to poor clinical outcomes in various cancer types, such as osteosarcoma, non-small cell lung cancer and papillary thyroid carcinoma, a finding that was further confirmed by the present study. Specifically, the potential of lncRNAHOXA-AS2 as a biomarker in assessing tumor stage, metastasis risk and OS in patients was demonstrated. However, the results of the present study also indicated that the expression of lncRNA HOXA-AS2 was not significantly associated with age or sex, suggesting its role in cancer progression might be independent of these factors. This insight may direct future research to place more focus on the relationship between lncRNA HOXA-AS2 and specific cancer types and clinical characteristics.

Correspondence to: Dr Wenzhe Gao, Department of Hepatopancreatobiliary Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, P.R. China
E-mail: gaowenzhexy@163.com

Abbreviations: PCa, prostate cancer; AML, acute myeloid leukemia; PTC, papillary thyroid cancer; NSCLC, non-small cell lung cancer; OS, overall survival; LNM, lymph node metastasis; HR, hazard ratio

Key words: HOXA-AS2, lncRNA, cancer, prognosis, meta-analysis

Introduction

Long non-coding RNAs (lncRNAs) represent one of the various types of non-protein-coding transcripts. By definition, lncRNAs are transcripts of >200 nucleotides that are not translated into proteins (1) and are composed of intergenic transcripts, enhancer RNAs and sense or antisense transcripts that overlap other genes (2). LncRNAs play pivotal roles across a diverse array of biological processes, regulating gene expression through mechanisms (3) that include functioning as signaling entities, molecular decoys, guides for chromatin-modifying enzymes, and scaffolding for multi-protein complexes. Beyond their critical involvement in the oncogenic pathways, the importance of lncRNAs in cellular differentiation, organogenesis, embryonic development, and the adaptive response to environmental stimuli has been highlighted (4). These findings illuminate the role of lncRNAs as essential molecules in maintaining homeostasis of physiological processes (5), participating in cell cycle control, apoptosis, and the cellular response to a broad spectrum of physiological and pathological stimuli. Consequently, lncRNAs emerge not only as potential therapeutic targets and biomarkersin cancer-related processes (6,7) such as proliferation, invasion, migration and angiogenesis, but also as promising drug targets and diagnostic tools (8) in a wider biological context.

LncRNA homeobox A cluster antisense RNA 2 (HOXA-AS2), located between the human HOXA3 and HOXA4 genes and with a length of 1,048 bp, has been extensively detected

and researched across various malignancies since its initial demonstration as an apoptosis inhibitor in NB4 promyelocytic leukemia cells in 2013 (9). As an oncogene, lncRNA HOXA-AS2 exhibits abnormally high expression in a wide array of solid and hematological malignancies, such as acute myeloid leukemia (AML) (10), gallbladder cancer (11) and glioma (12), promoting the progression of these cancer types. The mechanisms by which lncRNA HOXA-AS2 inhibits apoptosis and stimulates proliferation have been the most extensively studied (13-15), indicating that lncRNA HOXA-AS2 not only affects the proliferation, invasion and migration of cancer cells but is also closely related to patient prognosis. For instance, the upregulation of lncRNA HOXA-AS2 in AML (10) demonstrates its oncogenic role by interacting with the epigenetic inhibitor Enhancer of zeste homolog 2 (EZH2), subsequently repressing the expression of Large Tumor Suppressor 2 (LATS2). This mechanism elucidates how HOXA-AS2 contributes to the proliferation and inhibits the differentiation of AML cells, negatively impacting patient survival. The binding of HOXA-AS2 with EZH2 and the inhibition of LATS2 underscore its potential as an effective therapeutic target in AML, highlighting the significance of disrupting this interaction to modulate cell behavior and tumor progression. Additionally, high expression of lncRNA HOXA-AS2 is not only closely related to tumor size, staging, lymph node metastasis and distant metastasis (DM) but may also promote tumor progression and occurrence by acting as a competitive endogenous RNA (ceRNA) and affecting the distribution of microRNAs (miRs), especially in digestive system tumors such as gastric cancer, hepatocellular carcinoma and pancreatic cancer (16).

In summary, the expression level of lncRNA HOXA-AS2 and its mechanisms in cancer development, particularly its potential value in prognosis assessment, offers a compelling research direction. Therefore, the present meta-analysis aimed to explore the predictive value of lncRNA HOXA-AS2 in various patients with cancer, to strengthen the concept of lncRNA HOXA-AS2 as a prognostic biomarker and therapeutic target. Through the findings of the included studies, the present study aimed to provide a more comprehensive perspective on understanding the role of lncRNA HOXA-AS2 and its potential impact on cancer prognosis.

Materials and methods

Search strategy. The literature retrieval was performed by two independent researchers using the following online databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), PubMed Central (PMC, https://www.ncbi.nlm.nih.gov/pmc/), EMBASE (https://www.embase.com/), Web of Science (https://www.webofscience.com/wos/), China National Knowledge Infrastructure (CNKI, https://www.cnki.net/) and Wanfang Database (https://www.wanfangdata.com.cn/). The latest search was performed on January 4th, 2024. The following keywords were used in the search: 'lncRNA HOXA cluster antisense RNA 2' OR 'lncRNA HOXA-AS2' OR 'HOXA-AS2' OR 'HOXA cluster antisense RNA 2' The reference lists of relevant articles were also screened for additional eligible studies.

Inclusion and exclusion criteria. Eligible articles were identified based on the following inclusion criteria: i) The expression of lncRNA HOXA-AS2 was detected in any human solid malignant tumor; ii) association between lncRNA HOXA-AS2 and patient prognosis and/or other clinical pathological factors was reported; iii) The hazard ratio (HR) with 95% confidence interval (CI) was reported or sufficient data was provided to calculate the HR; and iv) patients were classified into high or low expression groups according to the lncRNA HOXA-AS2 expression level. While the literature search did not impose language restrictions, all studies included in the analysis were published in English due to their adherence to the inclusion criteria. Articles were excluded when they did not cover all of the aforementioned inclusion criteria. Reviews and meta-analyses were also excluded to prevent data duplication, as they may have reported on primary studies already included in the synthesis. In addition, retracted articles were excluded to ensure the integrity and reliability of the analysis. Articles lacking prognostic information or with insufficient data were also excluded, as they did not meet the requirements for the assessment of the impact of lncRNA HOXA-AS2 expression on cancer prognosis. Fig. 1 shows a detailed depiction of the literature screening process and the specific reasons for article exclusion.

Data extraction and quality assessment. Two investigators independently extracted data from eligible studies and followed a standardized protocol for consistency. The data extracted and analyzed included the following items: i) Name of first author, publication year, publication country and region, study design, cancer type, sample size, expression pattern, tumor stage, criterion of high expression (according to the mean or median value of expression), detection method, follow-up time, outcome measures and analysis type; ii) HR with 95% CI for overall prognosis of patients; and iii) patient characteristics, including number of patients with high and low HOXA-AS2 expression, age, sex, lymph node metastasis (LNM), tumor size, tumor stage and distance metastasis.

If a study reported the data from multivariate and univariate analyses, the HR with the corresponding 95% CI was directly extracted from the multivariate analysis. The survival curve of those studies that did not report HRs and 95% CIs directly were analyzed using Engauge Digitizer version 12.1 (https://markummitchell.github.io/engauge-digitizer/) and then the HRs and 95% CIs were estimated following the published method of Tierney *et al* (17).

The Newcastle-Ottawa Scale (NOS) with a score range of 0-9 was applied to assess the quality of all included studies. A high-quality study was identified as having a score of ≥7 (18-20).

Statistical analysis. Stata version 15.0 (StataCorp LP) was used for all statistical analyses in this meta-analysis, applying a random-effects model to account for anticipated heterogeneity among studies. Higgins I^2 statistics and Cochran's Q-test were applied to assess the heterogeneity among studies. Begg's and Egger's test were utilized to detect the publication bias. Sensitivity analysis was performed by omitting each study one by one to assess the effects on the pooled results. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Study selection and characteristics. The literature screening process is illustrated in Fig. 1. An initial search across six electronic databases yielded a total of 348 articles, with PubMed

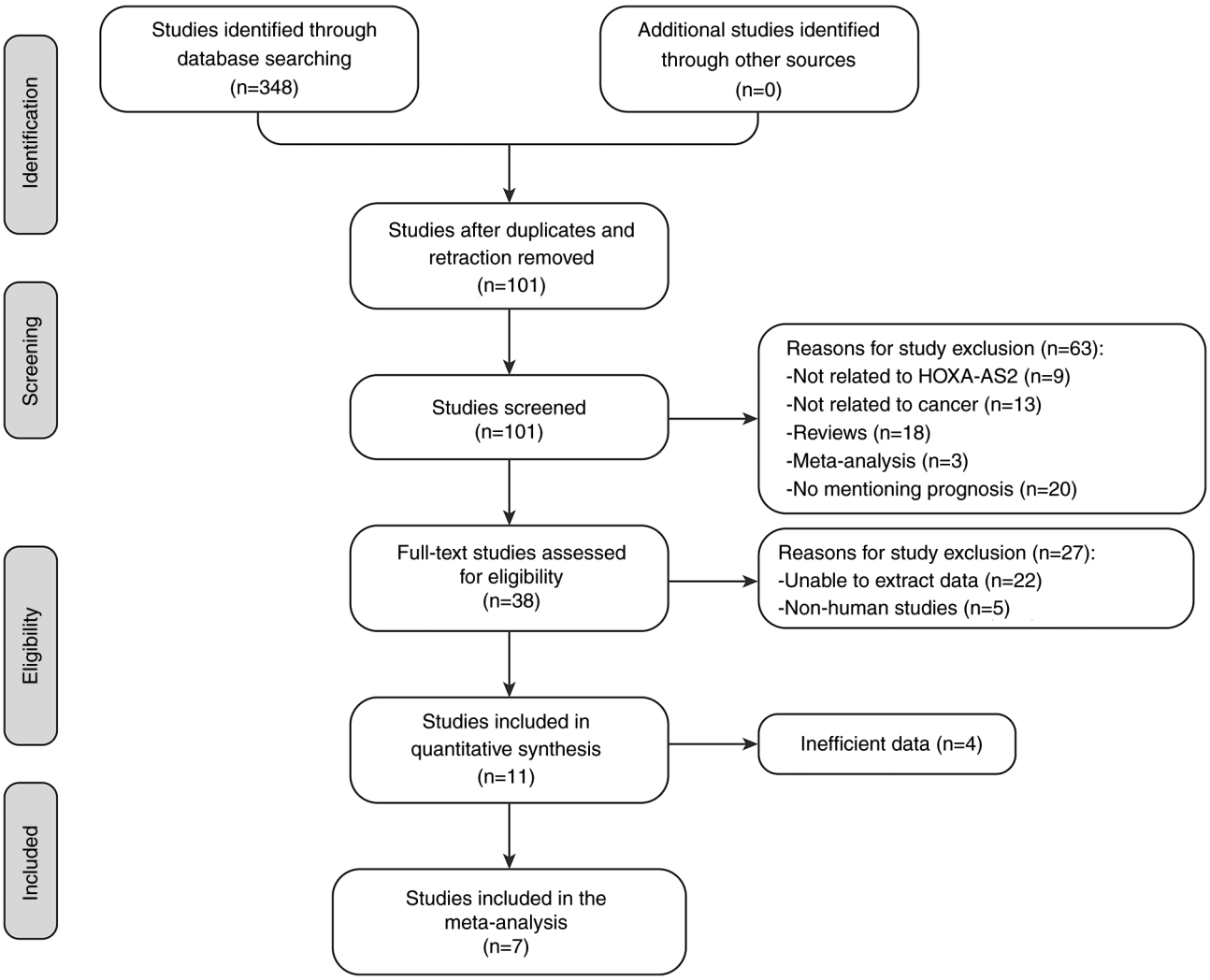

Figure 1. Steps for screening eligible articles.

contributing 69 articles, Wanfang 19, Web of Science 78, EMBASE 89, CNKI 66 and PMC 27. The next step involved the removal of duplicates and retractions, which reduced the pool by 247 articles, leaving 101 for further screening. Upon reviewing the titles and abstracts, 9 articles unrelated to lncRNA HOXA-AS2, 13 not related to cancer, 18 reviews, 3 previously published meta-analyses and 20 articles lacking prognostic information were excluded. This led to a full-text assessment of 38 articles for eligibility. Of these, 22 were excluded due to clinicopathologic characteristics data extraction issues and 5 due to being cell-based studies. A further 4 articles were excluded due to insufficient prognosis data. Ultimately, 7 articles were included in the present meta-analysis (14,21-26), encompassing a total of 454 patients.

The 7 selected studies were published from 2019 to 2021A total of 454 patients with cancer were enrolled in the pooled analysis, with a mean subject size of 64.8, ranging from 27 to 116. All studies measured the expression of lncRNA HOXA-AS2 in tissue specimens by reverse transcription-quantitative polymerase chain reaction. Of the included studies, 4 explored the relationship between lncRNA HOXA-AS2 expression and tumor staging, 4 assessed the relationship between lncRNA HOXA-AS2 expression and tumor size, and 4 investigated the presence of DM and LNM was addressed in 3 studies. The NOS scores of the included studies ranged from 7 to 9, denoting high-quality research. Only 3 studies provided HRs directly, with the remaining studies presenting Kaplan-Meier survival curves. The cancer types investigated consisted of osteosarcoma, NSCLC, PTC, prostate cancer (PCa), hepatocellular carcinoma, cervical cancer and AML. All included studies were retrospective and conducted in China. The main characteristics of the eligible studies are shown in Table I.

LncRNA HOXA-AS2 expression and patient overall survival (OS). The present meta-analysis investigated the impact of lncRNA HOXA-AS2 expression levels on the OS of patients with cancer, incorporating a total of 454 individuals. The pooled analysis indicated that patients with high lncRNA HOXA-AS2 expression had a significantly worse OS compared with those with low expression (HR=2.14; 95% CI, 1.40-3.27; P<0.001; Fig. 2).

Subgroup analysis further delineated the association across various demographics and clinical characteristics. A total of 6 subgroups were analyzed as follows: Research region (Northern China or Southern China; Fig. 3A), sample

Table I. Characteristics of studies included in the meta-analysis.

First author, year	Location	Sample size, n	Cancer type	lncRNA HOXA-AS2 expression, n		Detection method	Sample type	Survival analysis	Cut-off	HR statistic	HR method	HR (95% CI)	Follow-up time, months	NOS score	Multivariate analysis	(Refs.)
				High	Low											
Wang *et al*, 2019	Shandong, China	27	Osteosarcoma	15	12	RT-qPCR	Tissue	OS	Mean	KM survival curve	Indirectly	0.98 (0.25-3.81)	60	7	NM	(25)
Cui *et al*, 2019	Fujian, China	40	NSCLC	20	20	RT-qPCR	Tissue	OS	NM	KM survival curve	Indirectly	2.53 (0.67-9.58)	75	8	NM	(24)
Jiang *et al*, 2019	Beijing, China	68	PTC	30	38	RT-qPCR	Tissue	OS	Mean	KM survival curve	Indirectly	1.32 (0.26-6.58)	60	7	NM	(14)
Xiao and Song 2020	Shaanxi, China	68	Prostate cancer	34	34	RT-qPCR	Tissue	OS	Mean	KM survival curve	Indirectly	1.23 (0.11-13.85)	60	7	NM	(26)
Lu *et al*, 2020	Guangxi, China	116	HCC	58	58	RT-qPCR	Tissue	OS	Median	KM survival curve	Directly	2.478 (1.09-5.62)	25	9	YES	(21)
Qu *et al*, 2020	Liaoning, China	108	AML	54	54	RT-qPCR	Blood	OS	Median	KM survival curve	Directly	2.35 (1.17-6.05)	60	8	YES	(22)
Chen and, He 2021	Guangdong, China	27	Cervical cancer	14	13	RT-qPCR	Tissue	OS	Mean	KM survival curve	Directly	2.80 (1.00-7.90)	120	8	NM	(23)

AML, acute myeloid leukemia; PTC, papillary thyroid cancer; NSCLC, non-small cell lung cancer; HCC, hepatocellular cancer; NOS, Newcastle-Ottawa Scale; NM, not mentioned; lncRNA HOXA-AS2, long non-coding RNA homeobox A cluster antisense RNA 2; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; OS, overall survival; HR, hazard ratio; KM, Kaplan-Meier; CI, confidence interval.

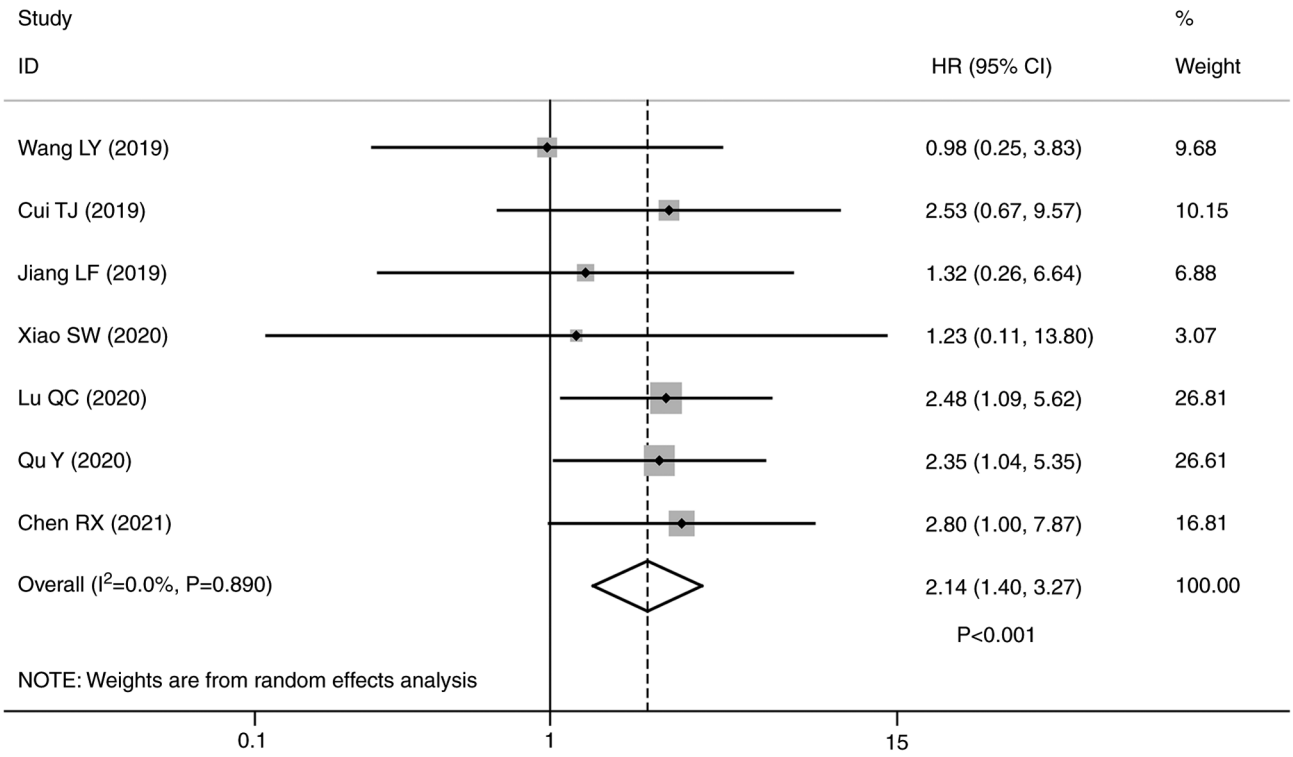

Figure 2. Forest plots for the association of long non-coding RNA homeobox A cluster antisense RNA 2 expression with overall survival. CI, confidence interval; HR, hazard ratio.

size (n≤60 or n>60; Fig. 3B), cancer type (reproductive system cancer or not, Fig. 3C; carcinoma or not, Fig. 3D), follow-up duration (≤60 or >60 months; Fig. 3E) and NOS score (≤7 or >7; Fig. 3F). It is noteworthy that, as reported in Table II, significant associations were found in certain subgroups. For instance, in Southern China, high expression of lncRNA HOXA-AS2 was significantly correlated with poorer overall survival (OS) (HR=2.58; 95% CI, 1.45-4.61; P=0.001), as well as in the study subgroup with sample sizes exceeding 60 (HR=2.19; 95% CI, 1.29-3.73; P=0.004). Furthermore, the analysis revealed significant associations between high lncRNA HOXA-AS2 expression and OS in the subgroups of non-reproductive system cancers (HR=2.07; 95% CI, 1.29-3.32; P=0.003) and in the Carcinoma subgroup (HR=2.33; 95% CI, 1.13-4.83; P=0.023). These findings highlight the potential prognostic significance of lncRNA HOXA-AS2 expression in specific cancer populations and underscore the value of stratifying patients in future research. Despite the low heterogeneity observed across the subgroups (I^2=0.0%), these significant results demonstrate the consistency of the effect across different patient populations and study designs, affirming the robustness of the association between high lncRNA HOXA-AS2 expression and poorer OS across diverse cancer types and study conditions, while also revealing potential differential factors.

LncRNA HOXA-AS2 expression and clinicopathological characteristics. In the present study, the relationship between lncRNA HOXA-AS2 expression levels and various clinicopathological features were explored in patients with cancer (Table III). In this study, a random-effects model was uniformly applied to account for observed and potential heterogeneity across studies in all analyses of clinicopathological features.

Association between lncRNA HOXA-AS2 expression and age or sex. The study found no significant association between the expression of lncRNA HOXA-AS2 and gender (OR=1.55; 95% CI, 0.72-3.34; P=0.258; Fig. 4A), despite the presence of moderate heterogeneity (I^2=55.9%; P=0.078), but the P-value was greater than 0.05. Similarly, there was no significant correlation between patient age and the expression of lncRNA HOXA-AS2 (OR=1.00; 95% CI, 0.63-1.59; P=0.991; Fig. 4B), with negligible heterogeneity in the studies (I^2=0%; P=0.409).

Association between lncRNA HOXA-AS2 expression and metastatic status. The study revealed that high expression of lncRNA HOXA-AS2 is significantly associated with an increased risk of metastasis. Specifically, there was an increased risk for both LNM and DM (OR for LNM=2.06; 95% CI, 1.07-3.99; P=0.032, and OR for DM=2.11; 95% CI, 1.15-3.88; P=0.016), respectively (Fig. 4C and D).

Association between lncRNA HOXA-AS2 expression and tumor stage or size. For tumor size, significant heterogeneity was observed (I^2=69.8%, P=0.019), and the results demonstrated a significant association between high lncRNA HOXA-AS2 expression and larger tumor size (HR=2.02; 95% CI, 0.86-4.78; P=0.006; Fig. 4E). Regarding tumor staging, the analysis revealed that high lncRNA HOXA-AS2 expression is associated with higher tumor stages (HR=2.71; 95% CI, 1.50-4.89; P=0.001; Fig. 4F), with a heterogeneity level of 33.5%, although not statistically significant (P=0.211). Subgroup analysis was conducted to investigate the sources of heterogeneity, indicating a more pronounced association between lncRNA HOXA-AS2 expression and tumor size in carcinomas (OR=2.92; 95% CI, 1.32-6.49; P=0.008;

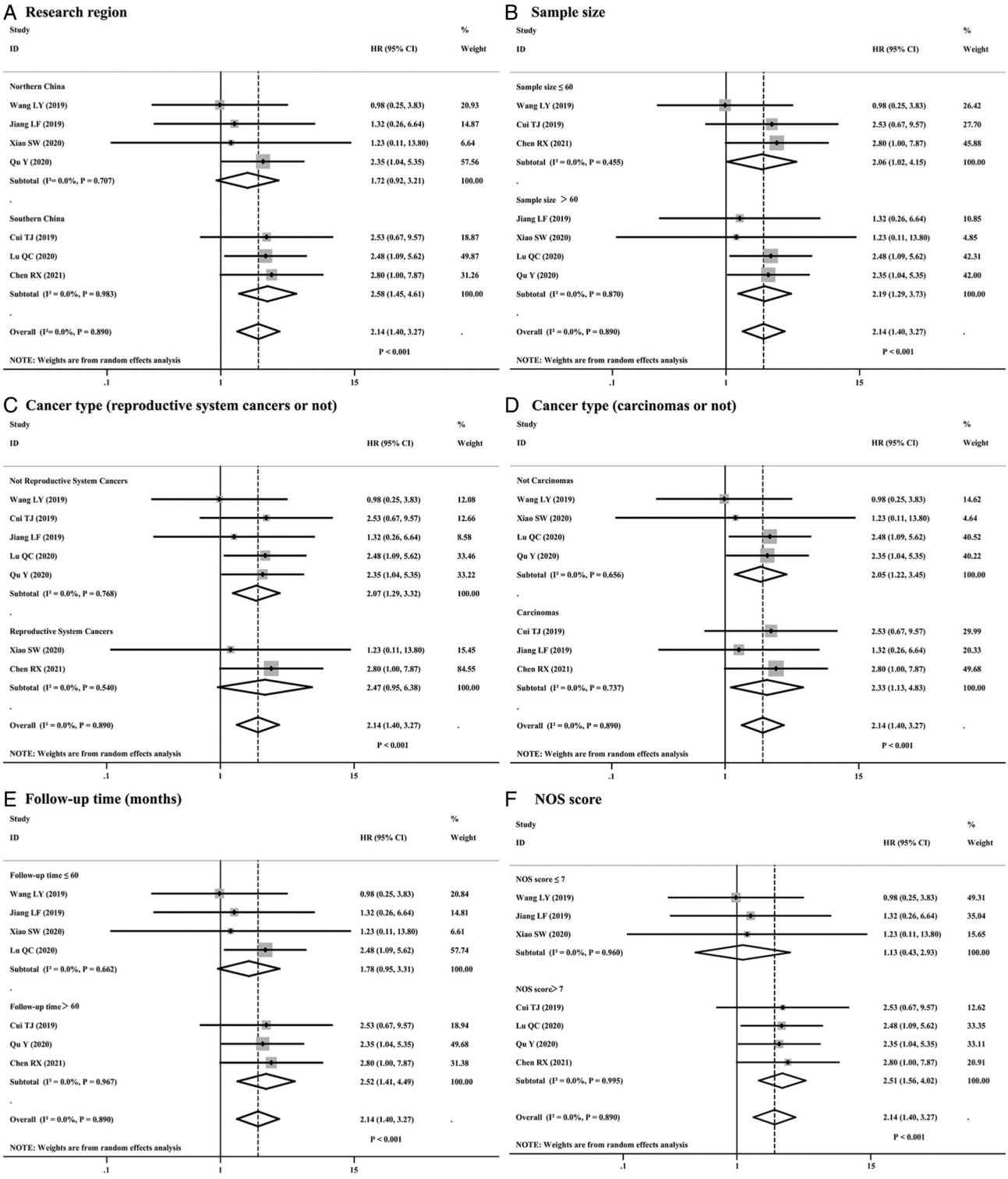

Figure 3. Subgroup analysis for overall survival. Subgroup analysis stratified by (A) Research region, (B) sample size, (C) cancer type (reproductive system cancer or not), (D) cancer type (carcinoma or not), (E) follow-up time (mouths) and (F) NOS score. CI, confidence interval; HR, hazard ratio; NOS, Newcastle-Ottawa Scale.

Fig. 4G). In contrast, no such significant association was found in non-carcinoma tumors (OR=1.51; 95% CI, 0.31-7.40; P=0.612; Fig. 4G), suggesting that these patients may have contributed to the observed heterogeneity. In summary, high expression of lncRNA HOXA-AS2 was significantly associated with adverse clinicopathological characteristics in patients with cancer, particularly in the risk of metastasis and tumor progression, and especially in carcinomas. However, lncRNA HOXA-AS2 expression was unrelated to patient age and sex.

Sensitivity analysis and publication bias. To ascertain the robustness of the meta-analysis, a meticulous sensitivity analysis was conducted using the leave-one-out method, and

Table II. Subgroup meta-analysis of the pooled HRs for overall survival.

Stratified analysis	Number of studies	Number of patients	HR (95% CI)	P-value	Heterogeneity (I^2, P)	Model
Region						
Northern China	4	271	1.72 (0.92-3.21)	0.087	0.0%, 0.707	Random
Southern China	3	183	2.58 (1.45-4.61)	0.001	0.0%, 0.983	Random
Cancer type 1						
Not reproductive system cancer	5	359	2.07 (1.29-3.32)	0.003	0.0%, 0.768	Random
Reproductive system cancer	2	95	2.47 (0.95-6.38)	0.063	0.0%, 0.540	Random
Cancer type 2						
Not carcinoma	4	319	2.05 (1.22-3.45)	0.007	0.0%, 0.656	Random
Carcinoma	3	135	2.33 (1.13-4.83)	0.023	0.0%, 0.737	Random
Sample size, n						
≤60	3	94	2.06 (1.02-4.15)	0.043	0.0%, 0.455	Random
>60	4	360	2.19 (1.29-3.73)	0.004	0.0%, 0.870	Random
Follow-up time, months						
≤60	4	279	1.78 (0.95-3.31)	0.070	0.0%, 0.662	Random
>60	3	175	2.52 (1.41-4.49)	0.002	0.0%, 0.967	Random
NOS score						
≤7	3	163	1.13 (0.43-2.93)	0.806	0.0%, 0.960	Random
>7	4	291	2.51 (1.56-4.02)	<0.001	0.0%, 0.995	Random

HR, hazard ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale.

Table III. Association of long non-coding RNA homeobox A cluster antisense RNA 2 expression with clinicopathological features.

Clinicopathological parameters	OR (95% CI)	P-value	Heterogeneity (I^2, P)	Model
Age (elderly vs. young)	1.00 (0.63-1.59)	0.991	0.0%, 0.409	Random
Sex (male vs. female)	1.55 (0.72-3.34)	0.258	55.9%, 0.078	Random
Lymph node metastasis (positive vs. negative)	2.06 (1.07-3.99)	0.032	24.9%, 0.264	Random
Tumor size (large vs. small)	2.02 (0.86-4.78)	0.006	69.8%, 0.019	Random
Tumor stage (III + IV vs. I + II)	2.71 (1.50-4.89)	0.001	33.5%, 0.211	Random
Distance metastasis (yes vs. no)	2.11 (1.15-3.88)	0.016	30.7%, 0.228	Random

the presence of publication bias was examined using a Begg's funnel plot and Egger's regression test.

Sensitivity analysis. The leave-one-out sensitivity analysis involved sequentially omitting each study to evaluate its impact on the overall effect estimate. The analysis revealed that omitting any single study did not significantly alter the combined HRs (Fig. 5A), which underscored the stability of the meta-analysis results.

Publication bias. The Begg's funnel plot was scrutinized for asymmetry to detect publication bias, and the plot presented no overt asymmetry, suggesting an absence of bias (Fig. 5B). Additionally, the Begg's test yielded a P-value of 0.133, indicating no significant publication bias. Egger's regression test (Fig. 5C), which is sensitive to funnel plot asymmetry, corroborated these findings by showing no significant publication bias (intercept=-1.199832; P=0.107). While there was a hint of asymmetry in the Egger's plot, the non-significant P-value implied that the effect sizes of the included studies were symmetrically distributed around the overall effect size, thereby providing no substantial evidence of publication bias.

Collectively, the leave-one-out sensitivity analysis and the publication bias assessments affirmed the credibility of the meta-analysis. The consistent results across these analytical approaches demonstrated the robustness of the conclusions drawn from the pooled data, free from the undue influence of any single study or publication bias.

Discussion

Since Zhao *et al* (9) published their results indicating that lncRNA HOXA-AS2 repressed apoptosis in trans retinoic acid-treated NB4 promyelocytic leukemia cells in 2013, it has been demonstrated (23,27,28) that lncRNA HOXA-AS2

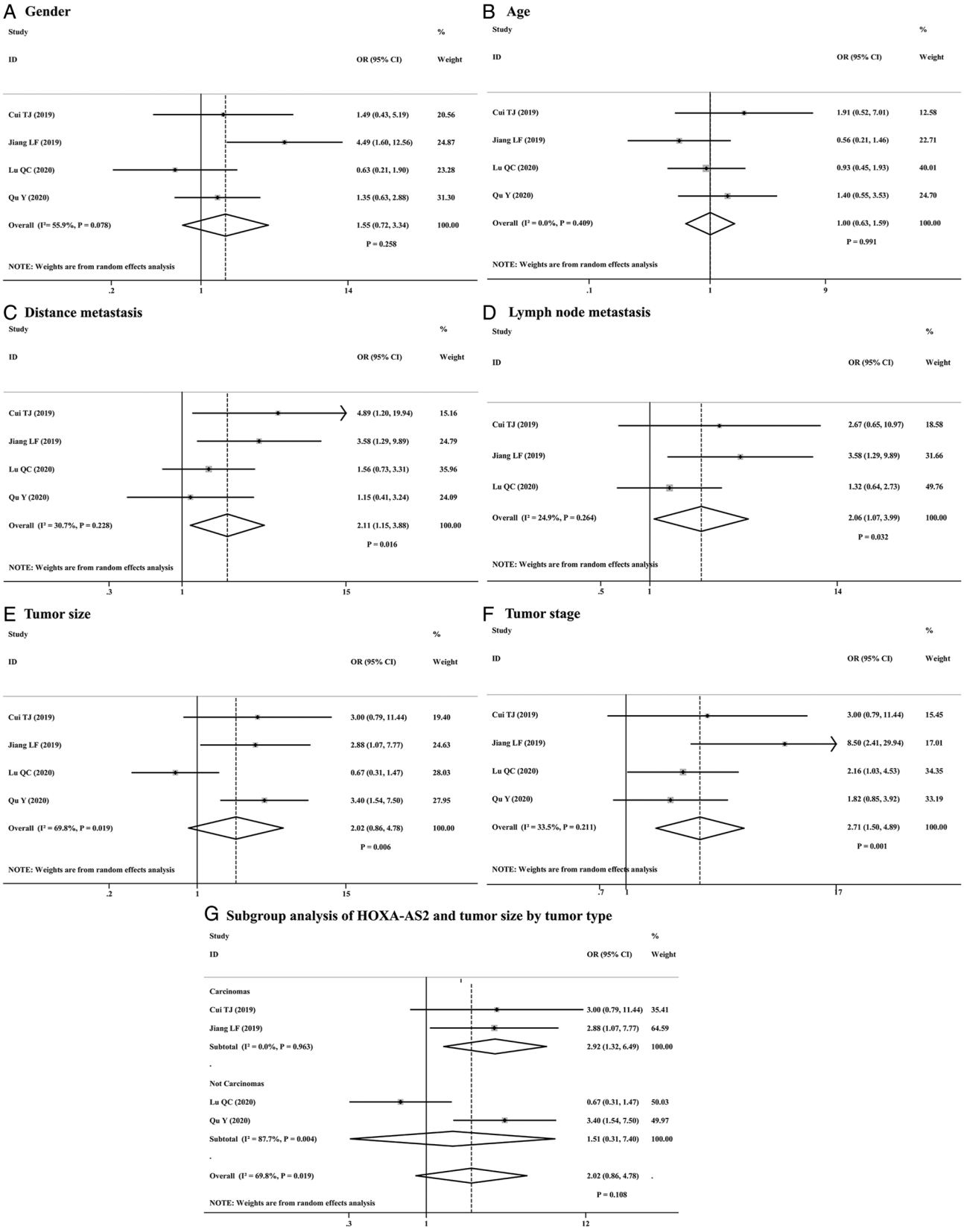

Figure 4. Forest plots for the association of lncRNA HOXA-AS2 expression with clinicopathological features. Forest plots for (A) sex, (B) age, (C) distant metastasis, (D) lymph node metastasis, (E) tumor size and (F) tumor stage. (G) Subgroup analysis of lncRNA HOXA-AS2 and tumor size by tumor type. CI, confidence interval; lncRNA HOXA-AS2, long non-coding RNA homeobox A cluster antisense RNA 2; OR, odds ratio.

is upregulated in multiple solid tumors and promotes various malignant behaviors and clinical manifestations. In addition to the studies included in the present meta-analysis, there are additional studies that have explored the oncogenic role of lncRNA HOXA-AS2 in tumors. For instance, Lian *et al* (29) found that lncRNA HOXA-AS2 was upregulated in

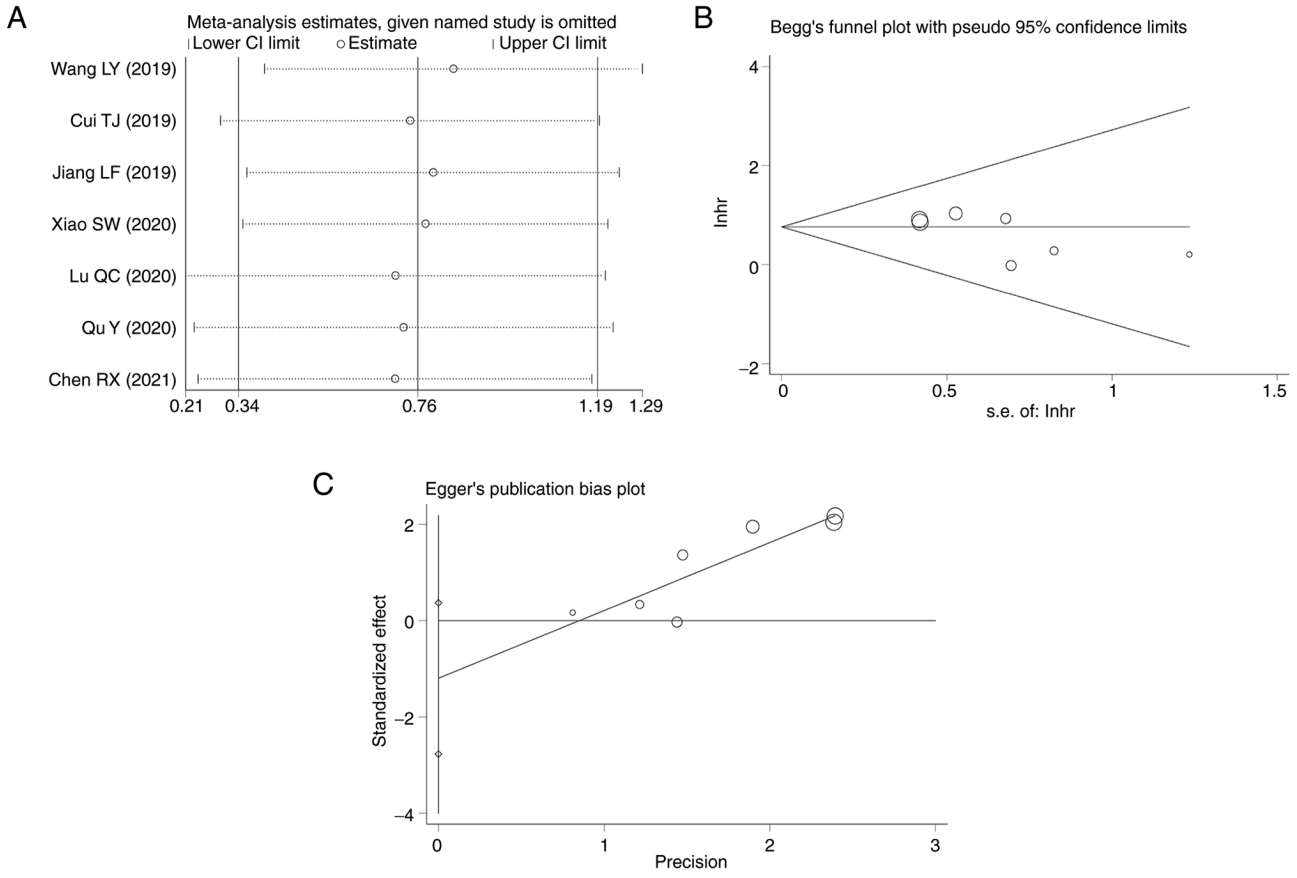

Figure 5. Sensitivity and publication bias analyses for overall survival. (A) Influence plot for sensitivity analysis. (B) Begg's funnel plot for publication bias. (C) Egger's test for publication bias. CI, confidence interval; s.e., standard error; lnHR, natural logarithm of the hazard ratio.

pancreatic cancer (PC); moreover, the interaction between HOXA-AS2 and EZH2 and lysine specific demethylase 1 promoted PC cell proliferation *in vitro*. Similar results were also discovered in malignant glioma (30,31), kidney renal clear cell carcinoma (32) and oral cancer (33). These studies were not included in the present meta-analysis due to a lack of necessary clinical data.

In terms of the molecular mechanism, available research indicates the following regulatory functions of lncRNA HOXA-AS2: i) ceRNA regulatory mechanism: The role of lncRNA HOXA-AS2 as a ceRNA is its most well-studied and established function. Extensive research, as evidenced by numerous publications, has highlighted lncRNA HOXA-AS2 as a pivotal element in the ceRNA network across a variety of cancer types, including AML (34), bladder cancer (35), PCa (27,36) and lower-grade glioma (26). This mechanism primarily involves lncRNA HOXA-AS2 sponging various miRNAs such as miR-520c-3p (34), miR-125b (35), miR-885-5p (27), miR-509-3p (26) and miR-184 (36) in different cancer contexts. These interactions significantly impact the expression of downstream genes, thereby influencing the progression of cancer. For instance, studies by Yang *et al* (27) and Xiao and Song (26) have shown that reducing the levels of lncRNA HOXA-AS2 affects cell proliferation, migration, invasion and epithelial-mesenchymal transition (EMT), subsequently promoting the development and progression of PCa. Meanwhile, Chen *et al* (36) conducted a comprehensive transcriptomic analysis using multiple datasets from the Chinese Glioma Genome Atlas and The Cancer Genome Atlas. The results confirmed the role of lncRNA HOXA-AS2 as a ceRNA, inducing cell proliferation in lower-grade gliomas. ii) EMT promoting function: Zhang *et al* (37) demonstrated that high expression of lncRNA HOXA-AS2 in gall bladder cancer could increase the expression levels of Vimentin (a mesenchymal marker), whereas the expression of E-cadherin (an epithelial marker) is decreased, resulting in an upregulation of the migration of cancer cells. iii) Protein binding function: Ding *et al* (38) demonstrated that in gastric cancer, the competitive binding of lncRNA HOXA-AS2 and EZH2 causes the dissociation between EZH2 and the promoter of the P21, polo-like kinase 3 and DNA damage inducible transcript 3 genes, inhibiting H3K27 trimethylation and leading to the repression of these tumor suppressing genes. iv) Activator of adjacent genes: Zhao *et al* (39) previously found that lncRNA HOXA-AS2 could directly elevate the expression levels of HOXA3 mRNA and protein but not that of HOXA4 in acute lymphoblastic leukemia cells.

While the upregulation of HOXA-AS2 in various cancer types and its role in promoting malignant behaviors and clinical manifestations have been established, the specific mechanism of its secretion into the circulatory system remains a focal point of scientific investigation. The current research on the secretion mechanism of lncRNA HOXA-AS2 is insufficient. Generally, the secretion of lncRNAs may involve more complex cellular mechanisms than cytokines

or proteins, including but not limited to pathways involving extracellular vesicles. A study has shown that extracellular vesicles, especially exosomes, contain extracellular lncRNAs and mediate the horizontal transfer of lncRNAs between tumor cells to disseminate drug resistance (40). Compared with miRNAs, although lncRNAs are found in plasma-derived exosomal RNA, only a subset of lncRNAs are selectively loaded into exosomes, which may be associated with physiological and cellular factors (41). These extracellular vesicles capable of carrying and transporting RNA molecules, including lncRNAs, may thus be involved in the secretion process of lncRNA HOXA-AS2. However, the specific application of this mechanism to lncRNA HOXA-AS2 remains speculative and requires further investigation. Despite the lack of direct evidence regarding the secretion mechanism of lncRNA HOXA-AS2, the present study, along with that of others, has highlighted the significant potential of lncRNA HOXA-AS2 as a cancer biomarker, particularly in predicting the prognosis of patients with cancer. Future studies are required not only to explore the role of lncRNA HOXA-AS2 in cancer development but also to unveil how it is secreted into the circulatory system. This will be crucial for leveraging lncRNA HOXA-AS2 as a non-invasive biomarker for cancer diagnosis and prognosis assessment.

In the present comprehensive study investigating the role of lncRNA HOXA-AS2 expression in cancer, its relationship with a variety of clinicopathological characteristics was examined. The present systematic review and meta-analysis, encompassing 454 patients across 7 independent studies, revealed that high lncRNA HOXA-AS2 expression was significantly negatively associated with OS in patients with cancer, yielding an OR of 2.14 (95% CI, 1.40-3.27; P<0.001). Further analysis of the data from 6 critical studies underscored the complex relationship between lncRNA HOXA-AS2 expression and clinical features. The findings of the present study indicated that there was no significant association between lncRNA HOXA-AS2 expression with patient age or sex. Specifically, despite a moderate level of heterogeneity in the sex of patients (I^2=55.9%, P=0.078), there was no substantial link between lncRNA HOXA-AS2 expression and sex (OR=1.55; 95% CI, 0.72-3.34; P=0.258). In addition, age displayed very low heterogeneity (I^2=0%) and no significant association with lncRNA HOXA-AS2 expression (OR=1.00; 95% CI, 0.63-1.59; P=0.991). Significantly, our analysis confirmed the crucial role of lncRNA HOXA-AS2 in promoting metastasis and advancing tumor severity, as evidenced by its strong association with lymph node and distant metastasis, and with higher tumor stage and size. These associations align with earlier studies which also reported lncRNA HOXA-AS2 as a key player in cancer progression. These findings further emphasized the potential of lncRNA HOXA-AS2 as a prognostic biomarker for cancer, paving the way for new diagnostic and therapeutic approaches in oncology.

In updating the literature review to January 4, 2024, the present study incorporated the latest research findings on lncRNA HOXA-AS2, extending beyond the scope of previous meta-analyses (20,42,43). Unlike these prior studies, the present study provided an exhaustive subgroup analysis, considering six clinically relevant factors not previously analyzed together. By examining age, sex, DM and LNM and including eight aspects such as research region, sample size, involvement of reproductive system cancer and whether the cancer is a carcinoma or non-carcinoma, the present study offers a more comprehensive perspective on the multifaceted clinical value of lncRNA HOXA-AS2. Furthermore, updated statistical methods and more stringent quality assessment standards were employed, ensuring a high degree of credibility and applicability of the results. Notably, we delved into the complex functions of lncRNA HOXA-AS2, including its ceRNA regulatory mechanism, EMT promoting function, protein binding capability and its role as an activator of adjacent genes. These insights provide a nuanced understanding of lncRNA HOXA-AS2's involvement in cancer progression and its potential as a non-invasive biomarker for cancer diagnosis and prognosis assessment. Unlike previous research, this study also ventures into the preliminary discussion on the secretion mechanisms of lncRNA HOXA-AS2 into the circulatory system, a crucial step towards its application in clinical settings. By exploring these novel aspects, our research not only significantly updates but also expands the existing knowledge on lncRNA HOXA-AS2, laying a solid foundation for future investigations into its clinical applications and mechanisms of action. This unique contribution marks a significant step forward in the understanding of lncRNA HOXA-AS2's potential as a diagnostic and prognostic tool, highlighting areas that warrant further exploration and validation in future research.

Despite adhering to strict procedures and rigorous statistical methods, the present study still faces certain limitations that should be addressed. Firstly, the total sample size and the individual sample sizes of the included studies were relatively small, and the types of cancers covered did not comprehensively represent all common cancer types. Through precise selection, the quality of the included studies and specificity to lncRNA HOXA-AS2 related prognosis studies were ensured. Secondly, approximately half of the pooled HRs were derived from Kaplan-Meier survival curves published in the original articles using the statistical method published by Tierney *et al* (17), potentially leading to inaccuracies and heterogeneity in the final results. Thirdly, although the studies were meticulously selected for inclusion, not all the studies contained key clinicopathological characteristics such as tumor size, stage, DM and LNM, limiting the capacity for a more comprehensive analysis. Fourthly, all the studies included were from China, and while subgroup analyses based on geographical regions within China were conducted, these results might not be sufficiently representative on a global scale. Finally, the cut-off values for high/low lncRNA HOXA-AS2 expression varied and were not uniform; thus, more research is needed before applying the findings of the present study to clinical practice.

In summary, the results of the present meta-analysis underscored a significant association between high HOXA-AS2 expression and adverse clinicopathological features in patients with cancer, particularly in relation to risk of metastasis and tumor progression in carcinomas. The results also reinforced the potential of lncRNA HOXA-AS2

as a prognostic biomarker in cancer. Finally, the findings suggested that lncRNA HOXA-AS2 expression is independent of patient demographic factors, such as age and sex, highlighting its broad applicability across diverse patient populations. However, we acknowledge the complexities underlying the regulatory functions of lncRNA HOXA-AS2 in various cancer types, which are influenced by the localization and expression of downstream molecules. Therefore, while the present study provided a foundational understanding of the association between lncRNA HOXA-AS2 expression and cancer, it should be seen as a preliminary step in a much larger investigative landscape. To fully delineate the clinical value of lncRNA HOXA-AS2 and to solidify its role in cancer diagnostics and therapeutics, more comprehensive studies of higher quality are indispensable. Future research is required to delve deeper into the multifaceted mechanisms of lncRNA HOXA-AS2, which will be crucial for developing innovative diagnostic and treatment strategies in cancer care.

Acknowledgements

Not applicable.

Funding

This study was supported by The National Science Fund for Distinguished Young Scholars (grant no. 82203494), the key project of the Scientific Research Project of the Hunan Education Department (grant no. 22A0534), the project of Hunan Province Health Commission (grant no. 202204015341) and the project of Shao yang Science and Technology Bureau (grant no. 2021052ZD).

Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

WG and TX contributed to the study's conception and design. Data collection from databases was performed by WG, HZ, and AY. Data analysis was conducted by WG, TX, LT, AY, and HZ. The initial draft and revisions of the manuscript were co-written by TX and HZ. WG and AY confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Mattick JS and Makunin IV: Non-coding RNA. Hum Mol Genet 15 Spec No 1: R17-29, 2006.
2. Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, Guernec G, Martin D, Merkel A, Knowles DG, *et al*: The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression. Genome Res 22: 1775-1789, 2012.
3. Kung JT, Colognori D and Lee JT: Long noncoding RNAs: Past, present, and future. Genetics 193: 651-669, 2013.
4. Fatica A and Bozzoni I: Long non-coding RNAs: New players in cell differentiation and development. Nat Rev Genet 15: 7-21, 2014.
5. Bhan A, Soleimani M and Mandal SS: Long noncoding RNA and cancer: A new paradigm. Cancer Res 77: 3965-3981, 2017.
6. Wang KC and Chang HY: Molecular mechanisms of long noncoding RNAs. Mol Cell 43: 904-914, 2011.
7. Schmitt AM and Chang HY: Long noncoding RNAs in cancer pathways. Cancer Cell 29: 452-463, 2016.
8. Choudhari R, Sedano MJ, Harrison AL, Subramani R, Lin KY, Ramos EI, Lakshmanaswamy R and Gadad SS: Long noncoding RNAs in cancer: From discovery to therapeutic targets. Adv Clin Chem 95: 105-147, 2020.
9. Zhao H, Zhang X, Frazão JB, Condino-Neto A and Newburger PE: HOX antisense lincRNA HOXA-AS2 is an apoptosis repressor in all trans retinoic acid treated NB4 promyelocytic leukemia cells. J Cell Biochem 114: 2375-2383, 2013.
10. Feng Y, Hu S, Li L, Peng X and Chen F: Long noncoding RNA HOXA-AS2 functions as an oncogene by binding to EZH2 and suppressing LATS2 in acute myeloid leukemia (AML). Cell Death Dis 11: 1025, 2020.
11. Zhang P, Liu L, Zhang W, Fang J, Li G, Zhang L, Li J, Deng X, Ma J, Li K and Chen Z: Effects of long noncoding RNA HOXA-AS2 on the proliferation and migration of gallbladder cancer cells. J Oncol 2022: 6051512, 2022.
12. Zhong C, Tao B, Li X, Xiang W, Peng L, Peng T, Chen L, Xia X, You J and Yang X: HOXA-AS2 contributes to regulatory T cell proliferation and immune tolerance in glioma through the miR-302a/KDM2A/JAG1 axis. Cell Death Dis 13: 160, 2022.
13. Wu Q, Lu S, Zhang L and Zhao L: LncRNA HOXA-AS2 activates the notch pathway to promote cervical cancer cell proliferation and migration. Reprod Sci 28: 3000-3009, 2021.
14. Jiang L, Wu Z, Meng X, Chu X, Huang H and Xu C: LncRNA HOXA-AS2 facilitates tumorigenesis and progression of papillary thyroid cancer by modulating the miR-15a-5p/HOXA3 axis. Hum Gene Ther 30: 618-631, 2019.
15. Zhao Z, Xing Y, Yang F, Zhao Z, Shen Y, Song J and Jing S: LncRNA HOXA-AS2 promotes oral squamous cell proliferation, migration, and invasion via upregulating EZH2 as an oncogene. Technol Cancer Res Treat 20: 15330338211039109, 2021.
16. Wang J, Su Z, Lu S, Fu W, Liu Z, Jiang X and Tai S: LncRNA HOXA-AS2 and its molecular mechanisms in human cancer. Clin Chim Acta 485: 229-233, 2018.
17. Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR: Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8: 16, 2007.
18. Liu Z, Cai L, Liu Y, Chen W and Wang Q: Association between prenatal cadmium exposure and cognitive development of offspring: A systematic review. Environ Pollut 254: 113081, 2019.
19. Zhang L, Yu CH, Guo KP, Huang CZ and Mo LY: Prognostic role of red blood cell distribution width in patients with sepsis: A systematic review and meta-analysis. BMC Immunol 21: 40, 2020.
20. Zhang F, Zhang G, Zhang H, Pu X, Chi F, Zhang D, Xin X, Gao M, Luo W and Li X: HOXA-AS2 may be a potential prognostic biomarker in human cancers: A meta-analysis and bioinformatics analysis. Front Genet 13: 944278, 2022.
21. Lu Q, Gao J, Tang S, Li Z, Wang X, Deng C, Hu J, Tao Y and Wang Q: Integrated RNA sequencing and single-cell mass cytometry reveal a novel role of LncRNA HOXA-AS2 in tumorigenesis and sternness of hepatocellular carcinoma. Onco Targets Ther 13: 10901-10916, 2020.
22. Qu Y, Wang Y, Wang P, Lin N, Yan X and Li Y: Overexpression of long noncoding RNA HOXA-AS2 predicts an adverse prognosis and promotes tumorigenesis via SOX4/PI3K/AKT pathway in acute myeloid leukemia. Cell Biol Int 44: 1745-1759, 2020.
23. Chen R and He P: Long noncoding RNA HOXA-AS2 accelerates cervical cancer by the miR-509-3p/BTN3A1 axis. J Pharm Pharmacol 73: 1387-1396, 2021.

24. Cui TJ, Lin GS, Dai YM, Zheng JP, Chen Z, Chen Q, Zheng Y and Lin X. LncRNA HOXA-AS2 regulates microRNA-216a-5p to promote malignant progression of non-small cell lung cancer. Eur Rev Med Pharmacol Sci 23(Suppl 3): S264-S273, 2019.
25. Wang L, Wang L and Zhang X: Knockdown of lncRNA HOXA-AS2 inhibits viability, migration and invasion of osteosarcoma cells by miR-124-3p/E2F3. Onco Targets Ther 12: 10851-10861, 2019.
26. Xiao S and Song B: LncRNA HOXA-AS2 promotes the progression of prostate cancer via targeting miR-509-3p/PBX3 axis. Biosci Rep 40: BSR20193287, 2020.
27. Yang Z, Zhang F, Cai K and Xu J: Long noncoding RNA HOXA-AS2 facilitates prostate cancer progression by inhibiting miR-885-5p to upregulate KDM5B. Kidney Blood Press Res 48: 45-55, 2023.
28. Wu J, Li M and Zhang Y: Long noncoding RNA HOXA-AS2 regulates the expression of SCN3A by sponging miR-106a in breast cancer. J Cell Biochem 120: 14465-14475, 2019.
29. Lian Y, Li Z, Fan Y, Huang Q, Chen J, Liu W, Xiao C and Xu H: The lncRNA-HOXA-AS2/EZH2/LSD1 oncogene complex promotes cell proliferation in pancreatic cancer. Am J Transl Res 9: 5496-5506, 2017.
30. Gao Y, Yu H, Liu Y, Liu X, Zheng J, Ma J, Gong W, Chen J, Zhao L, Tian Y and Xue Y: Long non-coding RNA HOXA-AS2 regulates malignant glioma behaviors and vasculogenic mimicry formation via the MiR-373/EGFR axis. Cell Physiol Biochem 45: 131-147, 2018.
31. Duan WW, Yang LT, Liu J, Dai ZY, Wang ZY, Zhang H, Zhang X, Liang XS, Luo P, Zhang J, *et al*: A TGF-β signaling-related lncRNA signature for prediction of glioma prognosis, immune microenvironment, and immunotherapy response. CNS Neurosci Ther, Oct 18, 2023 (Epub ahead of print).
32. Zhang Y, Zhuang T, Xin Z, Sun C, Li D, Ma N, Wang X and Wang X: Construction of a necroptosis-related lncRNA signature for predicting prognosis and immune response in kidney renal clear cell carcinoma. Cells 12: 66, 2023.
33. Doghish AS, Elshaer SS, Fathi D, Rizk NI, Elrebehy MA, Al-Noshokaty TM, Elballal MS, Abdelmaksoud NM, Abdel-Reheim MA, Abdel Mageed SS, *et al*: Unraveling the role of miRNAs in the diagnosis, progression, and drug resistance of oral cancer. Pathol Res Pract 253: 155027, 2024.
34. Dong X, Fang Z, Yu M, Zhang L, Xiao R, Li X, Pan G and Liu J: Knockdown of long noncoding RNA HOXA-AS2 suppresses chemoresistance of acute myeloid leukemia via the miR-520c-3p/S100A4 axis. Cell Physiol Biochem 51: 886-896, 2018.
35. Wang F, Wu D, Chen J, Chen S, He F, Fu H, Wu Q, Liu S, Li X and Wang W: Long non-coding RNA HOXA-AS2 promotes the migration, invasion and stemness of bladder cancer via regulating miR-125b/Smad2 axis. Exp Cell Res 375: 1-10, 2019.
36. Chen PY, Li XD, Ma WN, Li H, Li MM, Yang XY and Li SY: Comprehensive transcriptomic analysis and experimental validation identify lncRNA HOXA-AS2/miR-184/COL6A2 as the critical ceRNA regulation involved in low-grade glioma recurrence. Onco Targets Ther 13: 4999-5016, 2020.
37. Zhang P, Cao P, Zhu X, Pan M, Zhong K, He R, Li Y, Jiao X and Gao Y: Upregulation of long non-coding RNA HOXA-AS2 promotes proliferation and induces epithelial-mesenchymal transition in gallbladder carcinoma. Oncotarget 8: 33137-33143, 2017.
38. Ding J, Xie M, Lian Y, Zhu Y, Peng P, Wang J, Wang L and Wang K: Long noncoding RNA HOXA-AS2 represses P21 and KLF2 expression transcription by binding with EZH2, LSD1 in colorectal cancer. Oncogenesis 6: e288, 2017.
39. Zhao Q, Zhao S, Li J, Zhang H, Qian C, Wang H, Liu J and Zhao Y: TCF7L2 activated HOXA-AS2 decreased the glucocorticoid sensitivity in acute lymphoblastic leukemia through regulating HOXA3/EGFR/Ras/Raf/MEK/ERK pathway. Biomed Pharmacother 109: 1640-1649, 2019.
40. EL Andaloussi S, Mäger I, Breakefield XO and Wood MJ: Extracellular vesicles: Biology and emerging therapeutic opportunities. Nat Rev Drug Discov 12: 347-357, 2013.
41. Zhou G and Chen X: Emerging role of extracellular microRNAs and lncRNAs. ExRNA 1: 10, 2019.
42. Wang Q, Zhang W, Deng C, Lin S and Zhou Y: HOXA-AS2 may predict the prognosis of solid tumors among Chinese patients: A meta-analysis and bioinformatic analysis. Front Oncol 12: 1030825, 2022.
43. Lu B, Liu Z, Ji X and Zhang X: Assessment of the prognostic and clinicopathological significance of HOXA-AS2 in human cancers: A systematic review and meta-analysis. Transl Cancer Res 12: 605-615, 2023.