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Prognostic value of LncRNA-HOTAIR for patients with hepatocellular carcinoma: a meta-analysis

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Abstract. – OBJECTIVE: This study aims at evaluating the prognostic value of LncRNA-HOTAIR for patients with hepatocellular carcinoma (HCC).

MATERIALS AND METHODS: A comprehensive databases and literature search was performed on PubMed, EMBASE, Web of Science, the Cochrane Library, CNKI, CBM, Wanfang, and VIP database up to the end of February 2022, for published studies on the connection of HCC and HOTAIR. STATA 12.0 software was used for the meta-analysis.

RESULTS: Eight studies with 412 patients were selected to be entered in the meta-analysis. We found that high expression of HOTAIR was associated with III+IV tumor stage (HR=2.31, 95% CI:1.32, 4.01), and it was not associated with age (HR=0.86, 95% CI:0.55, 1.34), gender (HR=0.91, 95% CI:0.55, 1.46), tumor number (HR=1.58, 95% CI:0.72, 3.48), tumor size (HR=1.54, 95% CI:0.96, 2.49), lymph node metastasis (HR=0.66, 95% CI:0.38, 1.15), AFP (HR=0.81, 95% CI:0.46, 1.42), cirrhosis (HR=1.34, 95% CI:0.75, 2.41), or portal invasion (HR=1.76, 95% CI:0.83, 3.72). A high expression level of HOTAIR was associated with a poorer OS (HR=3.12, 95% CI:1.31-7.43, *p*=0.010) and RFS (HR=1.67, 95% CI:1.23-2.26, *p*=0.010) for patients with HCC.

CONCLUSIONS: A high expression level of HOTAIR was associated with III+IV tumor stage. Our meta-analysis clearly supports the prognostic value of HOTAIR to predict unfavorable prognostic outcomes for patients with HCC.

Key Words:
Hepatocellular carcinoma, Long non-coding RNA, HOTAIR, Overall survival.

Introduction

Hepatocellular carcinoma (HCC), the second leading cause of cancer-related death in the world, accounts for 90% of primary liver tumor cases[1]. At present, surgery, chemotherapy, radiotherapy, and targeted therapy are the main treatment approaches for patients with HCC[2]. Although effective techniques for diagnosis and treatment of HCC are available, the prognosis of patients remains poor[3]. There are approximately 626,000 newly diagnosed cases of HCC each year[4]. Worse yet, 70-80% of patients are in advanced stages[5]. Therefore, early detection of liver cancer and more sensitive and specific biomarkers have become an urgent clinical need.

Recent evidence[6-8] suggests that cancer-associated long non-coding RNAs (LncRNAs) including HOTAIR, HOTTIP, GAS5, BANCR, and SNHG3 are associated with prognosis in hepatocellular carcinoma. Among them, HOX transcript antisense RNA (HOTAIR) is one of the well-studied lncRNAs. Numerous studies[9-12] suggested that HOTAIR expression may play a negative prognostic role in human cancers, including breast cancer, cervical cancer, colorectal cancer, and endometrial cancer. Nevertheless, the reliability and degree of the prognostic impact of HOTAIR in HCC have not yet been methodically analyzed. Therefore, we performed a meta-analysis to clarify the prognostic role of HOTAIR for patients with HCC.

Materials and Methods

Search Strategies

A comprehensive literature search was performed in PubMed, EMBASE, Web of Science, the Cochrane Library, CNKI, CBM, Wanfang, and VIP database up to the end of February 2022, for published studies on the connection of HCC and HOTAIR. Search terms used in online databases: hepatocellular carcinoma, HCC, liver tumor, liver cancer, long non-coding RNA, LncRNA, HOX transcript antisense RNA, and HOTAIR. The literature search was limited to Chinese and English.

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Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Patients with hepatocellular carcinoma diagnosed by cytology or pathology, regardless of TNM stage; (2) The relationship between the HOTAIR expression level and HCC clinicopathological characteristics or survival outcomes was assessed; (3) The study was limited to humans and the sample type must have been tissue; (4) Sufficient data were provided to estimate a hazard ratio (HR) with a 95% confidence interval (95% CI) for the relationship between HOTAIR and clinicopathological parameters.

The exclusion criteria were as follows: (1) Reviews, expert opinions, case reports, and editorials; (2) Insufficient primary data or animal model studies.

Data Extraction

Two reviewers extracted the data from included studies, including: (1) characteristics of included studies, such as publication year, authors, country, sample size, cut-off value, follow-up duration, and LncRNA detection methods; (2) Clinical outcomes: patients age, genders, TNM stage, tumor size, lymph node metastasis, and the level of AFP. (3) Survival data: overall survival (OS), relapse-free survival (RFS), and its HRs value and 95%CIs.

Quality Assessment of Included Studies

The Newcastle-Ottawa Scale (NOS)[13] was used to assess the quality of included studies by two independent reviewers. Any disagreements were discussed and resolved by another reviewer. The NOS score ranged from 0 to 9, and a NOS score >7 was regarded as high quality.

Statistical Analysis

STATA 12.0 software (StataCorp LLC, College Station, TX, USA) was used for the meta-analysis. Statistical heterogeneity between studies was assessed by the Chi-based Q-test and the I^2 test. When I^2<50%, or Q-test p>0.1, there was no heterogeneity in the data analysis, and the fixed-effect model was adopted for the meta-analysis. Otherwise, the random-effect model was used for the meta-analysis. Sensitivity analysis was also conducted to assess the ability of the combined results and to determine the source of any heterogeneity. Publication bias was evaluated by using Begg's test.

Results

Characteristics of the Included Studies

A total of 342 studies were obtained from published databases by a systematic literature search. After removing the duplicates in Endnote X7, 174 studies remained for titles and abstracts screening. Finally, 8 studies[14-21] were included to conduct a meta-analysis (Figure 1).

In the 8 studies, there were 412 patients with HCC. Quantitative real-time PCR (qRT-PCR) was used to detect HOTAIR expression levels. The characteristics of included studies are shown in Table I.

Relationship Between the HOTAIR Expression Level and Clinical Characteristics

A meta-analysis was performed to evaluate the relationship between the HOTAIR expression level and clinical characteristics. A high expression of HOTAIR was associated with III+IV tumor stage (HR=2.31, 95% CI:1.32, 4.01), while it was not associated with age (HR=0.86, 95% CI:0.55, 1.34), gender (HR=0.91, 95% CI:0.55, 1.46), tumor number (HR=1.58, 95% CI:0.72, 3.48), tumor size (HR=1.54, 95% CI:0.96, 2.49), lymph

Table I. Characteristics of included studies.

Study	Country	Tumor number	Portal invasion	Sample size	Follow-up (months, Mean)	Detection methods	NOS score
Geng et al[15]	China	Single/Multiple	Yes	63	36	RT-PCR	7
Yang et al[14]	China	Single/Multiple	Yes	60	18.6	RT-PCR	7
Ishibashi et al[16]	Japanese	Single/Multiple	Yes	64	24	RT-PCR	8
Gao et al[17]	China	Single/Multiple	Yes	60	32	RT-PCR	8
Yang et al[18]	China	Single/Multiple	Yes	54	32	RT-PCR	7
Liu et al[19]	China	Single/Multiple	Yes	35	34	RT-PCR	8
Hu et al[20]	China	Single/Multiple	Yes	38	26	RT-PCR	8
El-Khazragy et al[21]	Egypt	Single/Multiple	Yes	38	28	RT-PCR	7

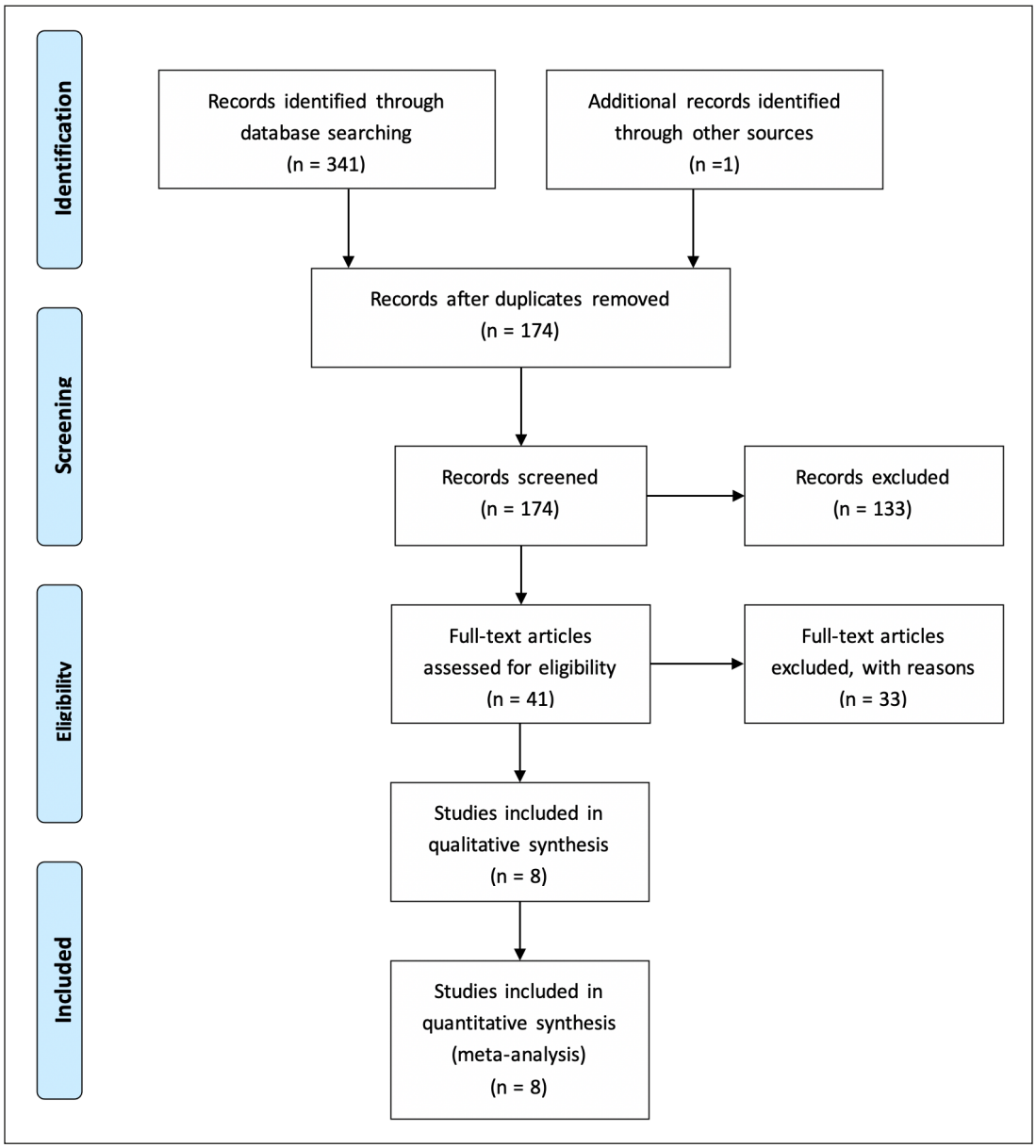

Figure 1. PRISMA flow chart of literature selection.

node metastasis (HR=0.66, 95% CI:0.38, 1.15), AFP (HR=0.81, 95% CI:0.46, 1.42), cirrhosis (HR=1.34, 95% CI:0.75, 2.41), or portal invasion (HR=1.76, 95% CI:0.83, 3.72) (Figure 2).

Meta-Analysis of the Expression of HORAIR and OS

Three included studies reported an association between the HOTAIR expression level and overall survival. Meta-analysis in a fixed-effect model (I^2=0.0%, p=0.440) showed that a higher expression level of HOTAIR was associated with poorer OS for patients with HCC (HR=3.12, 95% CI: 1.31-7.43, p=0.010) (Figure 3).

Meta-Analysis of the Expression of HORAIR and RFS

Four included studies reported an association between HOTAIR and RFS. Meta-analysis in a fixed-effect model (I^2=20.9%, p=0.285) showed that a higher expression level of HOTAIR was associated with poorer RFS for patients with HCC (HR=1.67, 95% CI: 1.23-2.26, p=0.010) (Figure 4).

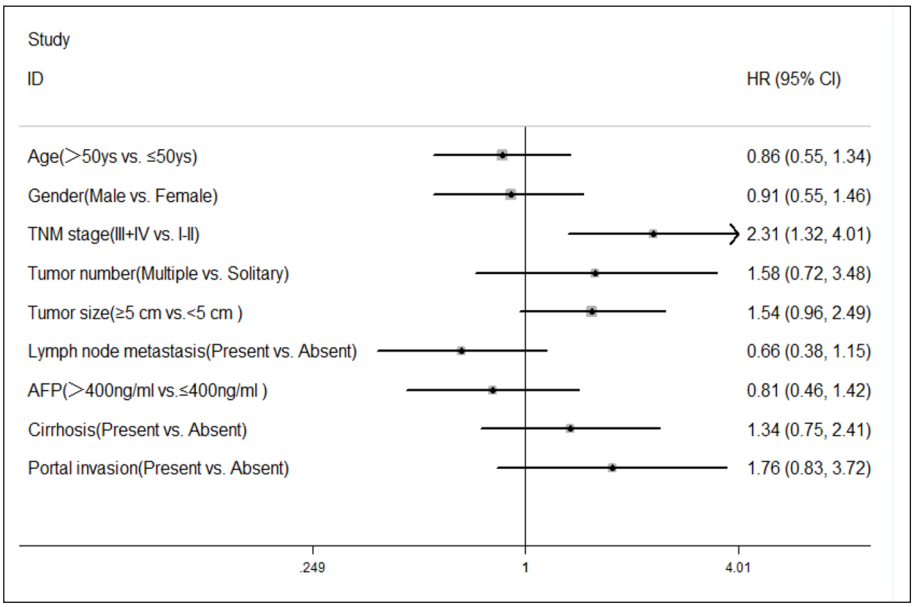

Figure 2. Meta-analysis of relationship between HOTAIR expression level and clinical characteristics.

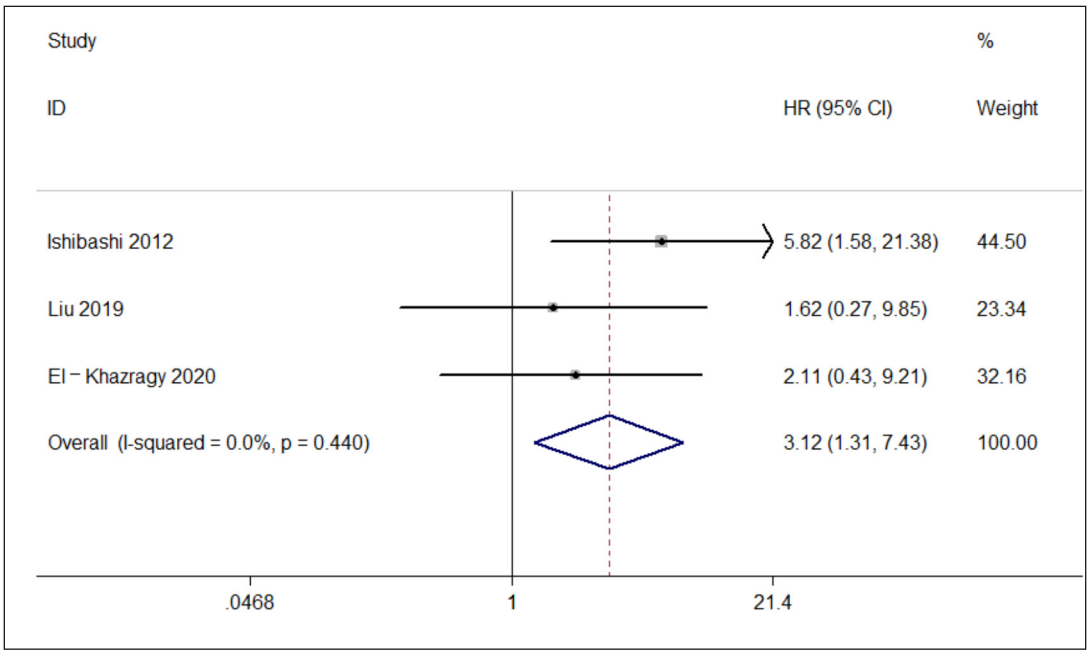

Figure 3. Meta-analysis of association between HOTAIR and OS for HCC patients (High-expression level *vs.* Low-expression level).

Discussion

Early detection of liver cancer can enable patients to receive early treatment and effectively prolong their survival time[22]. At present, the detection of serum AFP is the most commonly used method for the early screening of HCC, but this method cannot easily detect early micro-cancer lesions[23]. Therefore, it is very important to find tumor biomarkers with high sensitivity and specificity in order to diagnose HCC in the early stage and to improve the prognosis of HCC patients. HOTAIR is a lncRNA that plays an oncogenic role in a variety of tumors[24]. Recent

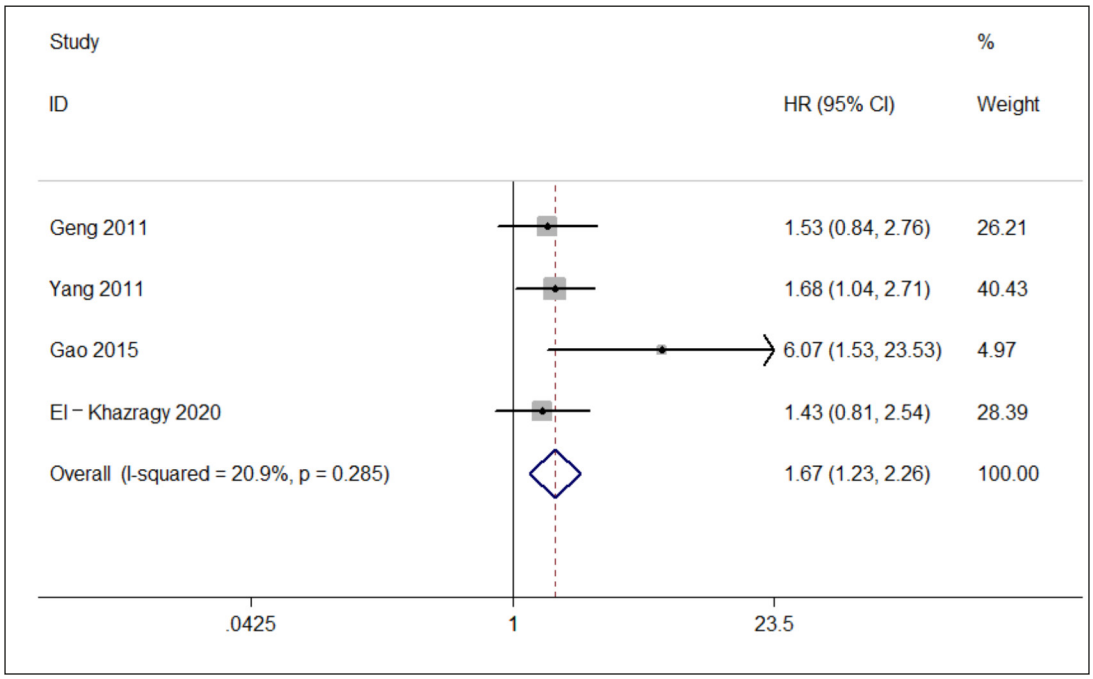

Figure 4. Meta-analysis of association between HOTAIR and RFS for HCC patients (High-expression level *vs.* Low-expression level).

studies[25,26] have showed that over-expression of HOTAIR has cancer-promoting activity and is associated with the inhibition of cancer characteristics such as apoptosis, cell differentiation, tumor growth, invasion, metastasis, and even radiotherapy sensitivity. HOTAIR may become a novel biomarker to evaluate the prognosis for patients with HCC.

In this meta-analysis, we found that a high expression of HOTAIR was associated with III+IV tumor stage (HR=2.31, 95% CI:1.32, 4.01), and it was not associated with age (HR=0.86, 95% CI:0.55, 1.34), gender (HR=0.91, 95% CI:0.55, 1.46), tumor number (HR=1.58, 95% CI:0.72, 3.48), tumor size (HR=1.54, 95% CI:0.96, 2.49), lymph node metastasis (HR=0.66, 95% CI:0.38, 1.15), AFP (HR=0.81, 95% CI:0.46, 1.42), cirrhosis (HR=1.34, 95% CI:0.75, 2.41), or portal invasion (HR=1.76, 95%CI:0.83, 3.72). A higher expression level of HOTAIR has been associated with poorer OS (HR=3.12, 95% CI: 1.31-7.43, p=0.010) and RFS (HR=1.67, 95% CI: 1.23-2.26, p=0.010) in patients with HCC. A previous meta-analysis[27] has also shown that a high HOTAIR expression was significantly correlated with poor OS (HR=2.37; 95% CI:1.80, 3.11; p=0.00001) and positive LNM (RR=1.96; 95% CI:1.07, 3.60; p=0.03) in patients with squamous cell carcinoma. Liu et al[28] suggested that a high expression of HOTAIR affected the occurrence and development of cervical cancer. Hao et al[29] found that a higher expression level of lncRNA PVT1 was associated with GC patients' poorer OS (HR = 1.68, 95% CI: 1.43-1.97, p=0.000), and DFS (HR = 1.74, 95% CI: 1.44-2.08, p=0.000), which also illustrated that lncRNA may be a novel biomarker to evaluate the prognoses in patients with cancer.

Limitations

This present meta-analysis has some limitations. First, the sample size was relatively small. Therefore, further larger studies are needed to confirm the findings of this meta-analysis. Second, most of the patients included in the meta-analysis were Chinese, and there were few studies[16,21] on other ethnicities, which may lead to publication bias. Third, since some studies[14,18] do not give raw values of HR and 95% CIs, they could only be calculated from data or extracted from Kaplan-Meier curves, which could lead to some inaccurate results. Fourth, there are differences in the definition of HOTAIR expression in different studies[15,16,20], and there is no consensus at present. Finally, as negative results are often not published, the role of HOTAIR in cancer may be exaggerated, which may lead to potential publication bias.

Conclusions

A high expression level of HOTAIR was associated with III+IV tumor stage. Our meta-analysis clearly supports the prognostic value of HOTAIR to predict unfavorable prognostic outcomes in patients with HCC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

Ethics approval is not required as this is a literature-based meta-analysis.

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Authors' Contribution

CLX and YHL designed the research and wrote the paper. CLX extracted and analyzed the data. Both authors approved the final version of the manuscript.

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