Prognostic and clinical significance of lncRNA NKILA in tumors: a meta-analysis

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Abstract

Background

lncRNA NKILA is a newly discovered long non-coding RNA, and some studies have shown that lncRNA NKILA has certain clinical prognostic value in malignant tumors. In this study, we used meta-analysis to integrate existing literature to further evaluate the clinic relevance between lncRNA NKILA expression level and cancers.

Materials and Methods

We conducted a meta-analysis based on literature reporting lncRNA NKILA expression in various cancers published before 25, May 2020 by PubMed, Embase, and Web of Science. The quality ratings of the included studies were assessed according to the Newcastle-Ottawa Scale. After rigorous screening, a total of 8 articles and 859 patients were included in our study. Hazard ratios (HRs) and odds ratios (ORs) were used to demonstrate the relationship between NKILA and prognosis by using Stata 15.0 software.

Results

The results show overexpression level of lncRNA NKILA is significantly associated with better overall survival (pooled HR = 0.45, 95%CI:0.35–0.59, P < 0.001, fixed-effects model). Furthermore, increased expression level of lncRNA NKILA was associated with negative lymph node metastasis (positive vs. negative,OR = 0.27, 95%CI:0.18–0.42, P < 0.001, fixed-effects model) and earlier clinical stage (TNM III/IV vs. I/II: OR = 0.34, 95%CI:0.25–0.46, p < 0.001, fixed-effects model).

Conclusions

Our study indicated lncRNA NKILA was a novel biomarker for prognosis in cancers. It could serve as a tumor-suppressive role.

Introduction

As the world's population ages rapidly, cancer has become the second leading cause of death after cardiovascular disease. According to GLOBOCAN 2018, there were 18.2 million new cases of cancer and 9.6 million deaths in 2018[1]. Despite increasing levels of cancer diagnosis and treatment in recent years, five-year survival rates for cancers remain low. The quality of life of cancer patients is also a major public health problem in the world[2]. In recent years, tumor biomarkers are becoming more and more important in medical practice[3]. Therefore, we urgently need to find a novel biomarker to evaluate the metastasis and prognosis of tumors.

Long non-coding RNA (lncRNA), which length is more than 200 nucleotides, cannot be transcribed and play important regulatory roles in the occurrence, development, and metastasis of tumors[4–6],such as MALAT1, H19, MEG3 and so on[7]. Recently, more and more lncRNA were used as biomarkers for tumor prognosis[8, 9].

NKILA is a Long non-coding RNA, which is encoded by a gene on chromosome 20q13. NKILA was first reported in human breast cancer[10]. In most cancer types, overexpression of NKILA could Suppresses progress of tumor [10, 11], such as tongue squamous cell carcinoma[12],esophageal squamous cell carcinoma[13, 14], laryngeal cancer[15], rectal cancer[16], hepatocellular carcinoma[17], colorectal cancer[18], Nasopharyngeal carcinoma[19], breast cancer[20]. However, the up-regulation of NKILA expression expedited the Warburg effect or angiogenesis in gliomas[21]. Furthermore, Numerous studies have demonstrated that NKILA expression associated with clinicopathological features and overall survival time in tumor patients. However, most of the studies have some limitations. For example, the sample size of patients is small. To further evaluate the relationship between NKILA and the clinical prognosis of tumors, a meta-analysis was performed.

Materials And Methods

Literature search strategy

In order to collect all needed articles of this research condition, we searched the different databases from the establishment to the 25, May 2020, including PubMed, Embase, Web of Science. Keywords and Mesh terms were used as follows: (‘Long non-coding RNA NKILA’ OR ‘lncRNA NKILA’) AND (‘neoplasm’ OR ‘tumor’ OR ‘cancer’ OR ‘carcinoma’).

Inclusion and exclusion criterion

Inclusion criteria were as below:1) patients were pathologically diagnosed with cancer; 2) articles published in English; 3) group according to the expression level of lncRNA NKILA; 4) The relationship of lncRNA NKILA expression level and the clinical characteristics or overall survival(OS) were reported; 5) Provide sufficient data to obtain the hazard ratio (HR) with the 95% confidence interval for OS, or the advantage ratio (ORs) with the 95% confidence interval for clinical parameters. Exclusion criteria were as below: 1) duplicate data; 2) reviews, letters, expert reviews, or case reports; 3) no clinical data was provided; 4) incorrect data. 5) NOS score<6.

Data extraction and quality assessment

According to the inclusion and exclusion criterion, the two authors extracted the necessary information from eligible studies independently. The disputes were settled by the third author. The extracted information as follows: first author, publication year, country, cancer types, number of high and low NKILA expression level groups, number of LNM patients, number of TNM stage(□/□) patients, hazard ratios

(HRs) and corresponding 95% CI for OS, follow-up times. The quality ratings of included studies were assessed by the Newcastle-Ottawa Scale (NOS)[22], High-quality studies demanded a NOS score≥6.

Statistical methods

Stata 15.0 software was used for statistical analysis. ORs or HRs with 95%CI were used to evaluate the prognostic and clinical value of high NKILA expression in various cancers. Some HRs with 95%CI for OS could not be obtained directly from the text, so we analyzed the Kaplan-Meier curve to obtain HRs with 95%CI for OS by using Engauge Digitiser 4.1 software and Tierney form[23]. The fixed-effects model was used to integrate data with statistical heterogeneity which was evaluated by the inconsistency index(I^2<50%) and the Q test (p>0.05)[24]. When there was significant heterogeneity (I^2>50% or p<0.05), the random-effects model was used. The Begg's test was applied to evaluate the publication bias and p values <0.05 means Significant publication bias. Also, the sensitivity analysis was used to assess the stability of the meta-analysis results.

Results

Literature search results

From the database, a total of 108 articles were included according to our retrieval strategy. First, we removed 62 duplicates. After reviewed the title and abstract, we excluded 20 articles, comprising 5 reviews, one comment, and 14 articles irrelevant to the prognosis of NKILA. In addition, we removed 17 articles because of no enough clinical data and no grouping high/low expression of NKILA. After reviewed the full-text, one provided incorrect data, so we excluded it. Ultimately, eight articles were included according to the inclusion and exclusion criteria, including 858 patients. The procession of the literature search was shown in Figure1.

Features of included studies

The general features of the enrolled studies were shown in Table 1. The publication year of the enrolled studies were from 2016 to 2020, and all came from China. The cancer types included tongue squamous cell carcinoma[12]、esophageal squamous cell carcinoma[13, 14], laryngeal cancer[15], rectal cancer[16], hepatocellular carcinoma[17], colorectal cancer[18], Nasopharyngeal carcinoma[19]. All studies detected the expression level of NKILA by qRT-PCR. Among them, five studies could be directly obtained HR and 95%CI of OS, two studies provided the Kaplan-Meier survival curve, and the remaining one article only provided clinical parameters.

Association between lncRNA NKILA expression and OS

In our study, 7 studies reported the relationship between NKILA expression level and OS. The results indicated that high NKILA expression predicted a longer overall survival time(pooled HR=0.51, 95%CI: 0.35-0.74, P<0.001, random-effects model) but there was significant heterogeneity(I^2=75.1%, p<0.001) 、Figure 2A、.Therefore, we adopted the random effect model. In order to explore the source of

heterogeneity, we conducted the subgroup analysis according to cancer type and sample size. The results of the subgroup analysis for OS were shown in Table2. Our results suggested that NKILA expression level was related to well OS in digestive system tumors (HR=0.59, 95%CI: 0.39-0.90, p<0.001, random-effects model) and others tumors (HR=0.39, 95%CI: 0.26-0.60, p=0.014, random-effects model) (Figure 2C). In the subgroup analysis of sample size, the NKILA expression level obviously associated with favorable OS in sample size≤90 group(HR=0.43, 95%CI: 0.26-0.71, p=0.001, random-effects model) and sample size range from 90 to 150 (HR=0.48, 95%CI: 0.34-0.67, p<0.001, random-effects model) (Figure 2D). Nevertheless, we found that combined HRs showed significant heterogeneity in the digestive system tumor group and the sample size >150 group. Importantly, the study of Jiang et al was in both groups. We hypothesized that heterogeneity might be due to a study published by Jiang et al[18]. Finally, Heterogeneity disappeared When we removed the study of Jiang et al and a stronger relationship between NKILA expression and OS (pooled HR=0.45, 95%CI:0.35-0.59, P<0.001, fixed-effects model) in the remaining 6 articles (Figure 2B).

Association between lncRNA NKILA expression and clinical parameters

A total of 7 studies with 768 cancer patients were used to analyze the association between lncRNA NKILA and TNM stage (III/IV vs. I/II) of cancer. The result showed that patients with high expression of lncRNA NKILA associated with an earlier clinical stage (III/IV vs. I/II, OR =0.34, 95%CI: 0.25-0.46, p< 0.001, fixed-effects model) and without significant heterogeneity (I^2=0.0%, p=0.658) (Figure 3A). Similarly, 4 studies with 373 cancer patients were included in LNM (positive vs. negative) analysis. The data analysis displayed that the overexpression of lncRNA NKILA was more likely to be associated with negative lymph node metastasis (OR=0.27, 95%CI:0.18-0.42, P<0.001, fixed-effects model) and no significant heterogeneity(I^2=0.0%, p=0.704) (Figure 3B).

Publication bias

Despite the small number of studies included(n<10), we examined the included studies by Begg's test. No significant publication bias was found in OS(p=0.368>0.05), TNM(p=0.072>0.05) and LNM(p=1.000>0.05) group. The funnel plot of Begg's test was shown in Figure 4.

Sensitivity analysis

Sensitivity analysis checked the stability of the results by removing one study at a time. We did not find that removing one study could affect the stability of the merged HR for OS (Figure 5A). In addition, our results also confirmed that the stability of the merged OR for the TNM stage (Figure 5B) and LNM (Figure 5C) would not be affected.

Discussion

LncRNA has been shown to be related to a variety of human diseases, especially tumors. LncRNA promotes or inhibits the occurrence and development of tumors by regulating gene transcription and

translation[25]. LncRNA NKILA has been found to be down-regulated in various tumors and there have been some discoveries about the complex mechanisms that regulate tumors. In breast cancer[26],LncRNA NKILA has been shown to control TGF-induced EMT by inhibiting NF-κB activation. Li et al. [27] indicated that AFPR suppresses the proliferation, migration, and invasion of breast cancer cells by regulating NKILA. In osteosarcoma, the expression level of NKILA in cancer tissues was significantly lower than that in normal tissues and has been linked to the spread of cancer. Further studies revealed that NKILA's anti-cancer effect may be related to NF-κB[28]. Liu et al. [29] found that LncRNA NKILA played an important role in inhibiting lung cancer metastasis via IL-11/STAT3 signaling. Lyu et al. [30]discovered Overexpression of lncRNA NKILA could reduce the proliferation and metastasis rate of retinoblastoma cells through degrading lncRNA XIST. These studies indicate that NKILA may play an important regulatory role in tumors.

In this study, our results have been confirmed that high NKILA expression has a longer overall survival in cancer patients. Furthermore, NKILA overexpression predicted better TNM stage and fewer lymph node metastasis. In OS group analysis, the results of pooled HR have obvious heterogeneity. After subgroup analysis, we thought Jiang et al. study may be a major source of heterogeneity. Firstly, the quantity of patients in the low expression group significantly more than the high expression group. Secondly, individual variation and regional diet may also be heterogeneous sources. When we excluded the study of Jiang et al., there was no significant heterogeneity. In short, our study showed that lncRNA NKILA could inhibit the occurrence and development of tumors and it may be a potential biomarker to predict the prognosis of tumors.

We are the first systematic review of the relationship between lncRNA NKILA expression level and prognosis value in tumors. Second, we followed prism's PRISMA statement as much as possible[31]. However, our study also has certain limitations. First, the number of studies included is small. Second, we did not explore the relationship between other clinical factors and NKILA expression, such as age and gender. Third, the HR and 95%CI of some included studies were extracted from the survival curve, this may lead to some deviation. Fourth, the cut-off value of lncRNA NKILA expression level is not consistent in different studies. We sincerely hope that more prospective, multicenter, high-quality studies will be performed in the future to assess the function of NKILA in tumor prognosis.

Conclusion

In conclusion, the high expression of lncRNA NKILA was related to well OS, earlier TNM stage, and negative lymph node metastasis in different cancers. It could serve as a tumor-suppressive role. Our meta-analysis suggested that lncRNA NKILA may be a novel potential biomarker for tumor prognosis.

Abbreviations

LncRNA
Long non-coding RNA

HRs
Hazard ratios
ORs
odds ratios
OS
overall survival
CI
confidence interval
I^2
inconsistency index
TNM
Tumor-Node-Metastasis
LNM
lymph node metastasis
TSCC
Tongue squamous cell carcinoma
ESCC
Esophageal squamous cell carcinoma
LC
Laryngeal cancer
RC
Rectal cancer
HCC
Hepatocellular carcinoma
CRC
Colorectal cancer
NPC
Nasopharyngeal carcinoma
NA
Not available
SC
Survival curve
RID
Reported in paper

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Our manuscript does not contain any individual person's data, so consent from any individual person is not applicable. Written informed consent for publication was obtained from all authors and participants.

Availability of data and materials

all data generated or used during the study appear in the submitted article.

Competing interests

The authors have no conflict of interests.

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Authors' contributions

(1)QhZ: Project design, general guidance, financial support; (2)XT&QsP: Complete the main work, including extract data and write; (3)XM, ML: Guidance and advice; (4)JxF,:Article revision; (5)YlJ: Language.

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Figures

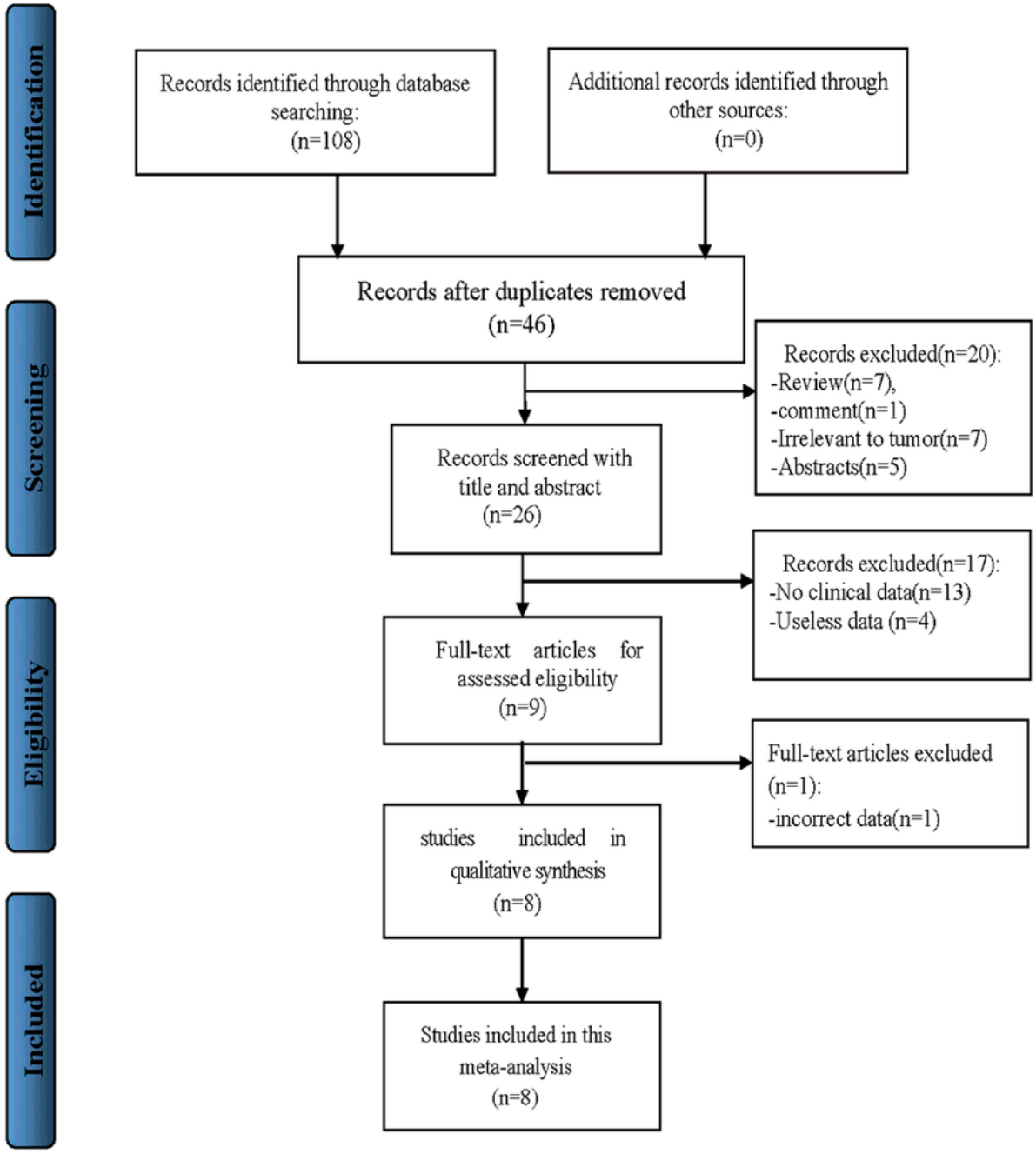

Figure 1

Flow chart of literature search

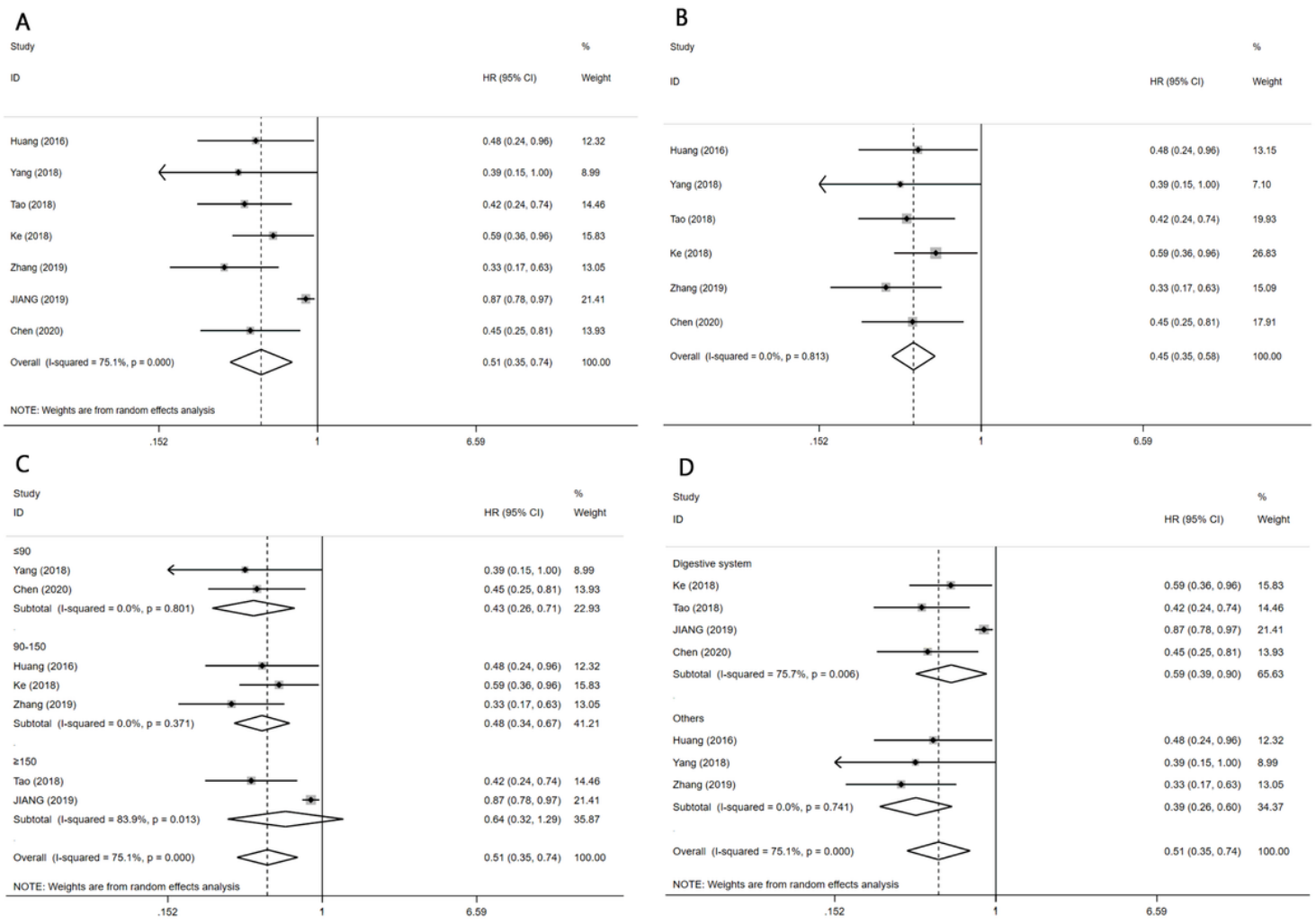

Figure 2

Forest plot of pooled HR with the association between NKILA expression and overall survival: A. OS; B. OS without Jiang's study; C. TNM; D. LNM

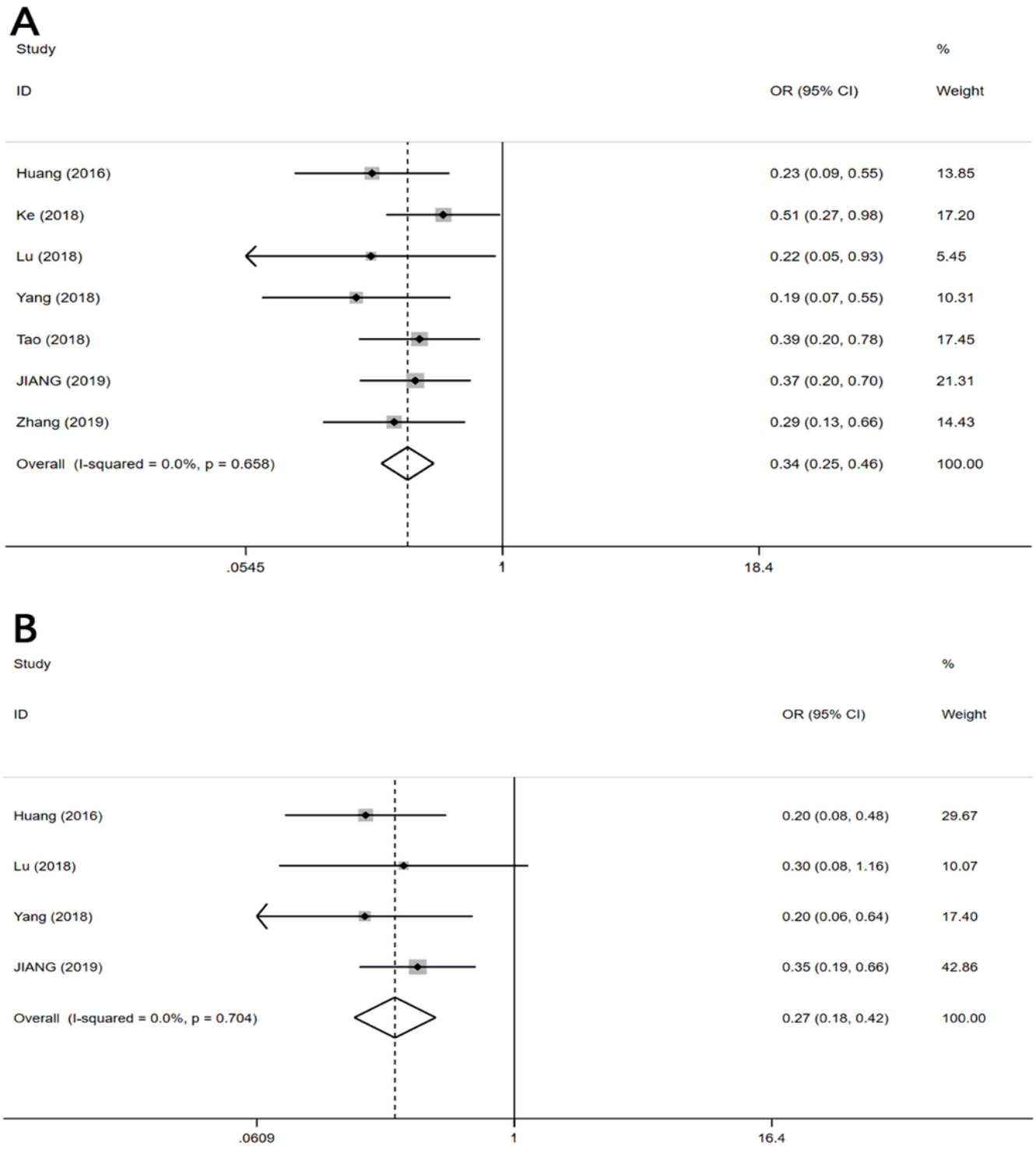

Figure 3

Forest plot of the OR with association between NKILA expression and clinical characteristics: A: TNM; B. LNM

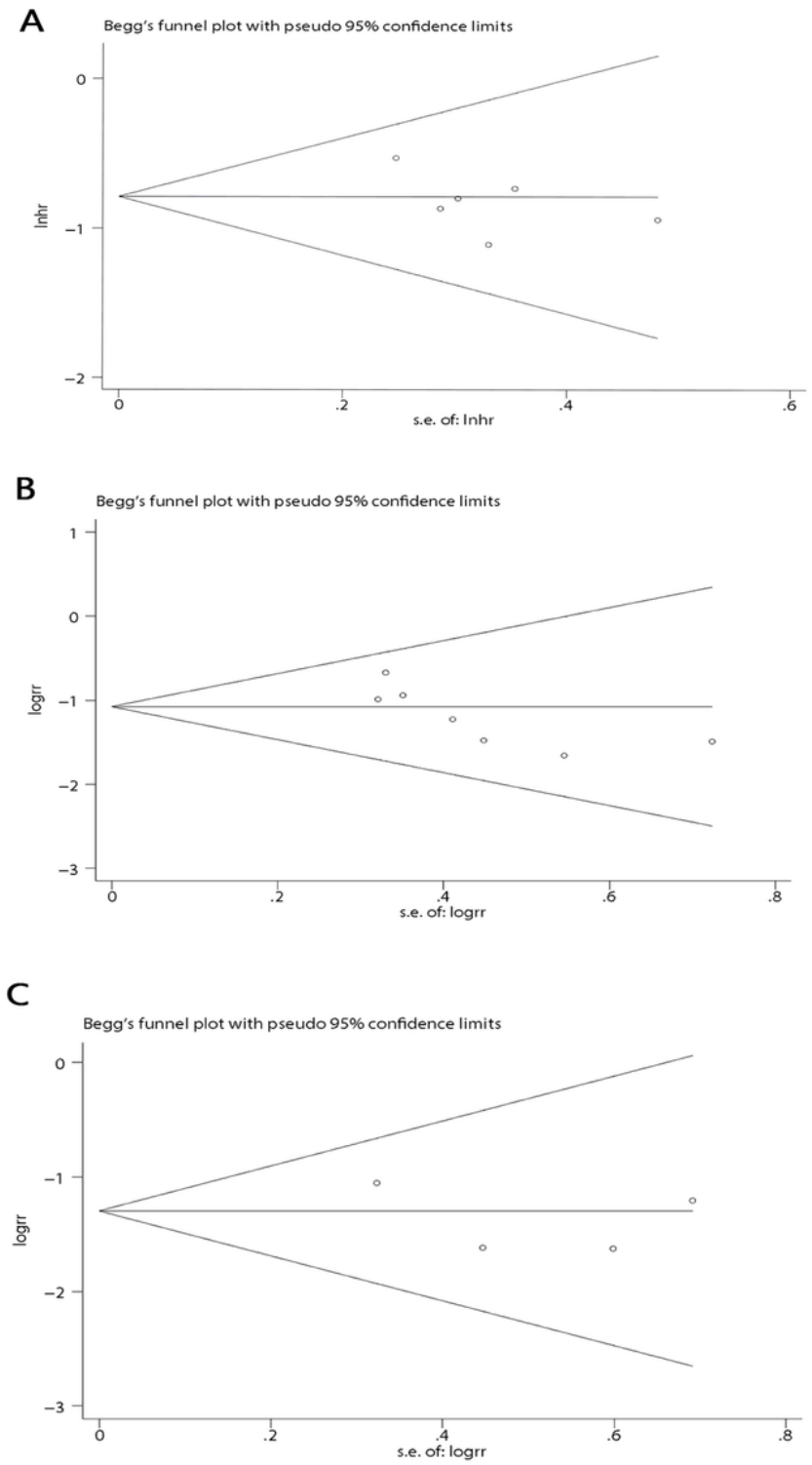

Figure 4

Funnel plot analysis of publication bias in this study (Begg's test): A. OS; B. TNM; C. LNM

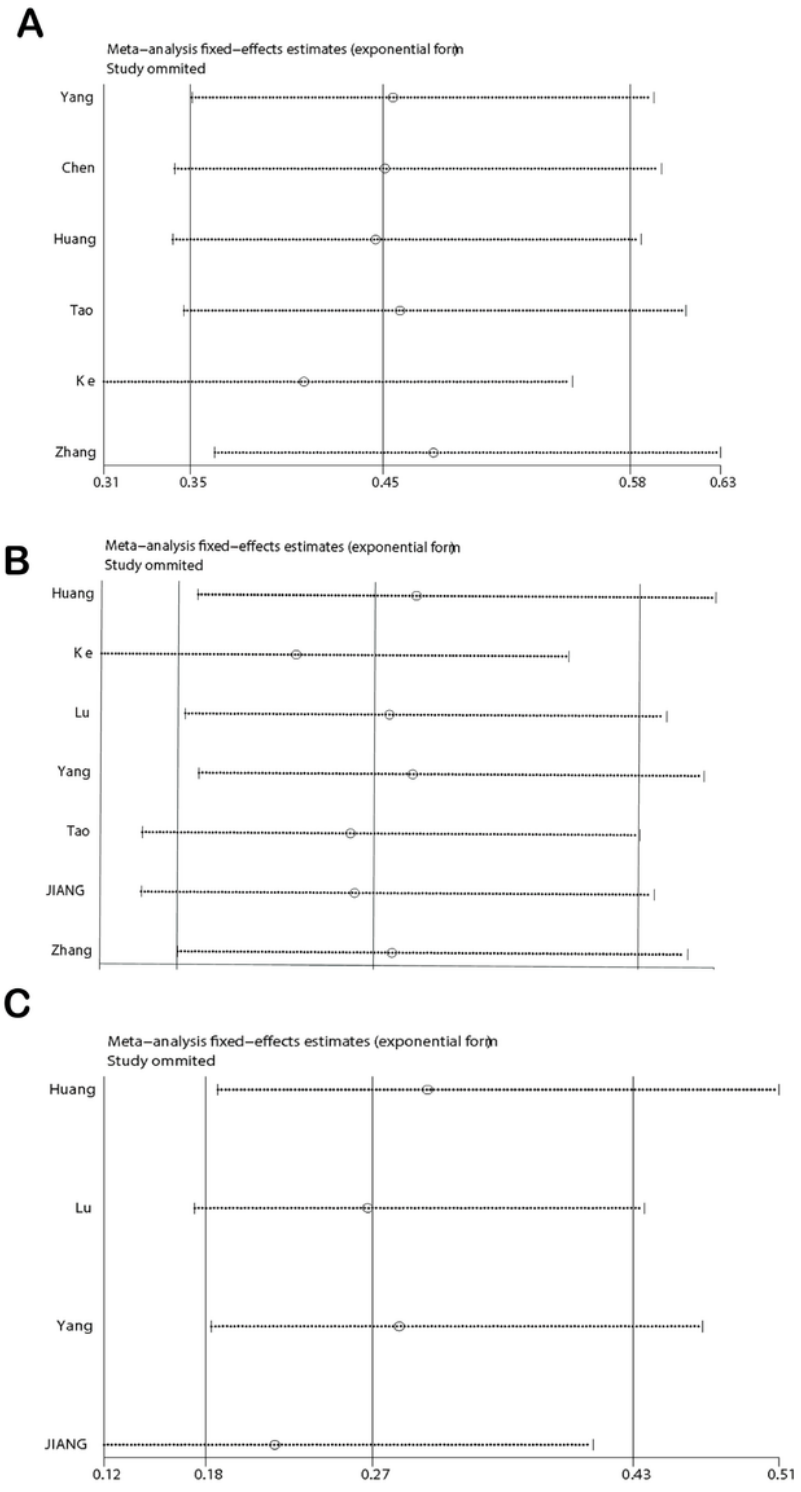

Figure 5

Results of sensitivity analysis: A. OS; B. TNM; C. LNM