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Review

# Prognostic value of long non-coding RNA TP73-AS1 expression in different types of cancer: A systematic review and meta-analysis

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ABSTRACT

*Background:* TP73 antisense RNA 1 (TP73-AS1), a newly discovered long non-coding RNA (lncRNA), has been reported to be upregulated in various kinds of tumors, and shows a variable influence on living quality and prognosis of patients. Thus, we conducted a meta-analysis to evaluate the overall prognostic value of the lncRNA TP73-AS1 in cancer patients.

*Results:* A systematic literature retrieval was carried out using the PubMed, Cochrane Library, EMBASE, and Web of Science databases. We calculated the pooled hazard ratio (HR) and odds ratio (OR) with 95% confidence intervals (CIs) to evaluate the association of TP73-AS1 expression with prognostic and clinicopathological parameters. A total of 15 studies including 1057 cancer patients were finally selected for the meta-analysis. The results demonstrated that high TP73-AS1 expression was significantly associated with shorter overall survival (OS) (HR = 1.97, 95% CI: 1.68–2.31, $P < 0.001$). According to a fixed-effects or random-effects model, elevated TP73-AS1 expression markedly predicted advanced clinical stage (OR = 3.30, 95% CI: 2.35–4.64, $P < 0.001$), larger tumor size (OR = 2.37, 95% CI: 1.75–3.22, $P < 0.001$), earlier lymph node metastasis (OR = 3.28, 95% CI: 1.59–6.76, $P = 0.001$), and distant metastasis (OR = 4.94, 95% CI: 2.61–9.37, $P < 0.001$).

*Conclusions:* High lncRNA TP73-AS1 expression appears to be predictive of a worse OS and clinicopathologic features for patients with various types of malignant tumors. These results provide a basis for utilizing TP73-AS1 expression as an unfavorable indicator to predict survival outcomes.



**Contents**



*Abbreviations:* AFP, alpha fetoprotein; CA125, carbohydrate antigen 125; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; DM, distant metastasis; HR, hazard ratio; lncRNA, long non-coding RNA; LNM, lymph node metastasis; MMP, matrix metallopeptidase; OR, odds ratio; OS, overall survival; PSA, prostate specific antigen; qRT-PCR, quantitative real-time polymerase chain reaction; ROR, regulator of reprogramming; SNHG1, small nucleolar RNA host gene 1; TP73-AS1, TP73 antisense RNA 1; ZEB1-AS1, Zinc finger E-box-binding homeobox 1 antisense 1.

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## 1. Introduction

Nowadays, cancer remains a major threat to human health and quality of life, representing a significant social economic load worldwide. According to preliminary statistics, nearly 1.76 million new cancer cases are likely to be diagnosed and more than 600,000 patients may die of cancer in the United States in 2019 alone [1]. Although great progress has been made in the diagnosis and treatment of cancer owing to continuous improvements of medical technologies, the long-term survival rates and quality life of patients are still unsatisfactory [2]. To date, the mechanisms of oncogenesis and tumor progression have not been completely elucidated, and the common specific biomarkers of tumors such as carbohydrate antigen 125 (CA125), carbohydrate antigen 19–9 (CA19–9), carcinoembryonic antigen (CEA), prostate specific antigen (PSA), and alpha fetoprotein (AFP) are still widely used as prognostic markers [3]. In recent years, the role of molecular biology in identifying new drug targets and novel therapeutics of tumors has become increasingly more prominent [4]. Therefore, constant efforts to find new biomarkers that could effectively predict the prognosis of patients from the perspective of tumor molecular mechanisms are imperative and significant for clinical applications.

Human genome sequence data demonstrate that the transcripts defined as noncoding RNAs (ncRNAs) account for more than 98% of

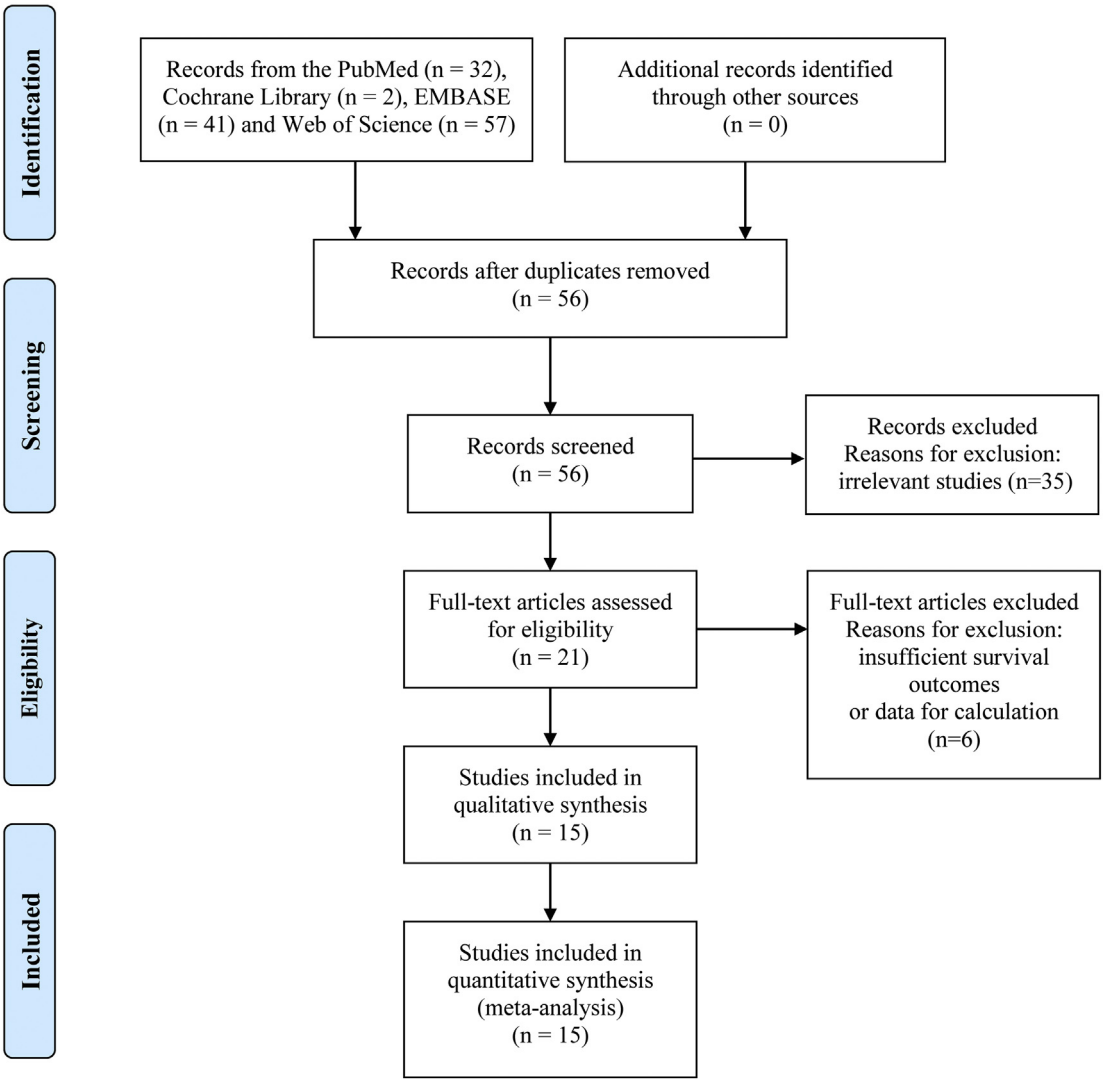


**Fig. 1.** The flow chart of literature search and selection.

**Table 1**
Basic characteristics of the included studies (15 studies).

| Study (15) | Year | Region | Cancer type | Sample size | HR (95% CI) | Date extraction | Expression pattern | Detection method | Follow-up time | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| Li S | 2017 | China | Hepatocellular carcinoma | 84 | 2.25 (1.14–4.43) | MVA | Up-regulation | qRT-PCR | <5 years | 7 |
| Chen X | 2018 | China | Osteosarcoma | 132 | 1.89 (1.15–3.13) | MVA | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Zhang R | 2018 | China | Brain glioma | 47 | 2.46 (1.13–5.35) | MVA | Up-regulation | qRT-PCR | <5 years | 8 |
| Yao J | 2018 | China | Breast cancer | 36 | 3.34 (1.03–10.82) | MVA | Up-regulation | qRT-PCR | <5 years | 6 |
| Wang Y | 2018 | China | Gastric cancer | 64 | 1.78 (1.04–3.08) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Liu C | 2019 | China | Lung adenocarcinoma | 80 | 2.01 (1.11–3.64) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Zhang W | 2018 | China | Gastric cancer | 76 | 1.90 (1.13–3.19) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Zhu D | 2019 | China | Non-small cell lung cancer | 72 | 2.07 (1.13–3.79) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Yang G | 2018 | China | Osteosarcoma | 46 | 2.26 (1.03–4.98) | SC | Up-regulation | qRT-PCR | <5 years | 7 |
| Tuo Z | 2018 | China | Bladder cancer | 128 | 0.41 (0.23–0.74) | SC | Downregulation | qRT-PCR | ≥5 years | 6 |
| Liu G | 2018 | China | Clear cell renal cell carcinoma | 40 | 3.08 (1.99–5.81) | SC | Up-regulation | qRT-PCR | <5 years | 7 |
| Ding Z | 2018 | China | Gastric cancer | 72 | 1.82 (0.97–3.43) | SC | Up-regulation | qRT-PCR | ≥5 years | 6 |
| Zhang L | 2018 | China | Non-small cell lung cancer | 45 | 2.61 (1.23–5.54) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |
| Cui XP | 2019 | China | Pancreatic cancer | 77 | 2.60 (1.53–4.43) | SC | Up-regulation | qRT-PCR | <5 years | 7 |
| Peng J | 2018 | China | Gastric cancer | 58 | 2.96 (1.56–5.60) | SC | Up-regulation | qRT-PCR | ≥5 years | 8 |

HR: hazard ratio, 95% CI: 95% confidence interval CI, MVA: multivariate analysis, SC: survival curve, qRT-PCR: quantitative real-time polymerase chain reaction, NOS: Newcastle-Ottawa quality assessment scale.

the total transcribed genome [5]. Although ncRNAs do not have the capacity to encode proteins, they nevertheless can regulate the activity of proteins by adjusting their subcellular localization [6]. Long non-coding RNAs (lncRNAs), defined as RNA molecules with a length of >200 bases located in the nucleus or cytoplasm, play roles in several cellular regulatory processes, including transcription of the eukaryotic genome and epigenome, and reprogramming of human induced pluripotent stem cells [7,8]. Moreover, lncRNAs have been shown to play crucial parts in the occurrence and progression of diseases, especially cancer [9]. With the exploitation of accurate and innovative research on lncRNAs, several lines of evidence have shown that abnormal expression of some lncRNAs is associated with worse clinicopathological features and poor prognosis of patients with various malignancies, including the lncRNA Zinc finger E-box-binding homeobox 1 antisense 1 (ZEB1-AS1), small nucleolar RNA host gene 1 (SNHG1), and regulator of reprogramming (ROR) [10,11,12].

TP73 antisense RNA 1 (TP73-AS1), located at chromosome 1p36, is a novel transcribed lncRNA containing complex and diverse sequences and proposed mechanisms of action [13]. Recent studies indicated that TP73-AS1 could promote the cell growth and progression of various human tumors through diverse signaling pathways such as the WNT/β-catenin, HMGB1/RAGE, and PI3K/Akt/mTOR pathways [14,15,16]. Moreover, TP73-AS1 was reported to be involved in the intricate processes of tumor formation, and its abnormal expression could affect the outcome measures and cause worse survival of cancer patients [17,18,19]. Thus, TP73-AS1 is likely to be a crucial and specific biological marker for the diagnosis and prediction of human cancer.

Despite several studies on the abnormal expression of TP73-AS1 in tumors, they show somewhat conflicting results and suffer from limitations of small sample size. Therefore, we performed a quantitative meta-analysis to comprehensively assess the prognostic value of TP73-AS1 in patients with different types of cancers from the

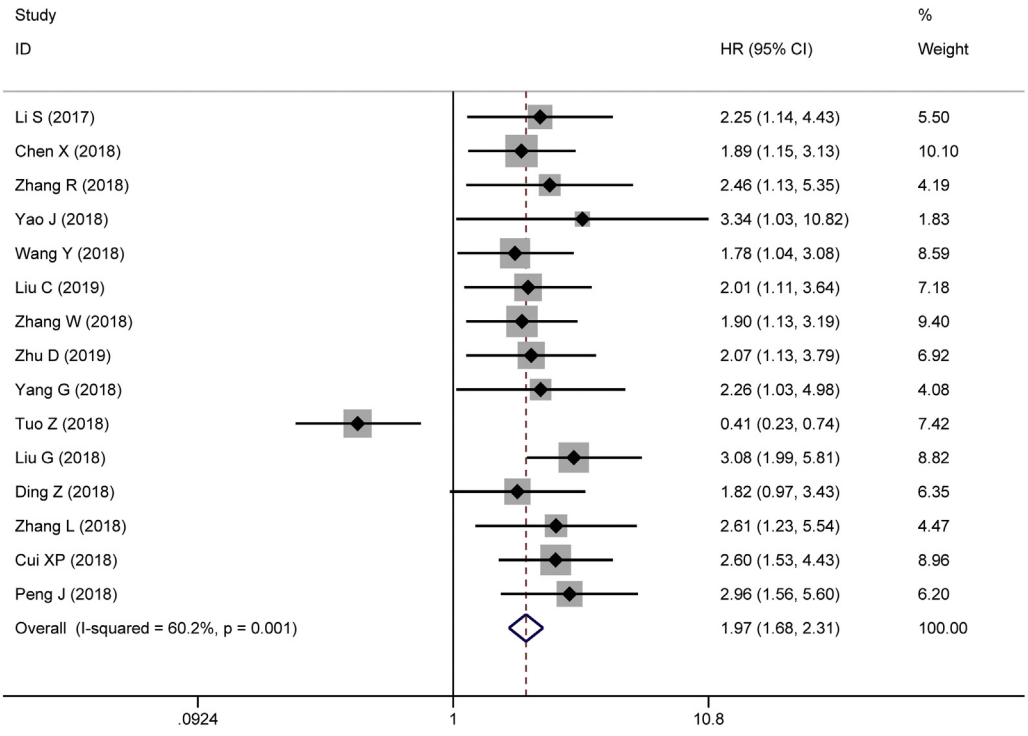


**Fig. 2.** Forest plot reflecting the association between lncRNA TP73-AS1 and OS.

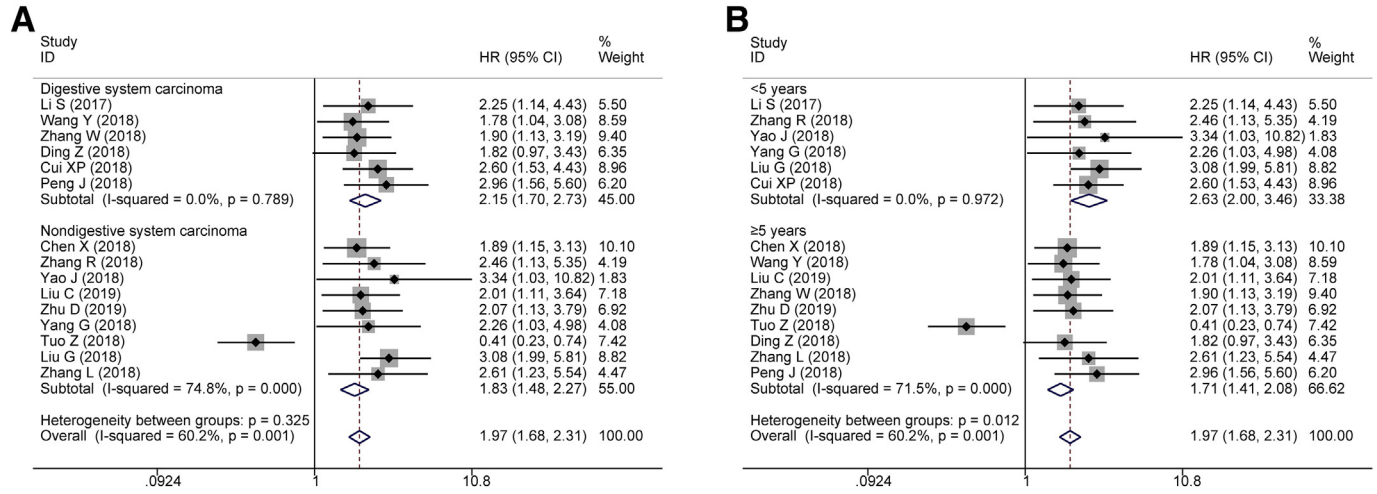


**Fig. 3.** Forest plot showing the subgroup analyses of the pooled HRs with lncRNA TP73-AS1 in cancer type (A) and follow-up time (B).

perspective of multiple indicators of outcome, including tumor size and stage, lymph node metastasis (LNM), distant metastasis (DM), and overall survival (OS).

## 2. Material and methods

### *2.1. Search strategy*

A systemically computer-based retrieval of the PubMed, Cochrane Library, EMBASE and Web of Science databases was performed by 2 authors independently up to June, 2019. The MeSH terms and related synonyms of Literature retrieval strategy were as follows: ("TP73-AS1" OR "TP73 antisense RNA 1" OR "long non-coding RNA TP73-AS1" OR "lncRNA TP73-AS1") AND ("tumor" OR "cancer" OR "carcinoma" OR "neoplasm" OR "malignancy") AND ("prognostic" OR "predict" OR "prognosis" OR "survival"). Beyond that, we also searched the reference lists of selected articles including reviews, meta-analyses and other forms of literature by means of manual retrieval. All eligible publications were carefully recruited by scanning the titles, abstracts, keywords and full texts. Notably, the review methodology was prospectively registered in PROSPERO (registration number: CRD42019128198).

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

### *2.2. Study selection*

The following inclusion criteria of all selected studies were listed: (1) studied the expression of TP73-AS1 in any type of human cancer; (2) detection of TP73-AS1 expression in tumor tissue, rather than in any other kinds of specimens; (3) sufficient survival information was provided for calculating the HR with 95% CIs. The excluded studies had the following characteristics: (1) reviews, letters, comments, meta-analysis, and meeting abstracts; (2) studies only reported the molecular mechanism or function of TP73-AS1; (3) duplicate publications.

### *2.3. Data extraction and quality assessment*

Two authors independently extracted the data from original publications and any disagreements were resolved by consensus. Publication information was as follows: name of first author, publication year, region, cancer type, sample size, adjusted HR and 95% CIs of TP73-AS1 for OS, date extraction, expression pattern, detection method and follow-up time. If a study afforded Kaplan–Meier curves in a single information, the data of HR and 95% CIs for OS were extracted and calculated from the graphical survival plots using the software of Engauge Digitizer 10.8 and the method provided by Tierney et al. [20]. If both univariate and multivariate analyses were applied in reporting the data, the latter was directly applied.

We seriously assessed the quality of recruited studies according to the Newcastle-Ottawa quality assessment scale (NOS) on a scores scale of 0 to 9 points [21]. If the score greater than or equal to 6, it was identified as high quality.

### *2.4. Statistical analysis*

Our meta-analysis was conducted using the Stata version 14.0 software (Stata Corporation, College Station, TX) to analyze the connection of lncRNA TP73-AS1 expression with survival outcomes and clinicopathological features. Among different studies, the heterogeneities were assessed by Cochran's Q-test and Higgin's $I^2$

**Table 2**
The meta-analysis for the association between lncRNA TP73-AS1 expression and clinicopathological parameters.

| Category | Enrolled studies | Patients (n) | OR (95% CI) | P | $I^2$ | Model |
|---|---|---|---|---|---|---|
| Gender (male vs. female) | 11 | 749 | 1.07 (0.80–1.44) | 0.656 | 0% | Fixed-effects |
| Clinical stage (III/IV vs. I/II) | 10 | 600 | 3.30 (2.35–4.64) | <0.001 | 0% | Fixed-effects |
| Tumor size (large vs. small) | 11 | 708 | 2.37 (1.75–3.22) | <0.001 | 22.8% | Fixed-effects |
| Differentiation grade (poor vs. good) | 4 | 352 | 1.77 (0.83–3.80) | 0.140 | 51.9% | Random-effects |
| LNM (positive vs. negative) | 7 | 436 | 3.28 (1.59–6.76) | 0.001 | 65.2% | Random-effects |
| DM (present vs. absent) | 4 | 276 | 4.94 (2.61–9.37) | <0.001 | 0% | Fixed-effects |

OR: odds ratio, 95% CI: 95% confidence interval, vs: versus, LNM: lymph node metastasis, DM: distant metastasis.

statistic, respectively. Noticeably, a random-effects model would be built if the heterogeneity had statistical significance ($P < 0.05$ or $I^2 > 50\%$). Moreover, the potential publication bias was assessed by constructing a funnel plot symmetry and using Begg's test and Egger's test. In the summary data, survival outcomes and clinicopathological features were assessed using pooled HR and OR with 95% CIs,

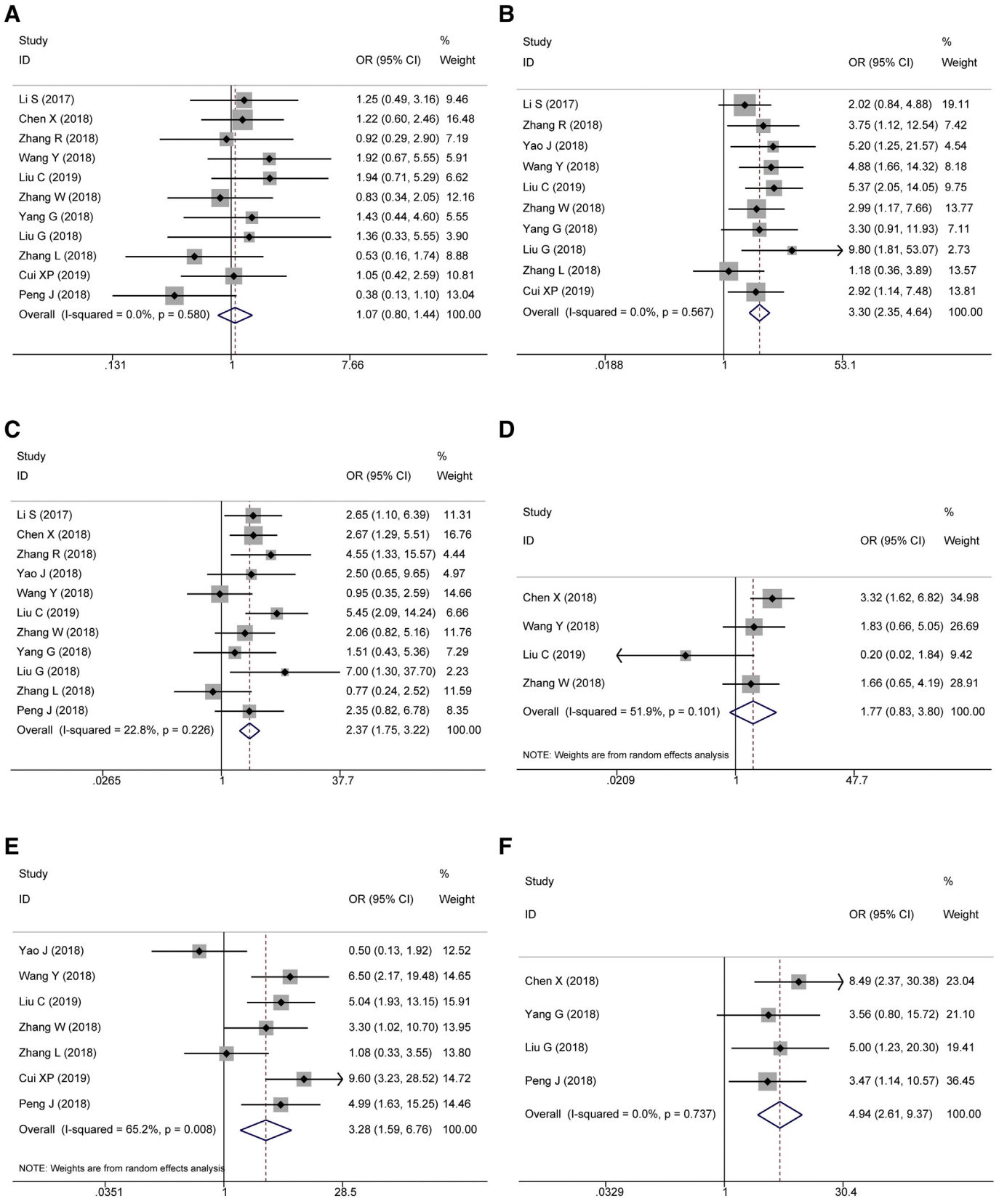


**Fig. 4.** Forest plot reflecting the association between lncRNA TP73-AS1 and clinicopathological features (A, Gender; B, Clinical stage; C, Tumor size; D, Differentiation grade; E, LNM; F, DM).

respectively. In addition, the stability of the statistical result was evaluated by sensitivity analysis. P values <0.05 were considered to be statistically significant.

## 3. Results

### 3.1. Included studies

According to the strategy for searching and screening the related literature (Fig. 1), a total of 132 articles were initially retrieved. After removing duplicates, 56 papers remained. The titles and abstracts of these articles were then carefully sifted, and 35 irrelevant items were subsequently excluded. Of the remaining 21 articles, seven were removed owing to violations of the established inclusion criteria. Ultimately, 15 studies involving 1057 patients with sample sizes ranging from 36 to 132 were enrolled into our meta-analysis.

### 3.2. Basic characteristics of the enrolled studies

The main characteristics of these 15 studies published from 2017 to 2019 are listed in Table 1. These studies covered a total of 10 different types of tumors, including respiratory system carcinoma (one lung adenocarcinoma and two non-small cell lung cancers) [22,23,24], digestive system carcinoma (one hepatocellular carcinoma, four gastric cancers, and one pancreatic cancer) [14,18,25,26,27,28], urinary system carcinoma (one clear cell renal cell carcinoma and one bladder cancer) [16,29], and carcinoma of other systems (two osteosarcomas, one brain glioma, and one breast cancer) [15,17,30,31]. The expression level of TP73-AS1 as detected by quantitative real-time polymerase chain reaction (qRT-PCR) was found to be elevated in most tumors, but was found to be downregulated only in bladder cancer [29]. Additionally, in eight of the studies, the patients were followed-up for more than 60 months, and the rest were followed-up within five years.

### 3.3. Correlation between lncRNA TP73-AS1 and OS

All studies evaluated the correlation between lncRNA TP73-AS1 expression and OS of cancer patients. The data of HR and 95% CIs for OS were directly extracted from four studies according to multivariate analysis and indirectly calculated from ten studies by Kaplan–Meier curves. As shown in Fig. 2, an evident correlation between elevated TP73-AS1 expression and shorter OS was detected in human cancer (HR = 1.97, 95% CI: 1.68–2.31, P < 0.001), while significant heterogeneity was observed ($I^2$ = 60.2%, PQ < 0.001). Furthermore, subgroup meta-analyses stratified by cancer type (digestive system or nondigestive system carcinoma) and follow-up time (fewer than 5 or more than 5 years) were conducted to assess the prognostic value of TP73-AS1. The results demonstrated that this lncRNA could act as a prognostic indicator of OS for cancer patients (Fig. 3).

Because of significant heterogeneity, we repeated the meta-analysis while omitting one and eventually identified the study performed by Tuo et al. [29] as a source of heterogeneity. After excluding this study, the significant heterogeneity disappeared ($I^2$ = 0%, PQ = 0.971), and the association between elevated TP73-AS1 expression and shorter OS was still significant (HR = 2.24, 95% CI: 1.90–2.64, P < 0.001). In addition, no evidence of covariates notably affecting OS was found in meta-regression. The above results sufficiently demonstrated that elevated TP73-AS1 expression might be associated with worse OS, and this lncRNA might be developed as an independent factor of survival outcomes among cancer patients.

### 3.4. Correlation between lncRNA TP73-AS1 and clinicopathologic features

Not all of the enrolled studies fully recorded the correlation between lncRNA TP73-AS1 expression and clinicopathological features. Cumulative meta-analysis was conducted to evaluate the role of TP73-AS1 in gender of 11 studies, clinical stage of 10 studies, tumor size of 11 studies, differentiation grade of 4 studies, LNM of 7 studies and DM of 4 studies. As presented in Table 2 and Fig. 4, there was no significant evidence to show that TP73-AS1 expression was related to gender (OR = 1.07, 95% CI: 0.80–1.44, P = 0.656) and differentiation grade (OR = 1.77, 95% CI: 0.83–3.80, P = 0.140). However, high TP73-AS1 expression was remarkably correlated with advanced clinical stage (OR = 3.30, 95% CI: 2.35–4.64, P < 0.001), larger tumor size (OR = 2.37, 95% CI: 1.75–3.22, P < 0.001) and DM (OR = 4.94, 95% CI: 2.61–9.37, P < 0.001), which performed by a fixed-effects model because of no significant heterogeneity. Similar results achieved by a random-effects model were found in terms of LNM (OR = 3.28, 95% CI: 1.59–6.76, P = 0.001).

### 3.5. Publication bias and sensitivity analysis

As presented in Fig. 5, no significant publication bias affecting the analysis of OS was observed according to Begg's test (P = 0.198) and Egger's test (P = 0.501). Furthermore, we did not find obvious publication biases in terms of clinicopathological parameters among the enrolled articles (Fig. 6). In addition, no dramatic reversal of conclusions was observed by the exclusion of any single study. Although our results were slightly affected by the study of Tuo et al. [29], the final results were relatively stable and robust according to sensitivity analyses for OS (Fig. 7).

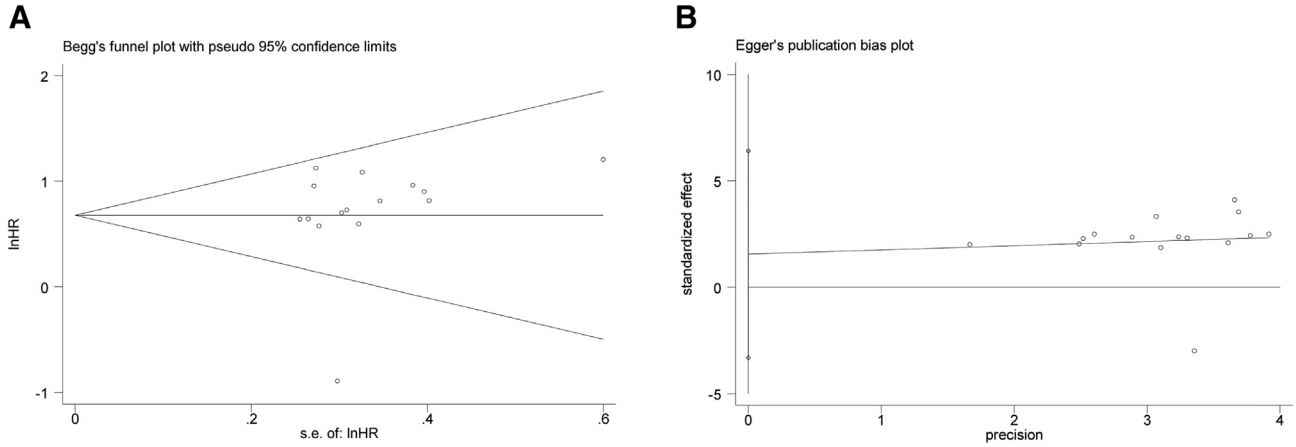


**Fig. 5.** Detection of publication bias for meta-analysis of OS (A, Begg's test; B, Egger's test).

## 4. Discussion

With improvement and innovation of RNA analysis technology, cell type separation, and culture technology, the catalog of RNA types is continuously expanding. Indeed, the biological roles of RNAs are now recognized to be nearly as crucial as those of proteins [32]. LncRNAs, a group of specific RNA molecules lacking an open reading frame, have been reported to be abnormally expressed in several pathological conditions such as diabetes, and digestive and cardiovascular diseases [33,34,35]. As the associations between lncRNAs and various types of tumors have gradually been demonstrated in recent years, there is now ample evidence to suggest a significant role of lncRNAs in tumorigenesis and disease progression [36,37]. The lncRNA TP73-AS1 has recently emerged as a novel prognostic biomarker. Its potential prognostic value was first reported in esophageal cancer by Zang and colleagues in 2016 [38]. Subsequently, many studies have consistently confirmed that the expression of TP73-AS1 was upregulated in various types of cancer tissues, including cholangiocarcinoma, lung

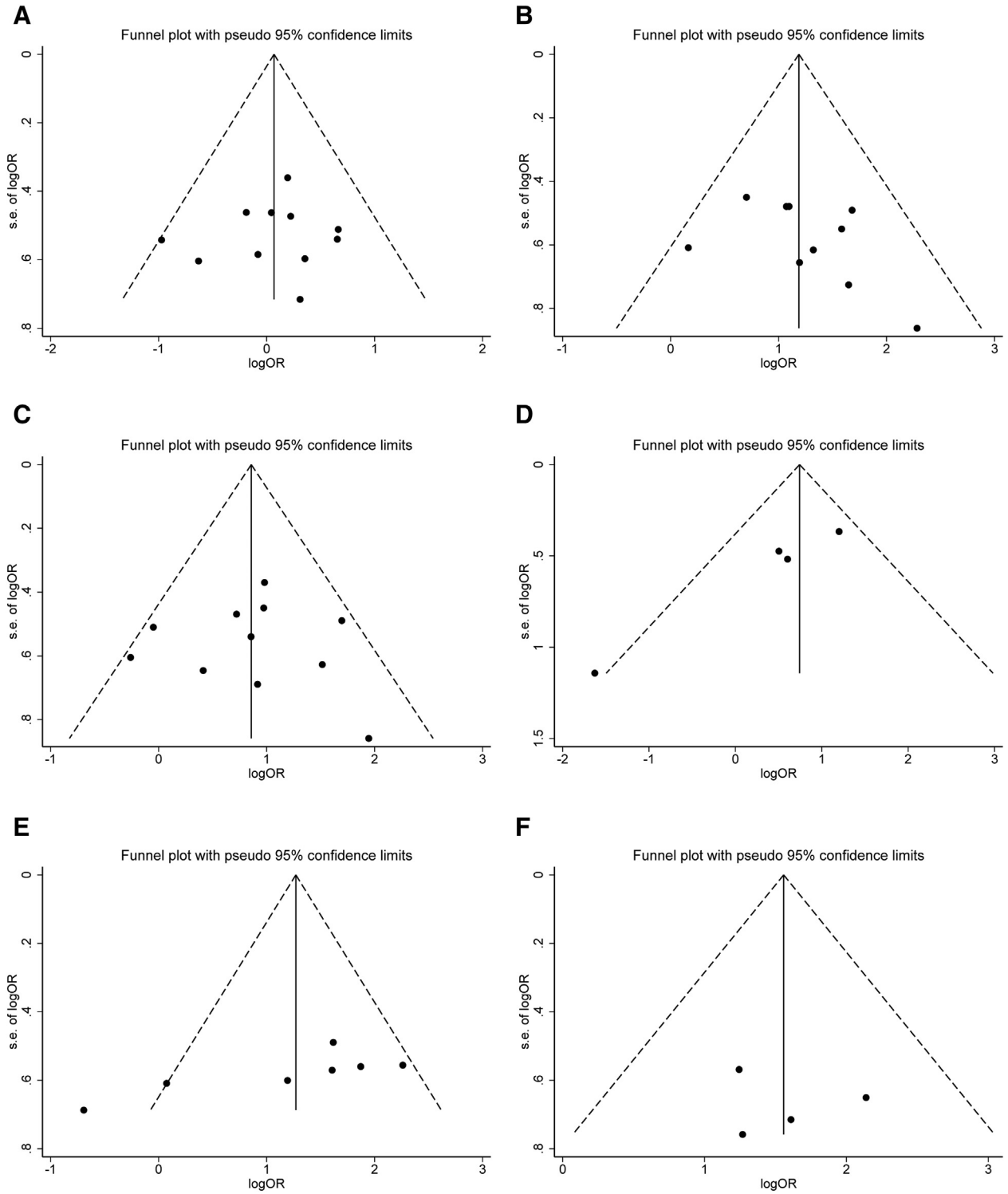


**Fig. 6.** Detection of publication bias for meta-analyses of clinicopathological features (A, Gender; B, Clinical stage; C, Tumor size; D, Differentiation grade; E, LNM; F, DM).

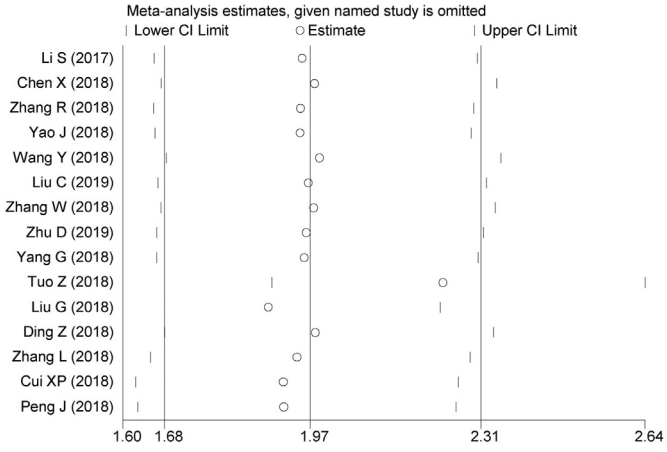


**Fig. 7.** Sensitivity analysis of the relationship between lncRNA TP73-AS1 and OS.

adenocarcinoma, and brain glioma, compared with normal or paracancerous samples [19,22,39]. Hence, it is meaningful to further demonstrate the potential of TP73-AS1 as a biomarker for diagnosing and monitoring tumors.

So far as we know, this is the first meta-analysis to comprehensively evaluate the relationship of lncRNA TP73-AS1 expression with the prognosis and clinicopathological features in different types of tumors. In this meta-analysis of 14 recently published studies, we discovered that cancer patients with high TP73-AS1 expression were strongly more likely to have a worse OS compared to those with low TP73-AS1 expression, thereby confirming the general prognostic value of this lncRNA in malignant tumors. Furthermore, we found that overexpression of TP73-AS1 was markedly associated with advanced clinical stage, larger tumor size, earlier lymph node metastasis, and organ metastasis. The one exception to these consistent findings is the study by Tuo et al. [29] on bladder cancer; however, these discrepant results did not affect the overall conclusion of our meta-analysis. Therefore, further large-scale and prospective studies should be performed to clarify the association of lncRNA TP73-AS1 expression with prognosis and clinicopathologic features in bladder cancer.

The molecular mechanisms of lncRNA TP73-AS1 in various cancers are likely complex. TP73-AS1, acting as an oncogenic lncRNA, has been suggested to promote the proliferation and invasion of tumor cells through activating different types of signaling pathways [14,15,22]. Moreover, some miRNA gene family members such as miR-141, miR-124 and miR-200a could act as sponges and direct targets for TP73-AS1 to regulate the occurrence and progression of various malignant tumors [28,39,40]. One study demonstrated that knockdown of TP73-AS1 could inhibit the migratory and invasive abilities of cancer cells by reversing the Snail-mediated epithelial-to-mesenchymal transition [26]. Furthermore, TP73-AS1 could modulate the levels of certain early response proteins such as matrix metallopeptidase 2 (MMP2) and MMP9 by exerting its molecular function to jointly promote carcinogenesis [41]. Hence, the crucial function of TP73-AS1 in different types of cancers is evident but with varied and complex mechanisms.

Notably, lncRNA TP73-AS1 not only shows potential as a useful marker to predict prognosis but could also serve as a novel and potential therapeutic target in various malignant tumors. In a study of 77 patients with pancreatic cancer, Cui et al. [28] revealed that TP73-AS1 could serve as an oncogene to enhance the metastasizing power of tumor cells, demonstrating its potential as a biological target for the treatment of pancreatic cancer. Mazor et al. [42] reported that high TP73-AS1 expression predicted poor outcomes in primary multiform glioblastomas, and suggested that this lncRNA could not only increase the invasive ability of tumor cells but also promote the resistance of glioblastoma stem cells to temozolomide. Moreover, Peng [27] demonstrated that a high TP73-AS1 expression level was correlated with a worse prognosis in patients with gastric cancer, suggesting the lncRNA as a potential therapeutic target to strengthen the chemotherapeutic response of gastric cancer cells to cisplatin. Consistent with these findings, Wang et al. [14] found that if TP73-AS1 was knocked out in gene sequences, the proliferation and invasion of gastric cancer cells were suppressed through the WNT/β-catenin signaling pathway. Therefore, the lncRNA TP73-AS1 is expected to play a crucial role in developing the molecular-targeted therapy and individual nursing plan for cancer patients in the future.

Admittedly, like all meta-analyses, our study is not without limitations. First, all the studies included in our meta-analysis were performed in China, which may affect the generalizability of the results. Second, there are inconsistencies with respect to determining the cut-off values for high and low expression of TP73-AS1 in different types of cancer, along with other pathological features such as the size, grade, and stage of tumors. Third, since some studies did not provide HR and 95% CI values directly, we had to manually extract data and estimate these values from the graphical survival plots, which may have cause potential heterogeneity. Finally, the sample sizes of eligible studies and included patients were relatively small, with only 15 studies comprising 1057 patients finally included in the present meta-analysis. Therefore, further large-scale and better designed studies may be needed to confirm the clinical utility of lncRNA TP73-AS1 in predicting the prognosis of patients with malignant tumors and guide clinicians and nurses to provide accurate molecular targeted therapy and intensive nursing for patients.

## 5. Conclusions

In summary, our study confirmed that high expression of lncRNA TP73-AS1 was significantly associated with worse survival outcomes, especially OS, and adverse clinicopathological features for patients with different types of cancer. The lncRNA TP73-AS1 could be used as a prognostic biomarker and novel therapeutic target for human cancer.

## Conflict of interest

The authors declare that they have no competing interests.

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