LncRNA HOXA-AS2 is a Prognostic and Clinicopathological Predictor in Cancer Patients

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Abstract

**Background:** Many individual studies confirmed that the elevated expression of Long non-coding RNA HOXA-AS2 (HOXA-AS2) held prognostic value in various solid tumors. Thus, the aim of this meta-analysis is to assess its prognostic potential and functions in malignancies.

**Methods:** Multiple databases were carefully searched for articles published about HOXA-AS2 in the past 10 years. Hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated to demonstrate prognostic value of HOXA-AS2 using Stata 15.0 software.

**Results:** 9 studies including 830 patients were ultimately enrolled in this meta-analysis. Pooled results showed that abnormal expression of HOXA-AS2 had a significantly correlation with unfavorable OS (pooled HR=1.58, 95% CI: 1.23-2.02) and in cancer patients. Additionally, high expression of HOXA-AS2 was also related to other clinicopathological factors, including advanced TNM staging (OR: 4.43, 95%CI: 2.98-6.58), lymph node metastasis (OR: 4.58, 95%CI: 2.85-7.35) and larger tumor size (OR: 3.26, 95%CI: 2.11-5.05).

**Conclusion:** Elevated expression of HOXA-AS2 was associated with poor clinical outcomes in multiple cancer types. More comprehensive and extensive studies are required to verify and strengthen the clinical value of HOXA-AS2 in human cancers.

Background

Long non-coding RNAs (lncRNAs) represent one of the various types of non-protein-coding transcripts. By definition, they are transcripts of more than 200 nucleotides that are not translated into proteins[1], which are composed of intergenic transcripts, enhancer RNAs (eRNAs), and sense or antisense transcripts that overlap other gene[2]. LncRNA has the following classic regulatory mechanisms: 1) as signal molecules participating in the regulation of multiple signaling pathways; 2) as decoys that titrate transcription factors or other RNAs and block their combination with genes. (the so called “ceRNA”); 3) as guides to recruit chromatin-modifying enzymes to target genes; 4) as scaffolds to bring together multiple proteins to form ribonucleoprotein complexes[3]. Recent research boom on lncRNAs suggests that they serve pivotal roles in the development and progression of cancer diseases. Adam M. Schmitt and his colleagues[4] summarized the functions of lncRNAs in cancer phenotypes, including proliferation, invasion, migration, angiogenesis, immortality and motility promotion, etc. After years of research, lncRNAs have been regarded as promising therapeutic targets and biomarkers that have potential for clinical application.

Long non-coding RNA-HOXA-AS2 (HOXA cluster antisense RNA 2), consisting of 1048 bp, locates in the HOXA gene cluster between and antisense to the human HOXA3 and HOXA4 genes. Since it is first proved to serve as an apoptosis repressor in NB4 promyelocytic leukemia cells in 2013[5], HOXA-AS2 has been widely detected and researched in multiple kinds of malignant diseases as an oncogene which shows abnormally high expression and promotes malignancy in multiple solid and blood malignancies. The mechanism by which HOXA-AS2 inhibit apoptosis and promote proliferation has been the most extensively studied. Except for the NB4 leukemia research, this mechanism has also been explored in hepatocellular carcinoma (HCC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC) and other tumors located in digestive system. Furthermore, most of the researches related to HOXA-AS2 have focused on its ceRNA function, including miR-373, miR-520c-3p, etc. All of the related researches above have been reviewed by Wang J[6].

Since HOXA-AS2 has been widely researched at the mechanism level, we wondered whether it had the potential to indicate the clinical prognosis or severity of cancer diseases in a clinical level. Thus, we performed this meta-analysis to clarify the predictive value of IncRNA HOXA-AS2 in various cancer patients.

Material And Methods

Search Strategy

The literature retrieval was performed by two reviewers (Gao W and Zhu H) independently. The following online databases were screened: PubMed, PMC, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database. The latest search was up to Sep. 4th, 2019. The following keywords were used for literature searching: "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 observed for additional eligible studies.

Inclusion and Exclusion Criteria

Eligible articles were identified based on the following inclusion criteria: 1) The expression of IncRNA HOXA-AS2 was detected in any human solid malignant tumors; 2) Correlation between IncRNA HOXA-AS2 and patients’ prognosis and/or other clinical pathological factors was reported; 3) The hazard ratio (HR) with 95% CI was reported or sufficient data was provided to calculate HR. 4) Patients were classified as high or low group according to IncRNA HOXA-AS2 expression level. Articles were excluded when they did not cover all of the points above.

Data Extraction and Quality Assessment
Two investigators (Gao W and Zhu H) independently extracted data from eligible studies according to the format we have previously developed. The extracted data included the following items: 1) 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; 2) Hazard ratio (HR) with 95% CI for overall prognosis of patients; 3) Patient number of high and low expression, lymph node metastasis (LNM), tumor size and tumor-node-metastasis (TNM) stage.

If a study reported the data in multivariate analysis and univariate analysis, the hazard ratio (HR) with the corresponding 95% CI was directly extracted from multivariate analysis. The survival curve of those researches that did not reported HRs and 95% CIs directly were analysed using Engauge Digitizer version 4.1 (https://sourceforge.net/projects/digitizer/) and then HR and 95% CI was estimated following the published method of Jayne F Tierney's article[1].

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

**Statistical Analysis**

Stata version 15.0 (Stata Corporation, College Station, TX, USA) was used for all statistical analyses in this meta-analysis. Higgins I2 statistics and Cochran's Q-test were applied to assess the heterogeneity among studies. The random-effects model was used when the percentage of I2 was greater than 50% or Phet less than 0.05. Otherwise, the fixed-effects model was used. Begg's and Egger’s test were utilized to detect the publication bias. Sensitivity analysis was performed by omitting the study one by one to assess the effects on the pooled results. A p-value < 0.05 was considered statistically significant.

**Results**

**Study Selection and Characteristics**

Following our research protocol, we initially found 48 original articles from all of the online databases. Then 28 researches were abandoned after reading titles and abstracts for following reasons: reviews, conference papers lacking data, no association reported between IncRNA HOXA-AS2 and patients’ outcome, or incomplete data reported. Finally, 9 available studies were considered applicable to this meta-analysis[8–16]. The detailed steps for screening eligible articles are presented in Fig. 1.

These selected studies were published from 2015 to 2019. They were all identified as high-quality. A total of 830 cancer patients were enrolled in the pooled analysis, with a mean subject size of 60.4, ranging from 30 to 112. All studies measured the expression of IncRNA HOXA-AS2 in tissue specimens by quantitative real-time polymerase chain reaction (qRT-PCR). 7 of 9 reported the relationship between IncRNA HOXA-AS2 expression and overall prognosis of cancer patients. None of the studies focus on RFS, DFS or PFS. 8 studies estimated the relationship between IncRNA HOXA-AS2 and TNM stage, 6 focused on LNM, while 5 focused on tumor size. The cancers investigated consisted of breast cancer (BRC), colorectal cancer (CRC), papillary thyroid cancer (PTC), non-small cell lung cancer (NSCLC), gastric cancer (GC), hepatocellular carcinoma (HCC), bladder cancer (BLC). All included studies were retrospective and conducted in China. Table 1 and Table 2 summarize the main information and data of all included studies.
### Table 1
Main characteristics of all studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Country, Region</th>
<th>Cancer Type</th>
<th>Study design</th>
<th>Sample size</th>
<th>HE (%)</th>
<th>TNM Stage</th>
<th>Cutoff Value</th>
<th>Follow-up years</th>
<th>Inc-HOXA-AS2 assay</th>
<th>Detected sample</th>
<th>Mentioned OS or not</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu F, 2017</td>
<td>China, Harbin</td>
<td>BRC</td>
<td>R</td>
<td>38</td>
<td>50.00%</td>
<td>I-IV</td>
<td>median</td>
<td>&gt;60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Li Q, 2016</td>
<td>China, Zibo</td>
<td>CRC</td>
<td>R</td>
<td>30</td>
<td>50.00%</td>
<td>II-III</td>
<td>median</td>
<td>&gt;60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Jiang L, 2018</td>
<td>China, Hangzhou</td>
<td>PTC</td>
<td>R</td>
<td>68</td>
<td>44.12%</td>
<td>I-IV</td>
<td>mean</td>
<td>&lt;=60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cui T, 2019</td>
<td>China, Fuzhou</td>
<td>NSCLC</td>
<td>R</td>
<td>40</td>
<td>50.00%</td>
<td>I-IV</td>
<td>median</td>
<td>&gt;60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Liu Y, 2019</td>
<td>China, Changchun</td>
<td>NSCLC</td>
<td>R</td>
<td>52</td>
<td>51.92%</td>
<td>I-IV</td>
<td>median</td>
<td>&lt;=60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Xie M, 2015</td>
<td>China, Nanjing</td>
<td>GC</td>
<td>R</td>
<td>55</td>
<td>50.91%</td>
<td>I-III</td>
<td>median</td>
<td>&lt;=60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Wang F(1), 2016</td>
<td>China, Xiamen</td>
<td>HCC</td>
<td>R</td>
<td>112</td>
<td>50.00%</td>
<td>I-IV</td>
<td>median</td>
<td>&gt;60 months</td>
<td>qRT-PCR tissue</td>
<td>yes</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Wang F(2), 2018</td>
<td>China, Haikou</td>
<td>BLC</td>
<td>R</td>
<td>80</td>
<td>50.00%</td>
<td>I-IV</td>
<td>median</td>
<td>NM</td>
<td>qRT-PCR tissue</td>
<td>no</td>
<td>7</td>
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</tr>
<tr>
<td>Ding J, 2016</td>
<td>China, Nanjing</td>
<td>CRC</td>
<td>R</td>
<td>69</td>
<td>50.72%</td>
<td>I-IV</td>
<td>median</td>
<td>NM</td>
<td>qRT-PCR tissue</td>
<td>no</td>
<td>7</td>
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</table>

### Table 2
HRs and 95% CIs of cancer prognosis and progression associated with HOXA-AS2 expression in all included studies (Notes: All the HR and 95% CI in Table 2 were calculated from K-M survival curves provided in the original literature.)

<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Country, Region</th>
<th>Cancer Type</th>
<th>Case number of HOXA-AS2 expression</th>
<th>HR(95%CI) for OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Yu F, 2017</td>
<td>China, Harbin</td>
<td>BC</td>
<td>19</td>
<td>19</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li Q, 2016</td>
<td>China, Zibo</td>
<td>CRC</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jiang L, 2018</td>
<td>China, Hangzhou</td>
<td>PTC</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cui T, 2019</td>
<td>China, Fuzhou</td>
<td>NSCLC</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu Y, 2019</td>
<td>China, Changchun</td>
<td>NSCLC</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Xie M, 2015</td>
<td>China, Nanjing</td>
<td>GC</td>
<td>28</td>
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<tr>
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<tr>
<td>Wang F(1), 2016</td>
<td>China, Xiamen</td>
<td>HCC</td>
<td>56</td>
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<td></td>
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</tr>
<tr>
<td>Wang F(2), 2018</td>
<td>China, Haikou</td>
<td>BLC</td>
<td>40</td>
<td>40</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ding J, 2016</td>
<td>China, Nanjing</td>
<td>CRC</td>
<td>35</td>
<td>34</td>
</tr>
</tbody>
</table>

# Results of the Meta-Analysis
Lnc-HOXA-AS2 Expression and Patients’ Overall Survival

7 clinical studies that comprised a total of 395 cancer patients were conducted to the pooled analysis of OS. A random effects model was applied for a significant heterogeneity (I-squared = 70.1%, p = 0.003). We concluded that high expression of IncRNA HOXA-AS2 was related to a poorer OS in cancer patients (HR = 1.58, 95% CI: 1.23–2.02; Fig. 2). This result basically indicated that the high expression of Inc-HOXA-AS2 in cancers is associated with poor OS in patients. However, the heterogeneity issue could still not be ignored and needed further explanation.

Exploring the Source of Heterogeneity

As we mentioned above, a significant heterogeneity (I-squared = 70.1%, p = 0.003) still needed to be specified to illustrate the credibility of the pooled OS result. Thus, we first conducted multiple subgroup analysis for common suspicious factors. In the stratified analysis, we found that elevated Inc-HOXA-AS2 expression could be a prognostic biomarker for patients with cancers in digestive system (HR: 1.44, 95% CI: 1.00–2.06, p < 0.001, Fig. 3A) or patients with non-digestive system cancers (HR: 1.70, 95% CI: 1.33–2.16, p < 0.001, Fig. 3A). However, it was still unable to explain the heterogeneity problem (non-digestive system cancer subgroup: I-squared = 0.0%, p = 0.624; digestive system cancer subgroup: I-squared = 70.1%, p = 0.003, Fig. 3A). Same results were found in the subgroup of follow-up time (< 60 months or ≥ 60 months, Fig. 3B), sample size (> 50 patients or ≤ 50 patients, Fig. 3C) and research location (in southern or northern China divided by Qinling-Huaihe boundary line, Fig. 3D). These common factors were still difficult to explain the causes of heterogeneity in our research.

We then noticed that the HR for OS in several studies seemed pretty weird, for instance, the HR value = 1.12 (95%CI: 1.05–1.22) in the first research from Xie M seemed too small, yet this research occupied a pretty high weight (26.12%) in the pooled HR result. Conversely, the HR value 4.24 (95%CI: 1.41–12.74) from the research of Li Q was too large. This phenomenon indicated that it was necessary to perform sensitivity analysis to detect the stability of our pooled result. Figure 4 showed the result of sensitivity analysis for OS. It was not hard to find that a big change took place after Xie M’s research was excluded. If we abandoned this result the pooled HR would be 1.643 (95%CI: 1.384–1.951). This result showed that Xie M’s result might be one of the most important heterogeneous sources in our research, the HR value and 95% CI mentioned in the previous result was likely to be conservative. However, the conclusion is still very constant that the elevated expression of Inc-HOXA-AS2 is associated with the poor prognosis for cancer patients.

Inc-HOXA-AS2 Expression and Clinicopathological Characteristics

8 studies comprising of 506 cancer patients reported the correlation between Inc-HOXA-AS2 and TNM stage in multiple tumors. The result showed a solid correlation between high expression of Inc-HOXA-AS2 and advanced TNM stage (OR: 4.43, 95%CI: 2.98–6.58, p < 0.001, Fig. 5A). A fixed effects model was used because of a small heterogeneity (I-squared = 0.0%, p = 0.447). Furthermore, the pooled result of another 6 studies showed a relationship between HOXA-AS2 and lymph node metastasis (LNM) (OR: 4.58, 95%CI: 2.85–7.35, p < 0.001; Heterogeneity: I-squared = 0.0%, p = 0.788, Fig. 5B). Higher expression of Inc-HOXA-AS2 was also related to the larger tumor size of patients in multiple cancers (OR: 3.26, 95%CI: 2.11–5.05, p < 0.001; Heterogeneity: I-squared = 22.9%, p = 0.269, Fig. 5C).

Publication Bias

Funnel plots and Begg’s and Egger’s test were used to evaluate the publication bias in this meta-analysis. We noticed an obvious asymmetry in Fig. 6A for OS, the egger’s test also confirmed our concern (p < 0.001). Although publication bias may exist, we have proved in the previous result that our result for OS was credible by subgroup and sensitivity analysis. In Figs. 6B -6D, the Begg’s funnel plots with pseudo 95% CIs were symmetric which indicated no significant publication bias for other results of TNM (B), LNM (C) and tumor size (D) in this meta-analysis.

Sensitivity Analysis for Clinicopathological Characteristics

As illustrated in Figs. 7A-7C, the analyzed results suggested that our results for TNM, LNM and tumor size were comparatively stable.

Discussion

Since Zhao H published their results that lnc-HOXA-AS2 repressed apoptosis in trans retinoic acid-treated NB4 promyelocytic leukemia cells in 2013[5], It has been proved that LncRNA HOXA-AS2 has an elevated expression in multiple solid tumors, which shows diverse function promoting malignant behavior and clinical manifestations. Except for the researches mentioned in the "Results" part, there are still other literatures discussing the oncogenic role of HOXA-AS2 in other tumors. For example, Lian Y[17] found that IncRNA HOXA-AS2 was over-expressed in pancreatic cancer (PC); moreover, the interaction between HOXA-AS2 and enhancer of zeste homolog 2 (EZH2) and lysine specific demethylase 1 (LSD1) could promote PC cell proliferation in vitro. Similar results were also discovered in malignant glioma[18], osteosarcoma[19], gallbladder cancer (GBC)[20], etc. These researches were not included in this meta-analysis for a lack of necessary clinical data.

In terms of molecular mechanism, the available researches have proved the following regulating functions of HOXA-AS2: 1) ceRNA regulatory mechanism: This is the most common and full-researched function for HOXA-AS2 acting a competitive endogeneous RNA (ceRNA). Dozens of
papers have proved this point, for instance, Dong X[21] found that HOXA-AS2 sponged miR-520c-3p at 3′UTR and then inhibit the expression of S100A4 at downstream in acute myeloid leukemia (AML). Similarly, wang F[15] found a HOXA-AS2-miR125b-Smad2 axis in bladder cancer, leading to the advanced migration, invasion and stemness of cancer cells. 2) Epithelial-mesenchymal transition (EMT) promoting function: Zhang[20] demonstrated that HOXA-AS2 highly expression in GBC could increase the expression levels of Vimentin (a mesenchymal marker), whereas the expression of E-cadherin (an epithelial marker) was decreased, which resulted in the stronger migration ability of cancer cells. 3) Protein binding function: Xie M[16] indicated that in GC, the competitive binding of HOXA-AS2 and EZH2 caused the dissociation between EZH2 and the promoter of P21, PLK3 and DDIT3 genes, inhibiting the H3K27 trimethylation and finally leading to the repression of these tumor suppressing genes. 4) Activator of adjacent genes: Zhao Q[22] recently found HOXA-AS2 could directly elevate the expression level of HOXA3 mRNA and protein but not that of HOXA4 in acute lymphoblastic leukemia (ALL) cells.

In this meta-analysis, we combined all the relative researches for HOXA-AS2 at the clinical level. We suggested that high expression of HOXA-AS2 is related to the poor prognosis of cancer patients, the pooled HR of which was 1.58 (95%CI: 1.23–2.02). Admittedly, there was a significant heterogeneity and publication bias in this result, but we successfully found the suspicious resource of heterogeneity by means of subgroup analysis and sensitivity analysis and confirmed the reliability of our conclusion. Moreover, we proved that the overexpressed HOXA-AS2 is also a predictor for worse clinicopathological factors, including advanced TNM staging (HR = 4.43, 95%CI: 2.98–6.58), higher risk of lymph node metastasis (HR = 4.58, 95%CI: 2.85–7.35) and larger size for tumor (HR = 3.26, 95%CI: 2.11–5.05). These results are reliable verified by publication bias and sensitivity analysis.

To our knowledge, this is the first meta-analysis discussing the prognostic value of lnc-HOXA-AS2 for patients. Although we conducted this research with standard procedure and rigorous statistics, limits were still existed that need further clarified. First of all, the sample size for the total and each single study was relatively small and the enrolled cancer types were still not enough to represent all of the common cancer diseases. Secondly, the HR value for every study was extracted from the K-M survival curves published in the original articles followed Jayne's statistic method[7], none of the researchers provided their raw data for patients’ OS, this might cause the inaccuracy and heterogeneity in our research. Thirdly, the quantity of included studies was not sufficient for a more comprehensive analysis for other clinic-pathological features like distal metastasis, micro-vascular invasion and tumor differentiation and so on. Fourthly, all included studies were from China, although we performed subgroup analysis based on the geographical region of China, we still admitted that these results might not enough to extend to the world. Finally, the cut-off value for the expression of HOXA-AS2 was relative and not uniform; Thus, it still needed more research before clinical application of our results.

**Conclusion**

To put in a nutshell, these results show the clinical value of lncRNA HOXA-AS2 to be a prognostic marker and a clinicopathological predictor in cancer patients. Larger studies with higher quality are still required for a more extensive and in-depth exploration of its clinical value.

**Abbreviations**

BRC: breast cancer; NPC, CRC: colorectal cancer; PTC: papillary thyroid cancer; NSCLC: non-small cell lung cancer; GC: gastric cancer; HCC: hepatocellular cancer; BLC: bladder cancer; R: retrospective; HE: high expression; Cutoff value means the criterion of HE that is based on whether the mean or median expression level of lnc-HOXA-AS2; OS: over survival; qRT-PCR: quantitative real-time polymerase chain reaction; NM: not mentioned; LNM: lymph nodes metastasis.

**Declarations**

**Ethics approval and consent to participate**

Not Applicable.

**Consent for publication**

Not Applicable.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no conflict of interests.
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Authors' contributions

All authors contributed to the study conception and design. Designed the study were performed by Gao Wenzhe and Xiao Tijun. Data collection from database were performed by Gao Wenzhe and Zhu Hongwei. Data analysis were performed by Gao Wenzhe, Xiao Tijun, Tan Lifang, and Yan An. The first draft of the manuscript was written by Xiao Tijun and Zhu Hongwei. All authors read and approved the final manuscript.

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References


Figures

Figure 1

Steps for screening eligible articles
Figure 2

Meta-analysis of the pooled HRs of OS for patients with abnormally high Inc-HOXA-AS2 expression
Figure 3

Subgroup analysis for OS. (A): stratified by cancer type (digestive system cancers or not); (B): by follow-up time (≥60 months or not); (C): by sample size (≥50 or not); (D): by research region (in southern or northern China)
Figure 4

Sensitivity analysis for OS. The abscissa shows the ln(HR) calculated after a certain research was excluded.
Figure 5

Forest plots of combined analyses associated with Inc-HOXA-AS2 expression. (A): TNM; (B): LNM; (C): Tumor size
Figure 6

Begg's funnel plots of publication bias test. (A) OS; (B) TNM; (C) LNM; (D) tumor size
Figure 7

Sensitivity analysis under specific model. (A): for TNM; (B): for LNM; (C): for tumor size.