Original Article

Assessment of the prognostic and clinicopathological significance of HOXA-AS2 in human cancers: a systematic review and meta-analysis

Biyun Lu[1#^], Zhou Liu[2#^], Xiaoying Ji[1], Xianming Zhang[1]

[1]Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Guizhou Medical University, Guiyang, China; [2]School of Basic Medical Science, Guizhou Medical University, Guiyang, China

Contributions: (I) Conception and design: B Lu, X Zhang; (II) Administrative support: X Zhang; (III) Provision of study materials or patients: B Lu, Z Liu; (IV) Collection and assembly of data: Z Liu, X Ji; (V) Data analysis and interpretation: B Lu, Z Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Xianming Zhang, PhD. Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Guizhou Medical University, Guiyang, China. Email: zxm13078524367@163.com.

Background: Numerous studies have reported that abnormally HOXA cluster antisense RNA 2 (HOXA-AS2) expression plays a critical role in various cancers. Thus, we performed this meta-analysis to comprehensively evaluate the prognostic value of HOXA-AS2 in human cancers.

Methods: Databases, including PubMed, Web of Science, Embase, China National Knowledge Infrastructure, and Wanfang Data, were searched to retrieve articles on HOXA-AS2 and the prognosis of cancer patients, which were then screened. The association between HOXA-AS2 and overall survival (OS) and the clinicopathological characteristics of patients with cancers were assessed using hazard ratios (HRs) and odds ratios (ORs) combined with 95% confidence intervals (CIs). A subgroup analysis and the Begg test were used to assess the risk of bias of the included studies. Data from The Cancer Genome Atlas (TCGA) were analyzed to verify the results, and the potential regulation mechanism of HOXA-AS2 in cancers was revealed by an immune analysis.

Results: A total of 17 articles, comprising 1,176 patients, were included in this meta-analysis. The results showed that high HOXA-AS2 expression was associated with worse OS, advanced tumor node metastasis (TNM) stage, larger tumor size, lymph node metastasis, and distant metastasis in cancer patients but was not related to age, sex, or poor histological grade. The results of the analysis of TCGA data further supported our findings. Additionally, the immune analysis revealed that the expression of HOXA-AS2 was associated with immune cell infiltration and various immune checkpoints.

Conclusions: In summary, our results suggest that the high expression of HOXA-AS2 is associated with poor prognosis and the clinicopathological characteristics of cancer patients; thus, it could serve as a prognosis biomarker and therapeutic target for various cancers. However, the small sample size of this study and the inclusion of participants of a single race might have affected the generalizability of our findings. Thus, large-sample, multicenter studies need to be conducted to further evaluate the prognostic role of HOXA-AS2.

Keywords: Long noncoding RNA; HOXA-AS2; cancer; prognosis; clinicopathological characteristics

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^ ORCID: Biyun Lu, 0000-0002-1590-7356; Zhou Liu, 0000-0002-6773-1073.

Introduction

Cancer is a leading cause of human morbidity and mortality. It represents a severe threat to human health and is a challenging public issue that needs to be resolved. The American Cancer Society estimated that there would be 1,918,030 new cancer cases and 609,360 cancer deaths in the United States in 2022 (1). Substantial progress has been made in the diagnosis and treatment of malignant tumors; however, the poor prognosis of cancer patients is still a major clinical problem (2). Thus, the search for new therapeutic targets and prognostic biomarkers is of significant clinical value for cancer patients.

With the rise of next-generation sequencing technologies, long noncoding RNA (lncRNA), which lacks specific open reading frames and has no protein-coding ability, has been found to be a key molecule in various diseases (3-5). It has been widely reported that lncRNAs are involved in many physiological and pathological processes, and play an important role in transcriptional regulation, cell scaffold assembly, protein localization, and chromatin modification (6-8). A growing number of studies have demonstrated that lncRNAs can act as oncogenes or tumor suppressor factors, and their abnormal expression is closely related to the prognosis and poor clinicopathological characteristics of patients with cancer, which suggests that lncRNAs have the potential to serve as new biomarkers for cancer prognosis (9-13).

HOXA cluster antisense RNA 2 (HOXA-AS2), an antisense lncRNA with a length of 1,048 bp, is located on the HOXA gene cluster. Numerous studies have shown that HOXA-AS2 is abnormally expressed in a variety of cancers, including gastric cancer (14), hepatocellular carcinoma (15), colorectal cancer (9), bladder cancer (16), and non-small cell lung cancer (NSCLC) (17), and is closely correlated with poor prognosis and poor clinical features in patients with cancer (18,19). It also plays a significant role in the development and progression of cancer by regulating the proliferation, migration, invasion, differentiation, and other biological behaviors of cancer cells (20,21). Due to inconsistencies in the findings of published studies, we performed a meta-analysis to evaluate the difference in the overall survival (OS), disease-free survival, and clinicopathological features among patients who were histologically diagnosed as having cancer with high or low HOXA-AS2 expression to clarify the prognostic and clinicopathological significance of HOXA-AS2 in a variety of human cancers. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1998/rc).

Highlight box

Key findings

- The high expression of HOXA cluster antisense RNA 2 (HOXA-AS2) is related to poor prognosis and unfavorable clinicopathological features in those with cancer, which suggests that HOXA-AS2 may serve as a promising prognostic marker for these patients.

What is known and what is new?

- HOXA-AS2 expression plays a role in cancer development and is associated with the prognosis of cancer patients.
- HOXA-AS2 could be used as an efficient prognostic marker for cancer patients.

What is the implication, and what should change now?

- More high-quality and large-sample studies need to be conducted to confirm the significant role of HOXA-AS2 in pan-cancer patients.

Methods

Search strategy

Databases, including PubMed, Web of Science, Embase, Wanfang Data, and China National Knowledge Infrastructure, were searched from January 2015 to September 2022 to retrieve studies examining the association between HOXA-AS2 expression and patient prognosis. The retrieval keywords were as follows: "(HOXA-AS2 or HOXA Cluster Antisense RNA 2) and (cancer or tumor or malignancy)".

Literature screening

The literatures were screened according to the established inclusion and exclusion criteria. To be eligible for inclusion in this meta-analysis, the studies had to meet the following inclusion criteria: (I) include patients with a histopathological diagnosis, (II) include an intervention in which the expression level of HOXA-AS2 in the tissues of the patients was detected, (III) divide patients into a high expression group and low expression group based on the median or mean value, (IV) include sufficient data to calculate the hazard ratios (HRs) and odds ratios (ORs) and

their 95% confidence intervals (CIs) so that the relationship between the expression of HOXA-AS2 and the prognosis and clinicopathological characteristics of patients with malignant tumors could be evaluated, and (V) have a retrospective analysis study design. The exclusion criteria for literature were the following: (I) case reports, meta-analyses, animal studies, or editorial comments; (II) a lack of sufficient data available; and (III) published in a language other than English or Chinese.

Data extraction and analysis

The data of the included studies were extracted separately by 2 researchers (BL and ZL), and a third researcher (XJ) helped to resolve any disagreements. The following information was extracted from the articles: first author, gender, age, publication date, cancer type, sample size, detection method, follow-up time, clinicopathological characteristics, and prognosis information. If the results of both the univariate and multivariate analyses were provided in a study, the data of the latter were used. If the HRs and 95% CIs were not provided directly in the articles, Engauge Digitizer (v. 10.4) was used to extract them from the Kaplan-Meier survival curve. The quality of the included articles was assessed using the Newcastle-Ottawa Scale (NOS) with scores ranging from 0 to 9; articles with scores >6 were considered high quality.

The Cancer Genome Atlas (TCGA) data analysis

The information in TCGA database was analyzed using the Gene Expression Profiling Interactive Analysis (GEPIA) web tool, and the relationship between HOXA-AS2 and the clinical stage of the patients was assessed using the following criteria: |log2 fold change| ≥1 and a P value ≤0.01. The correlation between the expression of HOXA-AS2 and the OS of the 9,481 patients was also analyzed using the above criteria in the survival analysis.

Immunoassays

Using the CIBERSORT algorithm, the RNA-sequencing data of patients in TCGA database were analyzed using the R package "immunedeconv" (The R Foundation for Statistical Computing) The correlations between HOXA-AS2 expression and the expression of sialic acid binding immunoglobin (Ig)-like lectin 15 a (*SIGLEC15*), T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif (*ITIM*) domain protein (*TIGIT*), CD274, hepatitis A virus cellular receptor 2 (*HAVCR2*), programmed cell death 1 (*PDCD1*), cytotoxic T-lymphocyte–associated protein 4 (*CTLA4*), lymphocyte activating 3 (*LAG3*), and programmed cell death 1 ligand 2 (*PDCD1LG2*), which are the genes associated with immune checkpoints, were analyzed in a variety of cancers.

Statistical analysis

The statistical analysis was conducted using Stata software (v. 12.0, StataCorp). The HRs and ORs with 95% CIs were used to evaluate the relationship between HOXA-AS2 expression and prognosis and the clinicopathological parameters of patients with cancer. The heterogeneity among the included studies was evaluated using the Q and I^2 tests. If there was no heterogeneity (I^2<50% and P>0.05), a fixed-effects model was used; if there was heterogeneity (I^2≥50% and P≤0.05), a random-effects model was used. Subgroup and sensitivity analyses were conducted to explore the source of heterogeneity. In addition, the Begg test was used to assess potential publication bias. A P value <0.05 was considered statistically significant.

Results

Studies selection and characteristics

Details of the article screening process are provided in *Figure 1*. A total of 374 articles were retrieved from the relevant databases. After exclusion of duplicate articles, reviews, and other unrelated literature, the remaining 45 articles underwent full-text readings, and 17 eligible studies were ultimately included in the meta-analysis. All the included studies were published between 2015 and 2021, and had NOS scores ranging from 6 to 8. The sample sizes of the studies ranged from 27 to 128. In total, 11 types of cancer were analyzed, including oral squamous cell carcinoma (OSCC) (18), hepatocellular carcinoma (15,22,23), prostate cancer (21), NSCLC (17,24,25), bladder cancer (16), glioma (26), osteosarcoma (27,28), papillary thyroid cancer (19,29), colorectal cancer (9), breast cancer (30), and gastric cancer (14). The specific characteristics of the included articles are set out in *Table 1*.

Relationship between the expression of HOXA-AS2 and the prognosis of patients with cancer

Among the 17 studies, 10 studies, comprising 669 patients,

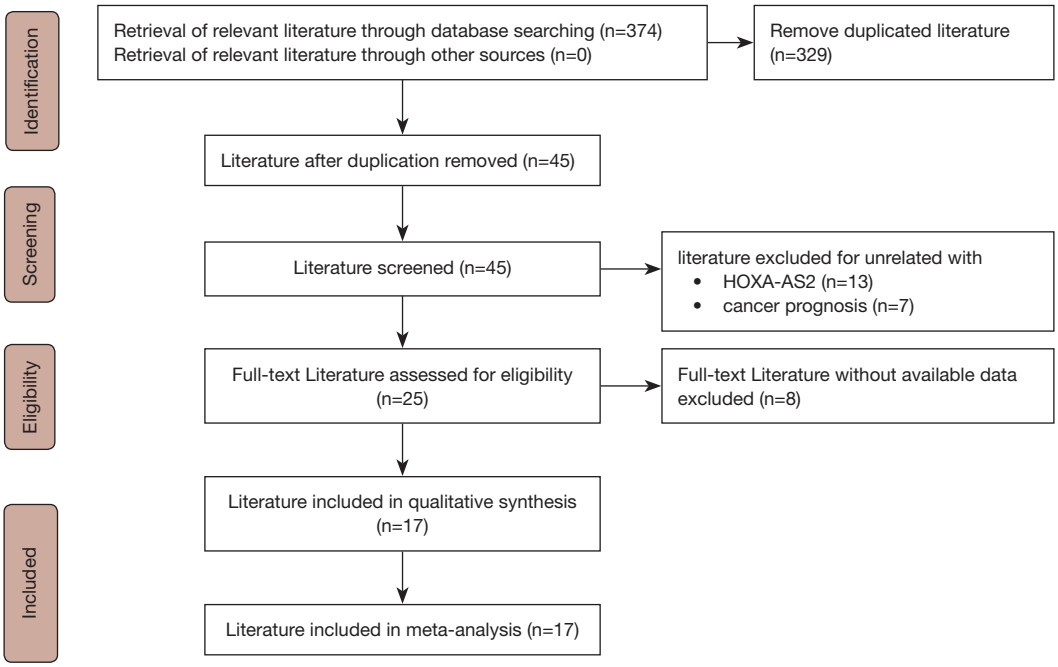

Figure 1 Flow diagram of the process used to identify articles in this meta-analysis. HOXA-AS2, HOXA cluster antisense RNA 2.

assessed the association between HOXA-AS2 expression levels and OS. As non-significant heterogeneity was found among the studies (I^2=0.0%, P=0.958), the fixed-effects model was used. The results showed that the OS of patients in the HOXA-AS2 high-expression group was worse than that of patients in the HOXA-AS2 low-expression group (HR =2.13; 95% CI: 1.50–2.76; P≤0.001; *Figure 2*).

No heterogeneity was found among studies related to OS; however, we performed a subgroup analysis based on the cancer type, HR extraction method, follow-up month, and sample size to exclude potential biases. As *Figure 3* shows, subgroup analysis demonstrated that the high expression of HOXA-AS2 could estimate unfavorable OS in the digestive system (I^2=0.0%, P=0.852; HR =2.06, 95% CI: 1.18–2.93, P≤0.001; *Figure 3A*), nondigestive system (I^2=0.0%, P=0.797; HR =2.21, 95% CI: 1.30–3.13, P≤0.001; *Figure 3A*), direct HR extraction (I^2=26.4%, P=0.244; HR =2.91, 95% CI: 0.76–5.05, P≤0.001; *Figure 3B*), indirect HR extraction (I^2=0.0%, P=0.990; HR =2.06, 95% CI: 1.40–2.72, P≤0.001; *Figure 3B*), sample size >60 (I^2=0.0%, P=0.609; HR =2.27, 95% CI: 1.37–3.17, P≤0.001; *Figure 3C*), sample size ≤60 (I^2=0.0%, P=0.949; HR =2.00, 95% CI: 1.11–2.88; P≤0.001; *Figure 3C*), follow-up month >60 (I^2=0.0%, P=0.729; HR =2.17, 95% CI: 1.40–2.94, P≤0.001; *Figure 3D*), follow-up ≤60 months (I^2=0.0%, P=0.895; HR =2.05, 95% CI: 0.94–3.16, P≤0.001; *Figure 3D*). These results revealed no significant bias in the study related to OS.

Relationship between the expression of HOXA-AS2 and the clinicopathological features

ORs and 95% CIs were used to evaluate the relationship between HOXA-AS2 expression and patients' clinicopathological characteristics. As *Figure 4* shows, the results revealed that elevated HOXA-AS2 expression was significantly correlated with high tumor stage (HTS) (OR =4.86, 95% CI: 3.51–6.74, P≤0.001; I^2=0.0%, P=0.917; *Figure 4A*), large tumor size (LTS) (OR =2.33, 95% CI: 1.51–3.60; P≤0.001; I^2=53.6%, P=0.018; *Figure 4B*), lymph node metastasis (LNM) (OR =4.69, 95% CI: 3.27–6.72, P≤0.001; I^2=43.4%, P=0.078; *Figure 4C*), and distant metastasis (DM) (OR =3.90, 95% CI: 2.28–6.68, P≤0.001; I^2=0.0%, P=0.833; *Figure 4D*). However, high HOXA-AS2 expression was not related to a poor histological grade (PHG) (OR =1.59, 95% CI: 0.92–2.74, P=0.094; I^2=53.3%, P=0.058), age (OR =1.07, 95% CI: 0.84–1.37, P=0.564; I^2=0.0%, P=0.551), or gender (HR =0.92, 95% CI: 0.70–1.21, P=0.548; I^2=4.6%, P=0.401).

Table 1 Main features of the included studies

Study	Year	Country	Tumor type	Sample size (n)	HOXA-AS2 expression		Outcome information	HR methods	Follow-up, months	Laboratory method	NOS score	Reference
					High	Low						
Chen	2021	China	Oral squamous cell carcinoma	46	23	23	–	–	–	qRT-PCR	7	(18)
Lu	2020	China	Hepatocellular carcinoma	116	58	58	OS	Directly	≤60	qRT-PCR	7	(15)
Xiao	2020	China	Prostate cancer	68	–	–	OS	Indirectly	≤60	qRT-PCR	8	(21)
Cui	2019	China	Non-small cell lung cancer	40	20	20	OS	Indirectly	>60	qRT-PCR	6	(24)
Liu	2019	China	Non-small cell lung cancer	52	27	25	OS	Indirectly	≤60	qRT-PCR	7	(17)
Wang	2019	China	Bladder cancer	80	40	40	–	–	–	qRT-PCR	8	(16)
Wu	2019	China	Glioma	50	25	25	–	–	–	qRT-PCR	7	(26)
Wang	2019	China	Osteosarcoma	27	–	–	OS	Indirectly	≤60	qRT-PCR	6	(27)
Jiang	2019	China	Papillary thyroid cancer	68	30	38	OS	Indirectly	≤60	qRT-PCR	6	(19)
Wang	2018	China	Osteosarcoma	66	33	33	–	–	–	qRT-PCR	7	(28)
Xia	2018	China	Papillary thyroid cancer	128	66	62	–	–	–	qRT-PCR	7	(29)
Zhang	2018	China	Hepatocellular carcinoma	58	38	20	–	–	–	qRT-PCR	7	(22)
Ding	2017	China	Colorectal cancer	69	35	34	–	–	–	qRT-PCR	8	(9)
Li	2017	China	Non–small cell lung cancer	103	52	51	OS	Directly	>60	qRT-PCR	7	(25)
Fang	2017	China	Breast cancer	38	–	–	OS	Indirectly	>60	qRT-PCR	8	(30)
Wang	2016	China	Hepatocellular carcinoma	112	56	56	OS	Indirectly	>60	qRT-PCR	6	(23)
Xie	2015	China	Gastric cancer	55	28	27	OS	Indirectly	≤60	qRT-PCR	7	(14)

Indirectly: HR extracted from survival curve; directly: HR extracted from paper; –, not available. HR, hazard ratio; NOS, Newcastle-Ottawa scale; OS, overall survival; qRT-PCR, quantitative real time-polymerase chain reaction.

Sensitivity analysis and publication bias

In the study of OS, the sensitivity analysis showed that the overall results were not significantly affected when the results of any single study were deleted (*Figure 5A*). The Begg test results also revealed no publication bias among the studies examining OS (Z =0.36; probability > |z| =0.721; *Figure 5B*).

TCGA database analysis

In this study, the GEPIA web tool was used to analyze TCGA data to further validate the above results. The results showed that the expression of HOXA-AS2 was significantly correlated with the clinical stage of patients (F =8.53; probability (> F) ≤0.001; *Figure 6A*). Importantly, the survival analysis indicated that patients with high HOXA-AS2 expression had shorter OS and a poorer prognosis than those with low HOXA-AS2 expression (HR =1.4; P≤0.001; n=9,389; *Figure 6B*).

Immunoassay

HOXA-AS2 was found to be significantly correlated with

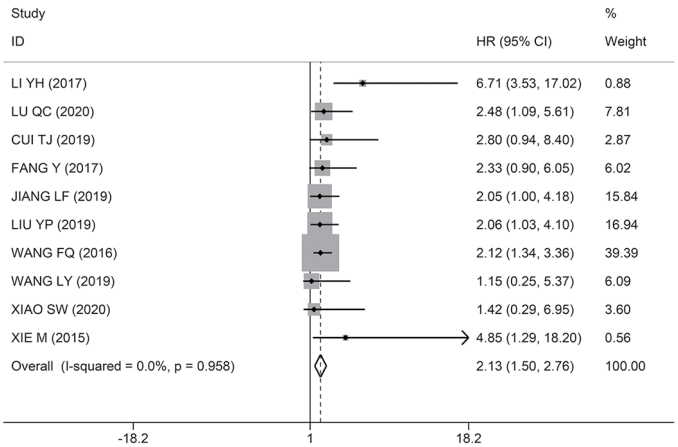

Figure 2 Forest plot for HR of HOXA-AS2 expression and OS. HR, hazard ratio; HOXA-AS2, HOXA cluster antisense RNA 2; OS, overall survival.

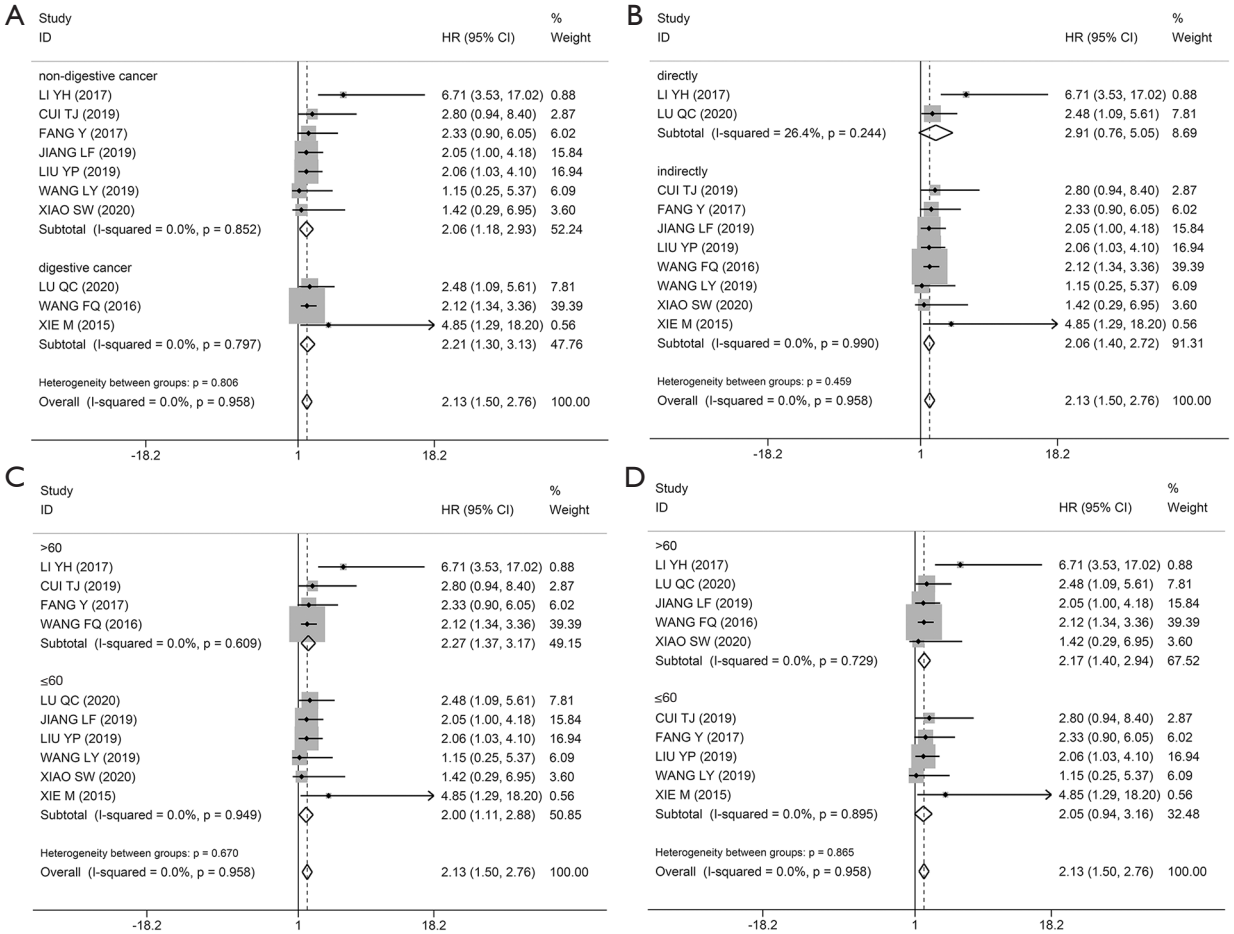

Figure 3 Forest plot of subgroup analysis for HOXA-AS2 expression and OS. (A) Subgroup analysis of cancer type. (B) Subgroup analysis of HR methods. (C) Subgroup analysis of sample size. (D) Subgroup analysis of follow-up month. HOXA-AS2, HOXA cluster antisense RNA 2; OS, overall survival; HR, hazard ratio.

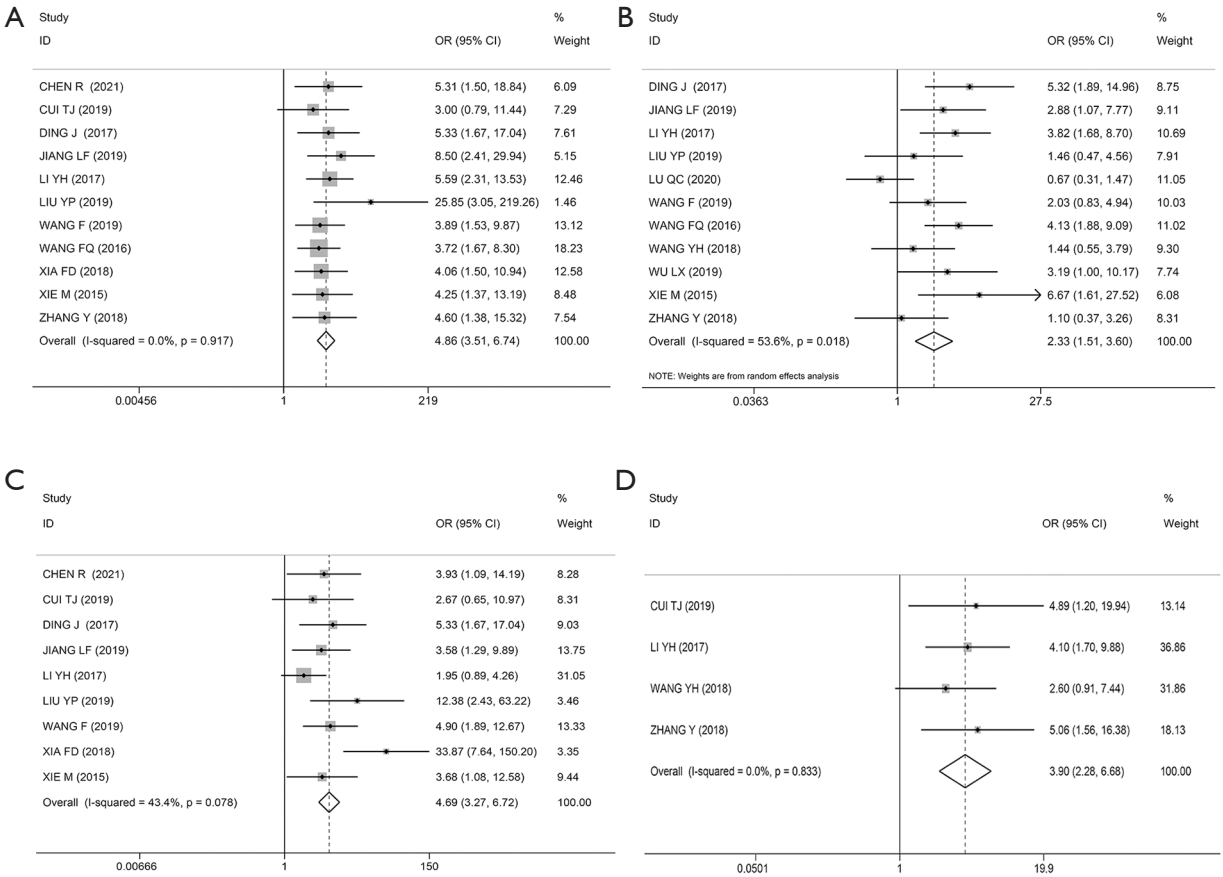

Figure 4 Forest plot of HOXA-AS2 expression and clinicopathological characteristics. (A) HOXA-AS2 expression and HTS. (B) HOXA-AS2 expression and LTS. (C) HOXA-AS2 expression and LNM. (D) HOXA-AS2 expression and DM. HOXA-AS2, HOXA cluster antisense RNA 2; HTS, high tumor stage; LTS, large tumor size; LNM, lymph node metastasis; DM, distant metastasis.

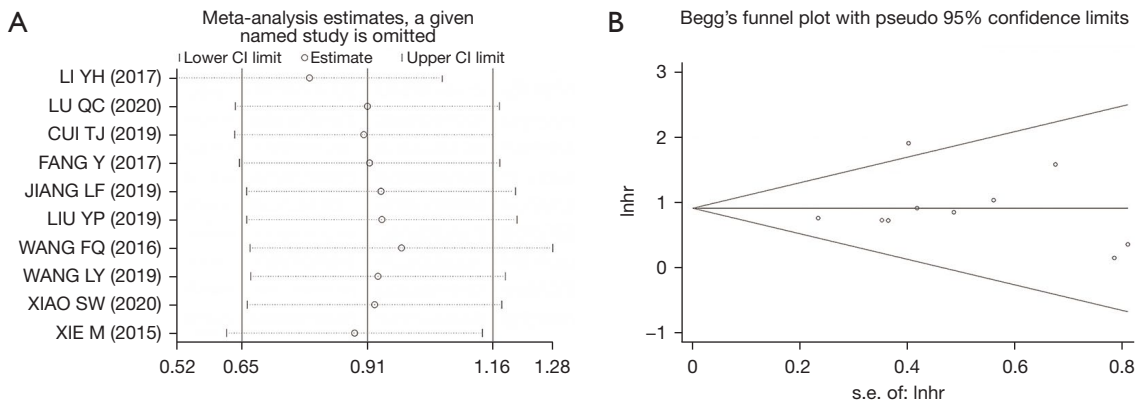

Figure 5 Sensitivity analysis and Begg test of included studies on OS. (A) Sensitivity analysis. (B) Begg test. OS, overall survival.

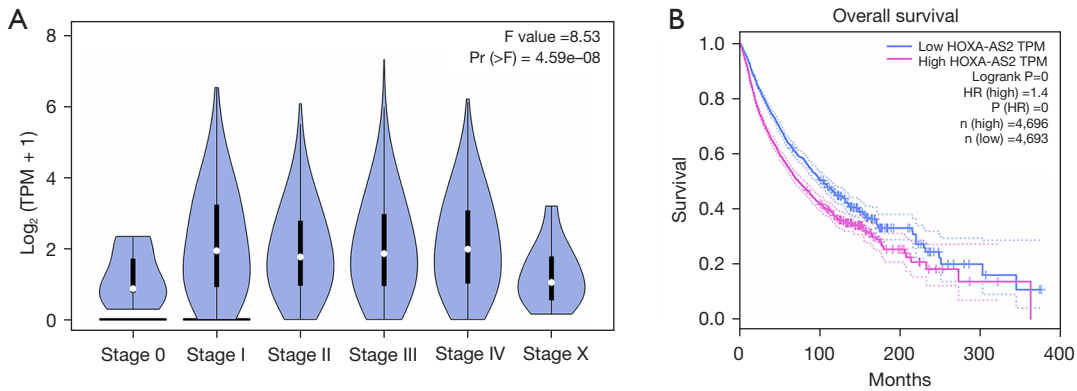

Figure 6 The expression and prognostic value of HOXA-AS2 in patients with various cancers were analyzed based on TCGA data. (A) Violin plot of HOXA-AS2 expression in different major clinical stages of pan-cancers. (B) Analysis of the correlation between HOXA-AS2 expression and OS in pan-cancer patients. HOXA-AS2, HOXA cluster antisense RNA 2; TPM, transcripts per million; TCGA, The Cancer Genome Atlas; OS, overall survival.

immune cell infiltration in a variety of cancers. For example, in bladder cancer, the expression of HOXA-AS2 was significantly and positively correlated with activated mast cells and memory-resting $CD4^+$ T cells, and significantly negatively correlated with memory-activated $CD4^+$ T cells and resting mast cells (*Figure 7A*). In uterine corpus endometrial carcinoma, the expression of HOXA-AS2 was significantly and positively correlated with activated natural killer cells and M1 macrophage infiltration, and significantly negatively correlated with regulatory T-cell and M0 macrophage infiltration. Additionally, the immune checkpoint analysis showed that in lung squamous cell carcinoma, the expression of HOXA-AS2 was significantly and positively correlated with *CD274*, *CTLA4*, *HAVCR2*, *LAG3*, *PDCD1*, *PDCD1LG2*, *SIGLEC15*, and *TIGIT* checkpoints, while in gastric cancer, the expression of HOXA-AS2 was significantly and negatively correlated with *CD274*, *HAVCR2*, *LAG3*, and *PDCD1* checkpoints (*Figure 7B*). The above results may provide new directions for studying the immunoregulatory mechanisms and immunotherapeutic targets involved in HOXA-AS2 in cancer.

Discussion

Cancers are not only a great threat to human health, but also place a serious burden on the global economy (31). Despite many significant advances, the prognosis of patients with cancer is still poor, which is mainly due to the lack of effective diagnostic markers and therapeutic targets (32). Previous studies have confirmed that lncRNAs can affect the occurrence and progression of tumors by regulating the proliferation, migration, invasion, differentiation, and apoptosis of cancer cells, and lncRNAs can be considered promising prognostic markers of cancer (33,34).

There is mounting evidence that lncRNA HOXA-AS2 is upregulated in a variety of cancers and is closely related to the poor prognosis and clinicopathological characteristics of patients with cancer (16,23,28). Thus, this meta-analysis sought to further evaluate the potential of HOXA-AS2 as a prognostic marker for cancer patients. A total of 17 articles, comprising 1176 patients and 11 different types of cancer, were included in this meta-analysis. The results showed that the elevated expression of HOXA-AS2 was significantly associated with the poor OS of those with tumor, and the subgroup analysis and Begg test results further verified the reliability of these results. In addition, patients with high expressions of HOXA-AS2 were vulnerable to LNM, LTS, HTS, and DM. However, the high expression of HOXA-AS2 was not related to the age, gender, or the PHG of patients. Moreover, consistent with above results, the analysis of TCGA data showed that the elevated expression of HOXA-AS2 is associated with poor OS and clinical stage in those with tumor, which further validated the results of our meta-analysis.

Numerous researchers have shown that the competing endogenous RNA network plays an important role in the regulation of lncRNAs in cancer (28,29). Chen *et al.* found that increased HOXA-AS2 expression suppresses the proliferation OSCC cells by inhibiting miR-567 (18). Cui *et al.* showed that HOXA-AS2 targets miR-216a-5p

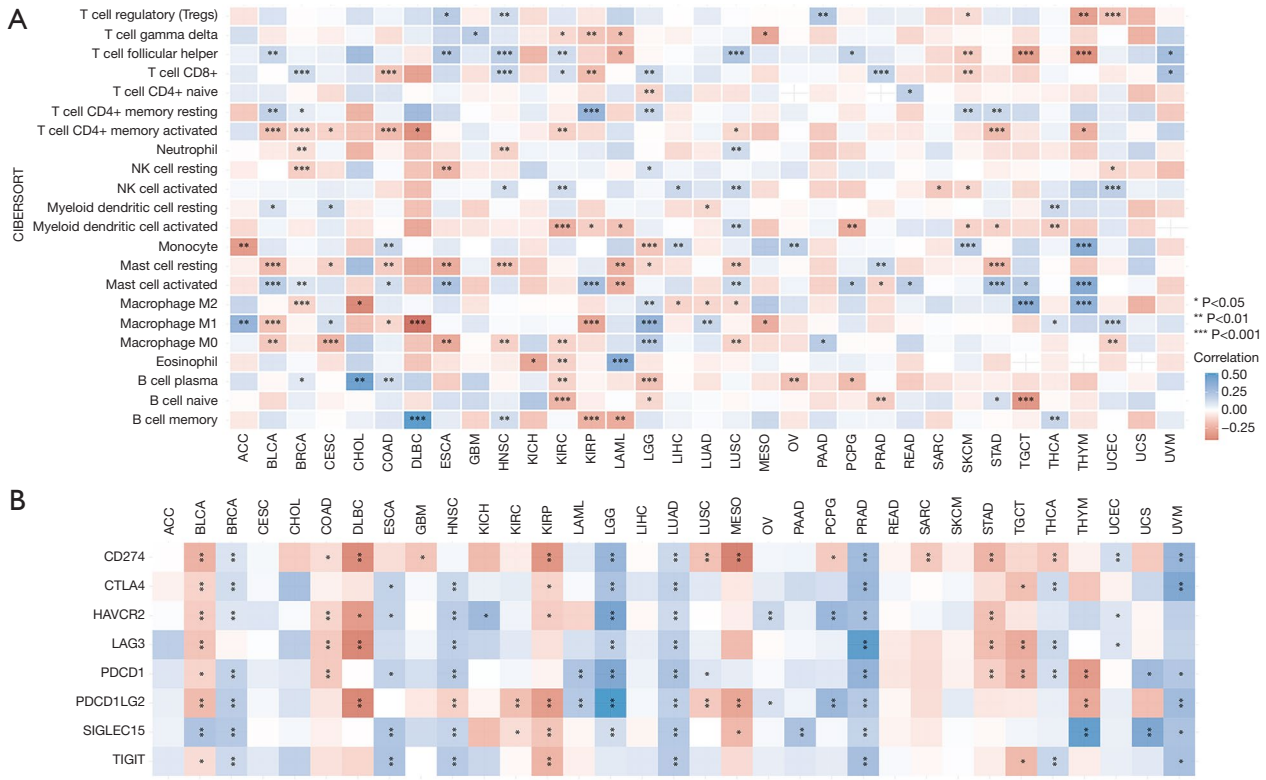

Figure 7 Immuno-correlation analysis of HOXA-AS2 in various cancers. (A) Analysis of immune cell infiltration. (B) Analysis of immune checkpoints. HOXA-AS2, HOXA cluster antisense RNA 2.

and thus affects the proliferation, progression, migration, and epithelial–mesenchymal transition process of NSCLC cells (24). Liu *et al.* also revealed that the high expression of HOXA-AS2 is related to the poor prognosis of patients with NSCLC through the regulation of proliferation, apoptosis, and migration of cancer cells via the repression of miR-520a-3p (17). In breast cancer, the inhibition of HOXA-AS2 expression was shown to promote cell-cycle arrest and apoptosis by competitively binding to miR-520c-3p, thereby inhibiting the proliferation, migration, and invasion of cancer cells (30).

Immunotherapy, such as chimeric antigen receptor T-cell immunotherapy, cell therapy, and immune checkpoint inhibitor programmed cell death protein 1 (PD-1), has shown great potential in the treatment of patients with cancer and has been proven to have good efficacy (35). Thus, this study performed an immune correlation analysis of HOXA-AS2 in cancers, and the results revealed a significant correlation between the expression of HOXA-AS2 and infiltration of immune cells and immune checkpoints in cancers. Thus, the above regulatory mechanisms found in this study may provide a new direction for studying the role of HOXA-AS2 in cancers.

Our study had some limitations. First, the included patients were all Chinese; thus, our findings may not apply to other races. Second, some HRs and 95% CIs were indirectly extracted from the survive curve, which might have affected the validity of our findings. Finally, the sample size of our study was relatively small, and further studies need to be conducted to comprehensively evaluate the prognostic role of HOXA-AS2 in patients with cancer.

Conclusions

The high expression of HOXA-AS2 is associated with poor prognosis and unfavorable clinicopathological features in patients with cancer, which suggests that HOXA-AS2 may serve as a promising prognostic marker for these patients. More high-quality, large-sample studies need to be conducted to further validate our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1998/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1998/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1998/coif). The authors have no conflicts of interest to declare except the funding.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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