Systematic Review and Meta-Analysis

Medicine

OPEN

The clinical prognostic value of lncRNA FOXP4-AS1 in cancer patients

A meta-analysis and bioinformatics analysis based on TCGA datasets

Qiang Shu, MD[a], Xiaoling Liu, MD[b], Jushu Yang, MD[a], Tinggang Mou, MD[a], Fei Xie, MD[a]

Abstract

Background: The mortality and recurrence of patients with cancer is of high prevalence. Long non-coding RNA (lncRNA) forkhead box P4 antisense RNA 1 (FOXP4-AS1) is a promising lncRNA. There is increasing evidence that lncRNA FOXP4-AS1 is abnormally expressed in various tumors and is associated with cancer prognosis. This study was designed to identify the prognostic value of lncRNA FOXP4-AS1 in human malignancies.

Methods: We searched electronic databases up to April 29, 2022, including PubMed, Cochrane Library, Embase, MEDLINE, and Web of Science. Eligible studies that evaluated the clinicopathological and prognostic role of lncRNA FOXP4-AS1 in patients with malignant tumors were included. The pooled odds ratios (ORs) and the hazard ratios (HRs) were calculated to assess the role of lncRNA FOXP4-AS1 using Stata/SE 16.1 software.

Results: A total of 6 studies on cancer patients were included in the present meta-analysis. The combined results revealed that high expression of lncRNA FOXP4-AS1 was significantly associated with unfavorable overall survival (OS) (HR = 1.99, 95% confidence interval [CI]: 1.65–2.39, $P < .00001$), and poor disease-free survival (DFS) (HR = 1.81, 95% CI: 1.54–2.13, $P < .00001$) in a variety of cancers. In additional, the increase in lncRNA FOXP4-AS1 expression was also correlated with tumor size ((larger vs smaller) (OR = 3.16, 95% CI: 2.12–4.71, $P < .00001$), alpha-fetoprotein (≥400 vs <400) (OR = 3.81, 95%CI: 2.38–6.11, $P = .83$), lymph node metastasis (positive vs negative) (OR = 2.93, 95%CI: 1.51–5.68, $P = .001$), and age (younger vs older) (OR = 2.06, 95% CI: 1.41–3.00, $P = .00002$) in patients with cancer. Furthermore, analysis results using The Cancer Genome Atlas (TCGA) dataset showed that the expression level of lncRNA FOXP4-AS1 was higher in most tumor tissues than in the corresponding normal tissues, which predicted a worse prognosis.

Conclusions: In this meta-analysis, we demonstrate that high lncRNA FOXP4-AS1 expression may become a potential marker to predict cancer prognosis.

Abbreviations: CI = confidence interval, DFS = disease-free survival, DM = distant metastasis, FOXP4-AS1 = forkhead box P4 antisense RNA 1, HCC = hepatocellular carcinoma, HR = hazard ratios, LncRNA = long non-coding RNA, MCL = mantle cell lymphoma, NPC = nasopharyngeal carcinoma, OR = odds ratio, OS = osteosarcoma, OS = overall survival, TCGA = the cancer genome atlas.

Keywords: cancer, disease free survival, FOXP4-AS1, long non-coding RNA, overall survival, prognosis

1. Introduction

Cancer is one of the leading causes of death worldwide.[1] However, the exact mechanism underlying this cancer remains unclear. Furthermore, surveillance of patients with early stage cancer remains difficult. Hence, many cancer cases are identified at an advanced stage and have a dismal prognosis. The official databases of the World Health Organization and American Cancer Society indicate that cancer poses the highest clinical, social, and economic burden among all human diseases. A total number of 18 million new cases have been diagnosed in 2018, the most frequent of which are lung (2.09

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

This meta-analysis was supported by the Key Discipline Construction Fund of the First People's Hospital of Neijiang.

The study was approved by the Human Research Ethics Committees of the First People's Hospital of Neijiang, Neijiang, Sichuan All data are included in this article.

[a] *Department of Hepatic-Biliary-Pancreatic Surgery, The Neijiang First People's Hospital affiliated to Chongqing Medical University, Neijiang City, Sichuan Province, China,* [b] *Department of Hospital Infection Management, The Neijiang Hospital of Traditional Chinese Medicine, Neijiang City, Sichuan Province, China.*

**Correspondence: Fei Xie, Department of Hepatic-Biliary-Pancreatic Surgery, The First People's Hospital of Neijiang, Shizhong District, Neijiang City 641000, Sichuan Province, China (e-mail: whitetower@163.com).*

How to cite this article: Shu Q, Liu X, Yang J, Mou T, Xie F. The clinical prognostic value of lncRNA FOXP4-AS1 in cancer patients: A meta-analysis and bioinformatics analysis based on TCGA datasets. Medicine 2022;101:42(e31439).

Received: 10 June 2022 / Received in final form: 29 September 2022 / Accepted: 30 September 2022

http://dx.doi.org/10.1097/MD.0000000000031439

million cases), breast (2.09 million cases), and prostate (1.28 million cases) cancers.[2] Therefore, early diagnosis and intervention have become vital for improving the overall survival (OS) of patients with cancer.

Long non-coding RNA (lncRNA) are defined as transcripts >200 nucleotides in length that display limited protein-coding potential.[3] In recent years, lncRNAs have been found to play significant regulatory roles in a variety of diseases, especially in the biological processes of malignant tumors, including differentiation, migration, apoptosis, and dose compensation effects.[4,5] Recent studies have proposed that LINC00675 is related to clinicopathological features and prognosis of various cancer patients by participating in cancer cell proliferation and invasion.[6,7] In cervical cancer, SIP1 expression is upregulated by lncRNA NORAD to promote proliferation and invasion of cervical cancer cells.[8] Studies have shown that lncNONHSAAT081507.1 (LINC81507) plays an inhibitory role in the progression of nonsmall cell lung cancer and acts as a therapeutic target and potential biomarker for the diagnosis and prognosis of nonsmall cell lung cancer.[9] These results provide evidence that lncRNAs may serve as novel prognostic biomarkers and therapeutic targets in human tumors.[10,11]

Forkhead box P4 antisense RNA 1 (FOXP4-AS1), a member of the lncRNA family, is an antisense lncRNA to FOXP4. The lncRNA FOXP4-AS1, which is an lncRNA related to tumors, is believed to participate in the occurrence of tumors and promote tumor proliferation, invasion, and migration. Extensive studies have indicated that FOXP4-AS1 is highly expressed in several malignancies, including hepatocellular carcinoma (HCC),[12] colorectal carcinoma,[13] and nasopharyngeal carcinoma (NPC).[14] Thus, its upregulation is usually related to tumor grade and poor prognosis.[15,16] However, no systematic meta-analysis has yet been conducted to support the prognostic value of FOXP4-AS1 in these cancers. Hence, a meta-analysis was performed to investigate the clinical prognostic value of lncRNA FOXP4-AS1 in patients with cancer.

2. Material and Methods

2.1. Literature search

This meta-analysis was conducted in accordance with the Guidelines for Preferred Reports of Systematic Reviews and Meta-Analysis and Meta-analysis of Observational Epidemiological Studies statements. A comprehensive literature search was conducted. In order to identify relevant articles, 2 reviewers independently searched electronic databases, including PubMed, Cochrane Library, EMBASE, Medline and Web of Science.Use the following search terms: "long non-coding RNA FOXP4-AS1," "lncRNA FOXP4-AS1," "Forkhead box P4 antisense RNA 1," "tumor," "cancer," and "prognosis." The issue will be discussed with a third reviewer if there

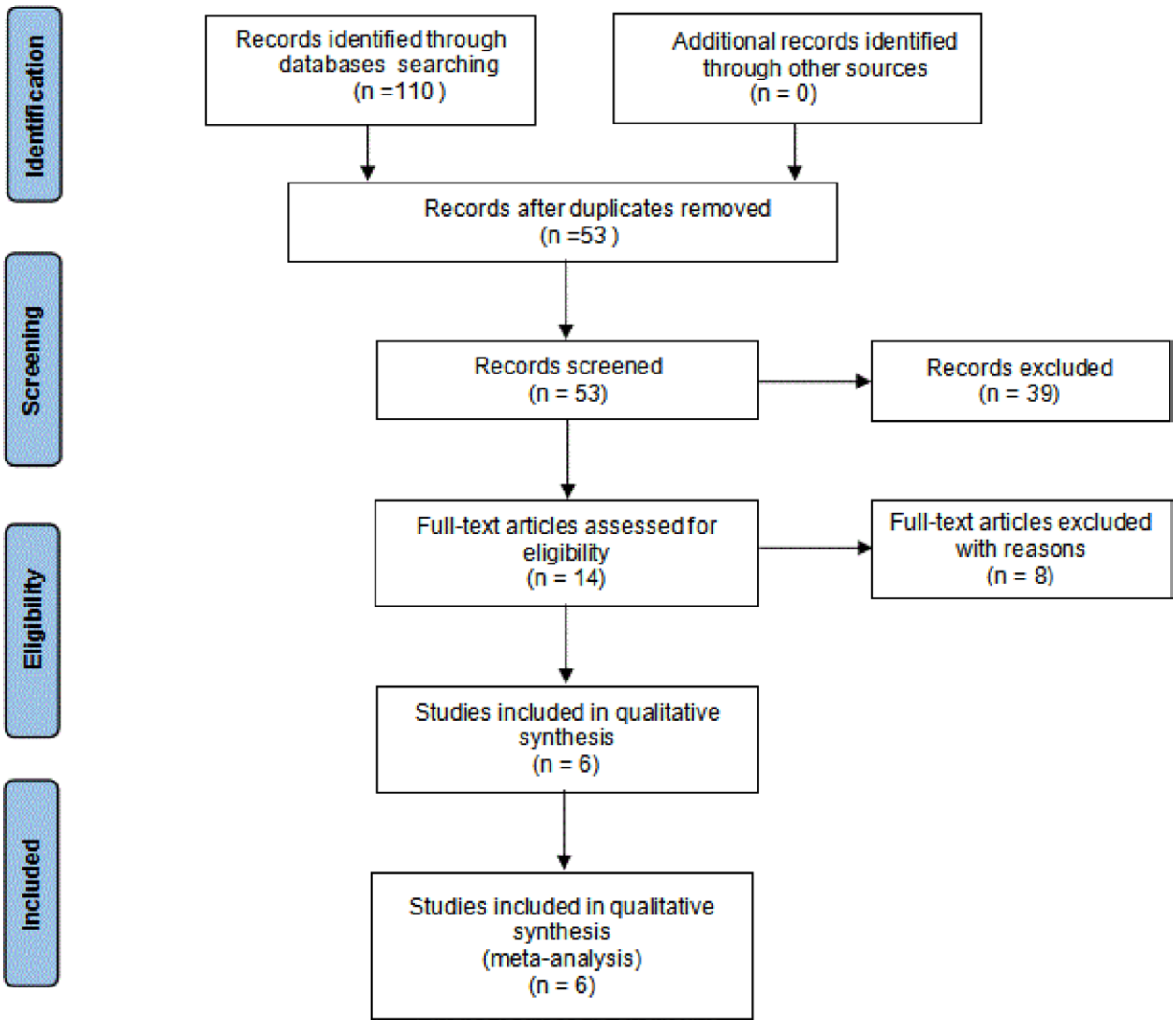

Figure 1. Flow diagram of the literatures selection in this meta-analysis.

are any inconsistencies. To select eligible studies, we used the following criteria: definitive diagnosis or histopathological diagnosis in cancer patients; survival and clinical prognostic parameters of lncRNA FOXP4-AS1 in cancer patients were reported. The combined disaster risk (HR) and 95% confidence intervals (CI) were calculated using sufficient information. The exclusion criteria were as follows: studies without prognostic outcome information, non-human studies, letters, case reports, review articles, duplicate publications, and studies without original data.

2.2. Data extraction and quality assessment

The following information was extracted from each study by 3 independent authors and a consensus was reached: author, country, publication year, tumor type, cancer size, follow-up time, detection method, and cutoff value. Based on distant metastasis (DM), tumor size, and cancer node metastasis stage, the number of patients was divided for each group, and the number of patients with high or low FOXP4-AS1 expression in each group. When the HR with 95% CI was reported in a univariate or multivariate analysis, it was directly extracted from the report (https://sourceforge.net/projects/digitizer/).[17] We used Engauge Digitizer to calculate HR and 95% CI based on Kaplan–Meier survival curves, and quality assessments for all included studies were based on the Newcastle–Ottawa quality assessment scale, which includes 3 dimensions: selection, comparability, and exposure. Each study was given a score ranging from 0 to 9. A study with a Newcastle–Ottawa quality assessment scale score of ≥6 was considered to be of high quality.[18]

2.3. Statistical analyses

All statistical analyses of the data were performed using Review Manager (RevMan) 5.3 software and Stata/SE 16.1 software. Sensitivity analysis was performed by omitting the literature one by one to determine whether the results were stable, and the publication bias of this meta-analysis was evaluated using the Begg test according to Stata/SE 16.1 software. The Q test and I^2 statistics were applied to estimate the heterogeneity of the results. A fixed-effects model was selected when an $I^2 < 50\%$ was observed. The synthetic estimate was calculated based on the random-effects model when heterogeneity was evident ($I^2 > 50\%$). Statistical significance was set at $P < .05$.

Table 1

The main characteristics of the eligible literatures included in the meta-analysis.

Study	Region	Tumor type	Sample size	TNM stage	FOXP4-AS1 expression		Cutoff value	Detection method	Outcome measure	NOS
					High	Low				
Wang et al 2019[12]	China	HCC	213	I-IV	137	76	Median	qRT-PCR	OS, DFS	8
Liang et al 2021[19]	China	HCC	121	I-IV	76	45	Median	qRT-PCR	OS, DFS	7
Yao et al 2021[14]	China	NPC	166	NA	83	83	Median	qRT-PCR	OS, DFS	7
Tao et al 2020[20]	China	MCL	60	I-IV	30	30	Median	qRT-PCR	OS, DFS	8
Shi et al 2021[13]	China	CRC	448	NA	NA	NA	Median	qRT-PCR	OS	6
Yang et al 2018[21]	China	OS	120	NA	60	60	Median	qRT-PCR	OS, DFS	7

CRC = colorectal cancer, HCC = hepatocellular carcinoma, MCL = mantle cell lymphoma, NOS = Newcastle–Ottawa Quality Assessment Scale, NPC = nasopharyngeal carcinoma, qRT-PCR = quantitative real-time fluorescent polymerase chain reaction.

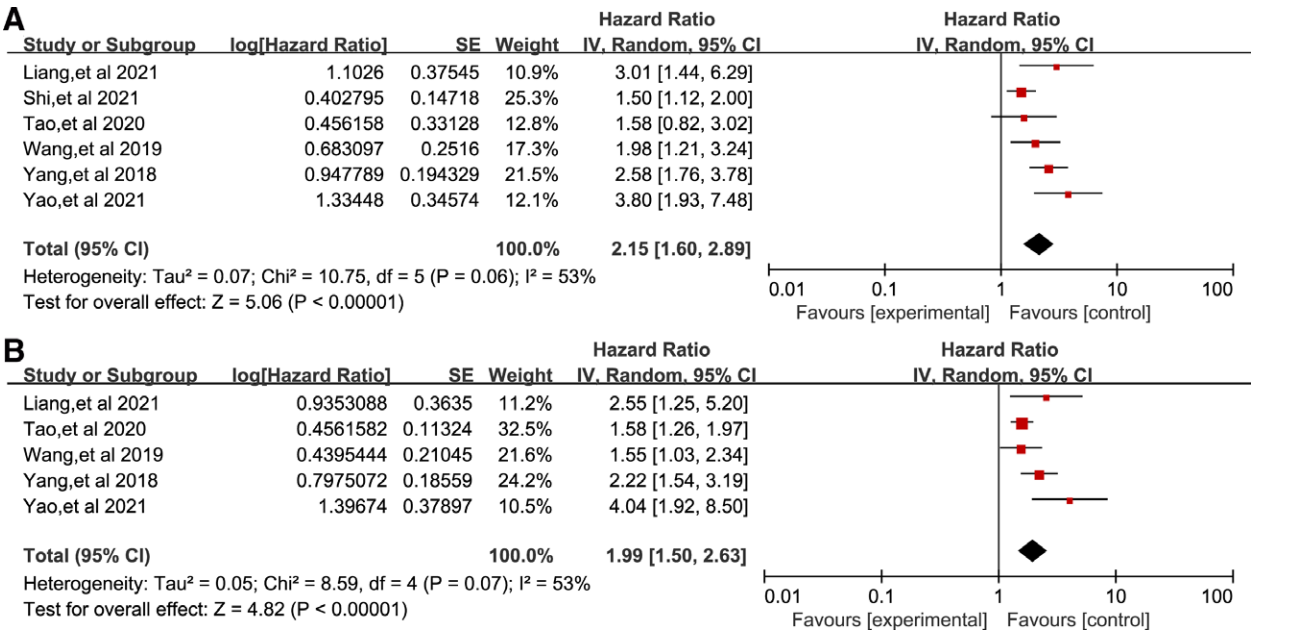

Figure 2. Forest plots for the association between lncRNA FOXP4-AS1 expression with OS (A) and DFS (B). DFS = disease-free survival, FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA, OS = overall survival.

3. Results

3.1. Literature search and selection

After the preliminary online search, the investigators retrieved 110 relevant studies from electronic databases. After the removal of duplicates, 57 studies were excluded. After thorough screening of titles and abstracts, 14 publications were included. After carefully assessing the full texts, 6 studies published between 2018 and 2021 were included in the present meta-analysis. The literature screening process is shown in Figure 1. These eligible studies included 1128 patients. In the present meta-analysis, a variety of tumor types were reported, including HCC,[12,19] NPC,[14] mantle cell lymphoma (MCL),[20] colorectal cancer,[13] and osteosarcoma.[21] The expression of lncRNA FOXP4-AS1 in these included studies was quantified using real-time fluorescent PCR. The median was selected as the cutoff value to distinguish between high and low expression of lncRNA FOXP4-AS1. Six eligible studies used the OS to estimate patient survival. The detailed clinical characteristics of the patients are summarized in Table 1.

3.2. Lncrna FOXP4-AS1 expression is highly correlated with OS and disease-free survival (DFS)

Overall, all the included studies investigated cancer prognosis. A total of 1128 patients were assessed for HR and 95% CI for OS. A random-effects model was used to analyze the pooled HR, and its 95% CI depended on obvious heterogeneity (P = .06, I^2 = 53%). We further elucidated the relationship between FOXP4-AS1 expression and OS, as illustrated in Figure 2. The pooled results revealed that high expression of lncRNA FOXP4-AS1 was related to poor prognosis of cancers (HR = 1.99, 95% CI:1.65–2.39, P < .00001, Fig. 2A). In terms of DFS, 5 studies were included, and the pooled results indicated that patients with high expression of lncRNA FOXP4-AS1 had poor DFS (HR = 1.81, 95% CI:1.54–2.13, P < .00001, Fig. 2B). Thus, the prognosis of cancer patients with lncRNA FOXP4-AS1 overexpression was worse than that of patients with low lncRNA FOXP4-AS1 expression. These results indicate that lncRNA FOXP4-AS1 may be a factor in predicting the prognosis of cancer patients.

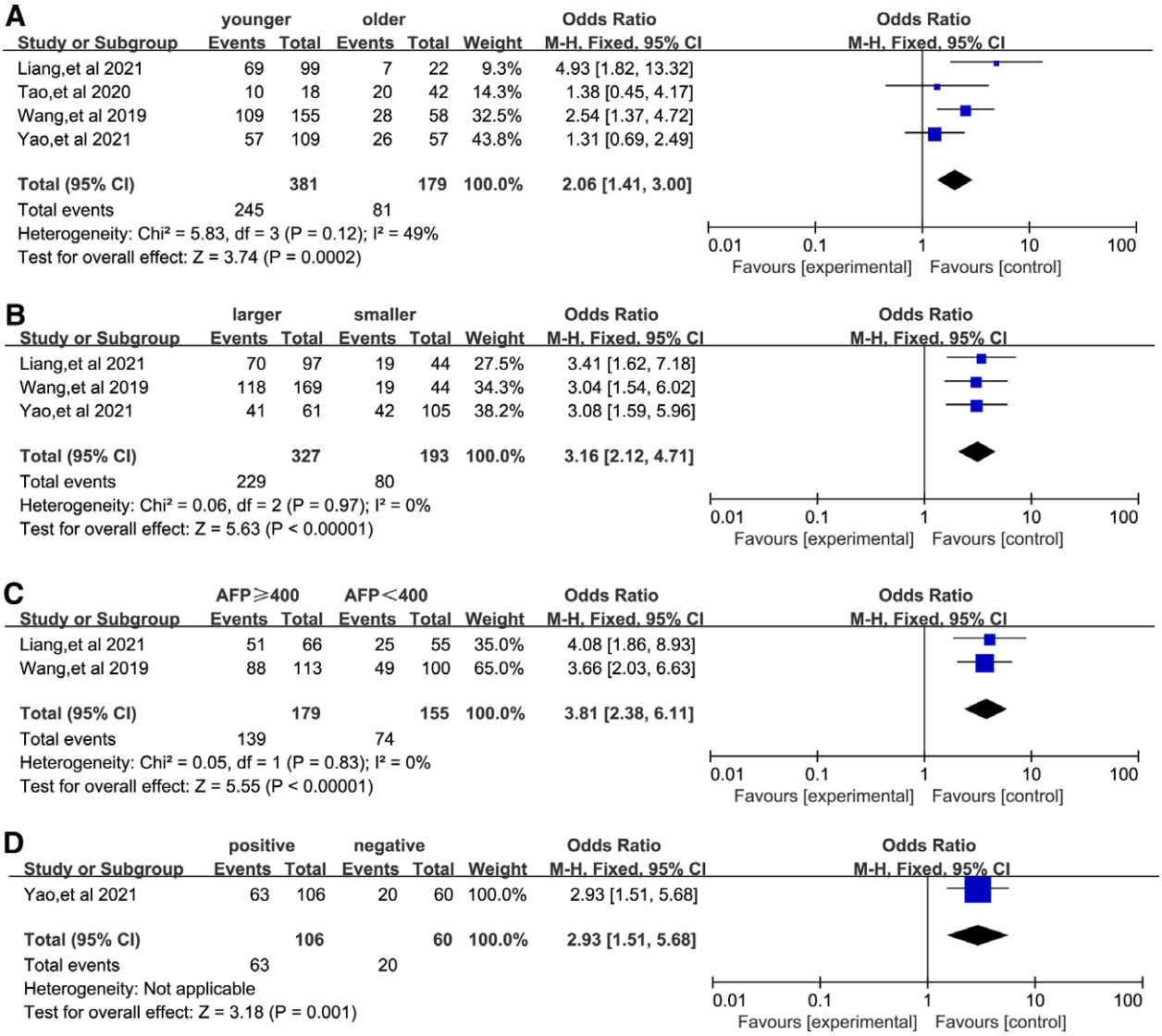

Figure 3. Forest plots for the correlation between lncRNA FOXP4-AS1 expression and clinicopathological characteristics: age (A), tumor size (B), AFP (C), lymph node metastasis (D). AFP = alpha-fetoprotein, FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA.

3.3. Relationship between lncRNA FOXP4-AS1 expression and clinicopathological characteristics

According to the evaluation of the 6 eligible studies that contained detailed clinicopathological characteristics, it was observed that the elevated expression of lncRNA FOXP4-AS1 positively correlated with tumor size (larger vs smaller) (OR = 3.16, 95%CI: 2.12–4.71, $P < .00001$, Fig. 3B). In particular, the overexpression of lncRNA FOXP4-AS1 was consistent with elevated alpha-fetoprotein (OR = 3.81, 95%CI: 2.38–6.11, $P = .83$, Fig. 3C) in HCC, and the fixed effects model was selected to estimate due to the inconspicuous heterogeneity. The analysis results revealed that the patients with lncRNA FOXP4-AS1 overexpression were more vulnerable to younger (OR = 2.06, 95%CI: 1.41–3.00, $P = .00002$, Fig. 3A) and lymph node metastasis (OR = 2.93, 95%CI: 1.51–5.68, $P = .001$, Fig. 3D) in patients with cancer. However, there were no significant differences between lncRNA FOXP4-AS1 expression and TNM stage (OR = 1.38, 95%CI: 0.42–4.48, $P = .59$, Fig. 4A), DM (OR = 0.84, 95%CI: 0.49–1.45, $P = .54$, Fig. 4B), gender (OR = 1.08, 95%CI: 0.70–1.67, $P = .72$, Fig. 4C), differentiation (OR = 0.91, 95%CI: 0.49–1.67, $P = .76$, Fig. 4D). This information is presented in Table 2.

3.4. Publication bias and sensitivity analysis

This meta-analysis evaluated the publication bias using the Begg test. The results showed no significant publication bias affecting OS analysis (Pr > IzI = 0.368) (Fig. 5). Figure 6 illustrates the sensitivity analysis we conducted to show that the HRs were robust even after removing all the studies individually.

3.5. Validation of the results in the cancer genome atlas (TCGA) dataset

As well, the investigators made use of TCGA dataset to analyze the expression of lncRNA FOXP4-AS1 in the different types of cancers. This database consists of 22 different types of human malignant tumors, including bladder urothelial carcinoma, breast invasive carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, cholangiocarcinoma, colon adenocarcinoma, esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma

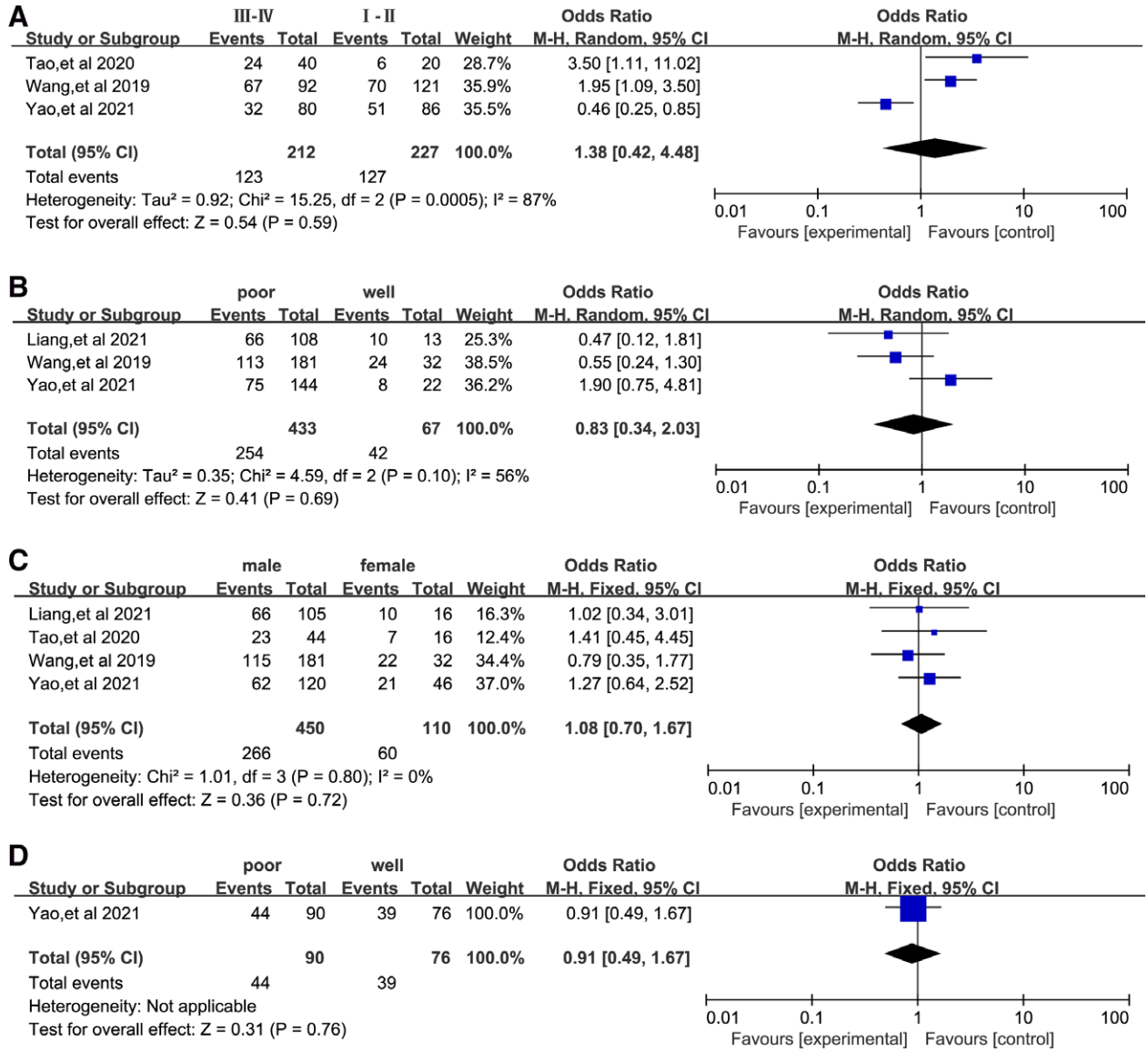

Figure 4. Forest plots for the correlation between lncRNA FOXP4-AS1 expression and clinicopathological characteristics: TNM stage (A), distant metastasis (B), gender (C), and differentiation (D). FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA.

Table 2

The main characteristics of the eligible literatures included in the meta-analysis.

Study	Region	Tumor type	Sample size	TNM stage	FOXP4-AS1 expression		Cutoff value	Detection method	Outcome measure	NOS
					High	Low				
Wang et al 2019[12]	China	HCC	213	I-IV	137	76	Median	qRT-PCR	OS, DFS	8
Liang et al 2021[19]	China	HCC	121	I-IV	76	45	Median	qRT-PCR	OS, DFS	7
Yao et al 2021[14]	China	NPC	166	NA	83	83	Median	qRT-PCR	OS, DFS	7
Tao et al 2020[20]	China	MCL	60	I-IV	30	30	Median	qRT-PCR	OS, DFS	8
Shi et al 2021[13]	China	CRC	448	NA	NA	NA	Median	qRT-PCR	OS	6
Yang et al 2018[21]	China	OS	120	NA	60	60	Median	qRT-PCR	OS, DFS	7

CRC = colorectal cancer, HCC = hepatocellular carcinoma, MCL = mantle cell lymphoma, NOS = Newcastle–Ottawa Quality Assessment Scale, NPC = nasopharyngeal carcinoma, qRT-PCR = quantitative real-time fluorescent polymerase chain reaction.

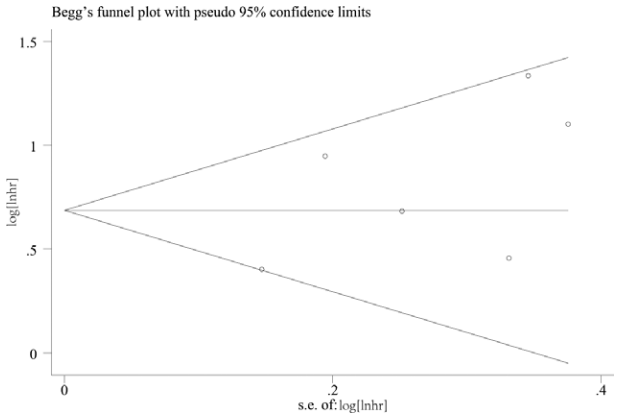

Figure 5. Publication bias assessment of lncRNA FOXP4-AS1expression based on OS. FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA, OS = overall survival.

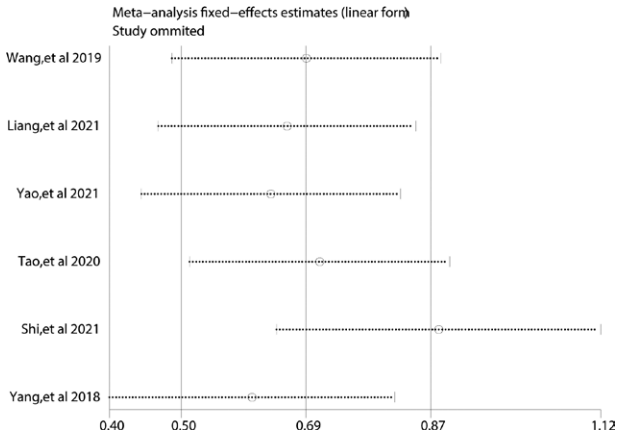

Figure 6. Sensitivity analysis of lncRNA FOXP4-AS1expression based on OS. FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA, OS = overall survival.

(KIRC), kidney renal papillary cell carcinoma (KIRP), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), thymoma (THYM), and uterine corpus endometrial carcinoma (UCEC). As shown in Figure 7, lncRNA FOXP4-AS1 was significantly overexpressed in tumor tissues, especially in patients with COAD, PRAD, READ, and STAD. We found that the expression of lncRNA FOXP4-AS1 in 6 malignant tumors was significantly different in clinical staging, such as KIRP, KIPAN (pan-kidney cohort), HNSC, KIRC, LIHC, and TGCT (testicular germ cell tumors) (Fig. 8). Moreover, the expression of lncRNA FOXP4-AS1 was significantly different in the differentiation of 6 malignant tumors, including ESCA, stomach and esophageal carcinoma (STES), STAD, HNSC, PAAD, and ovarian serous cystadenocarcinoma (OV) (Fig. 9). Additionally, the investigators explored whether lncRNA FOXP4-AS1 expression was associated with the survival and prognosis of cancer patients in the TCGA dataset.

The results revealed that upregulated lncRNA FOXP4-AS1 expression in different types of malignant tumors exhibited negative effects on OS (Fig. 10) and DFS (Fig. 11).

4. Discussion

As is well known, numerous cancers have a poor prognosis because early diagnosis is difficult. A high proportion of patients have an advanced stage of cancer at diagnosis, indicating that tumors have spread to adjacent or distant organs, tissues, and lymph nodes, indicating poor prognosis. Consequently, it is indispensable to develop novel biomarkers that are reliable for predicting cancer patient diagnosis and prognosis.

In recent years, human cancers can be predicted with the help of lncRNAs. The lncRNA FOXP4-AS1, in particular, has generated a lot of interest because accumulating studies suggest that it may play a key role in determining the clinical outcome of different types of cancers.[14] In most studies, there are a limited number of samples; therefore, more evidence is needed regarding the prognostic role of lncRNA FOXP4-AS1, which provides sufficient data for further investigation.

As far as we are aware, this is the first meta-analysis that provides insights regarding the precise role played by lncRNA FOXP4-AS1 in patient survival and clinicopathological parameters. The present study demonstrated that elevated lncRNA FOXP4-AS1 levels were significantly associated with inferior OS and DFS in various cancers, indicating that lncRNA FOXP4-AS1 may serve as an indicator for cancer prognosis, with the potential to support new therapies. On the basis of clinicopathological features, patients with high lncRNA FOXP4-AS1expression are more inclined to have a high risk of tumor growth than those with low lncRNA FOXP4-AS1 expression. Additionally, the inferiority of high lncRNA FOXP4-AS1 expression on alpha-fetoprotein and lymph node metastasis was observed, indicating that lncRNA FOXP4-AS1 overexpression was associated with worse clinicopathological characteristics. However, the high expression of lncRNA FOXP4-AS1 was not

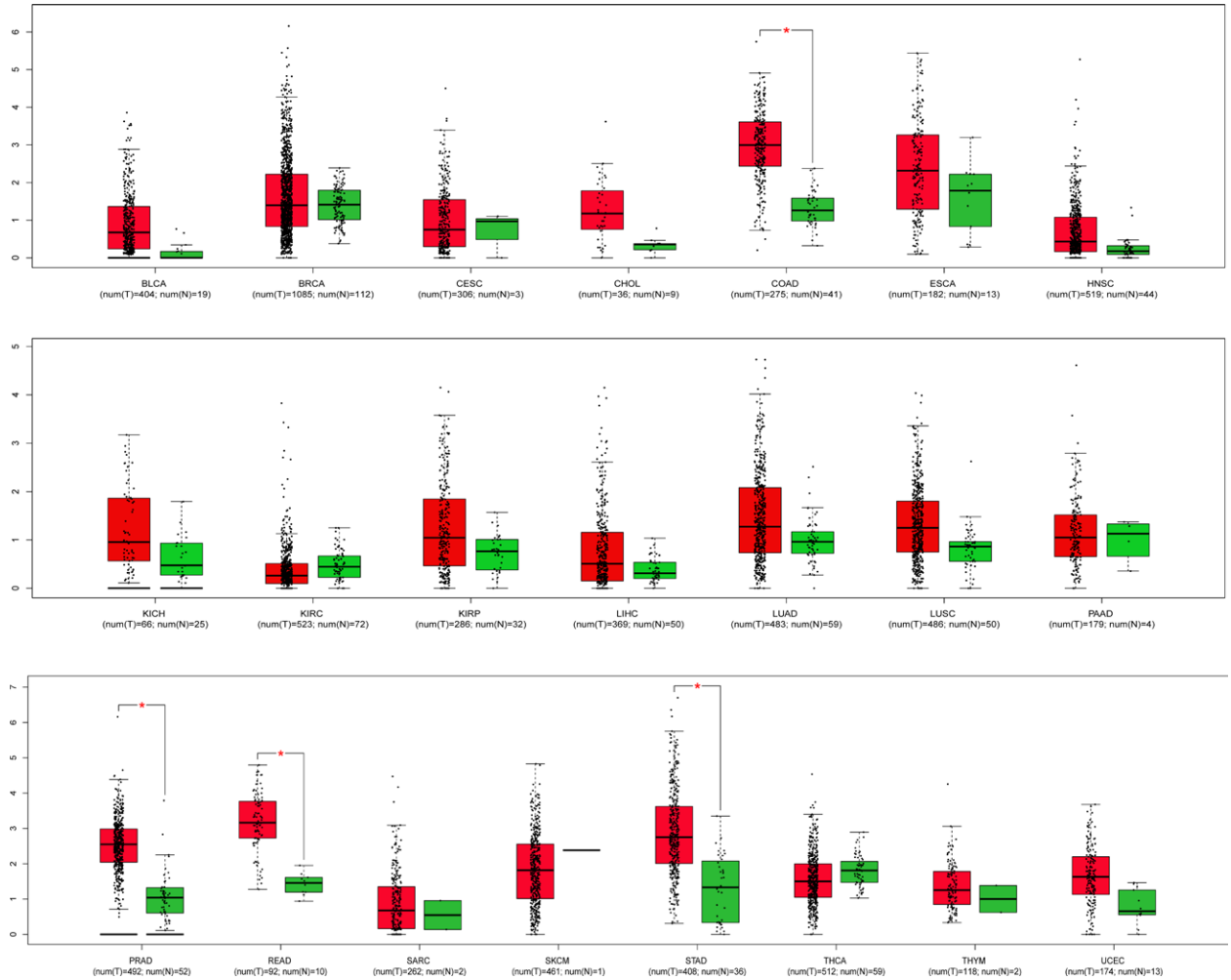

Figure 7. LncRNA FOXP4-AS1 expression in different types of human malignant tumor tissues and corresponding normal tissues. FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA.

associated with gender, DM, differentiation, or tumor node metastasis stage.

In cancers, abnormal expression of the lncRNA FOXP4-AS1 is associated with poor clinical prognosis, and the exact underlying mechanisms still need to be clarified. For accounting this significant association, there are several possible explanations. Wang et al proposed that lncRNA FOXP4-AS1 is involved in HCC development by mediating in the PI3K-Akt signaling Pathway.[12] Tao et al demonstrated that lncRNA FOXP4-AS1 predicts poor prognosis of MCL and accelerates its progression of MCL through the miR-423-5p/NACC1 pathway.[20] Yang et al revealed that the lncRNA FOXP4-AS1 participates in the development and progression of osteosarcoma by downregulating LATS1 via binding to LSD1 and EZH2. Furthermore, overexpression of lncRNA FOXP4-AS1 led to enhanced proliferation, migration, and invasion; shortened the G0/G1 phase; and inhibited the cell cycle.[21] The study of Zhong et al demonstrated that high expression of lncRNA FOXP4-AS1 in NPC portended poor outcomes. LncRNA FOXP4-AS1upregulated STMN1 by interacting with miR-423-5p as a competing endogenous RNA (ceRNA) to promote NPC progression.[22] Wu et al confirmed that the lncRNA FOXP4-AS1 is activated by PAX5 and promotes the growth of prostate cancer by sequestering miR-3184-5p to upregulate FOXP4.[23] Niu et al's research found that lncRNA FOXP4-AS1, which is upregulated in esophageal squamous cell carcinoma (ESCC), promotes FOXP4 expression by enriching MLL2 and H3K4me3 in the FOXP4 promoter through a "molecular scaffold." Moreover, FOXP4, a transcription factor of β-catenin, promotes the transcription of β-catenin and ultimately leads to malignant progression of ESCC.[24] Liu et al found that lncRNA FOXP4-AS1 may function in pancreatic ductal adenocarcinoma (PDAC) by participating in biological processes and pathways, including oxidative phosphorylation, tricarboxylic acid cycle, and classical tumor-related pathways such as NF-kappaB and Janus kinase/signal transducers, in addition to activators of transcription, cell proliferation, and adhesion.[25] Activation of DNA repair is one of the reasons for chemoresistance, and the myc-pathway has been associated with the acquisition of temozolomide resistance in glioblastoma through a c-Myc–miR-29c–REV3L network.[26] Through pathway analysis, Huang et al suggested that the DNA repair/MYC gene set is enriched in low-grade glioma patients with high expression of lncRNA FOXP4-AS1. Therefore, overexpression of lncRNA FOXP4-AS1may may affect temozolomide the prognosis of cancer. However, this result needs to be further explored.[27]

It is noteworthy that the present study had some limitations. First, only English language reports have been considered, so we might have missed important studies published in other languages, and the studies included were all from China, and the results may best reflect the clinical characteristics of Asian cancer patients. Second, considering the

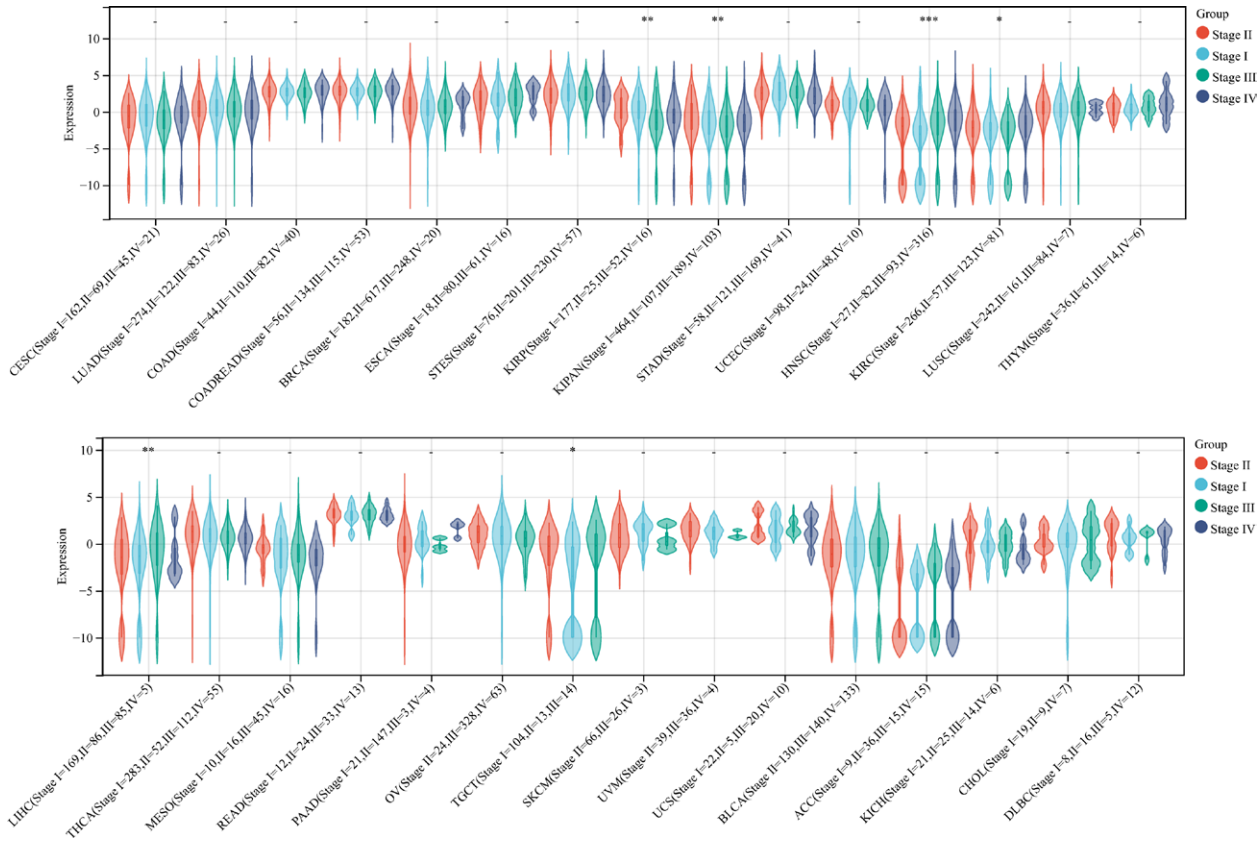

Figure 8. LncRNA FOXP4-AS1 expression in clinical stage of human malignancies. FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA.

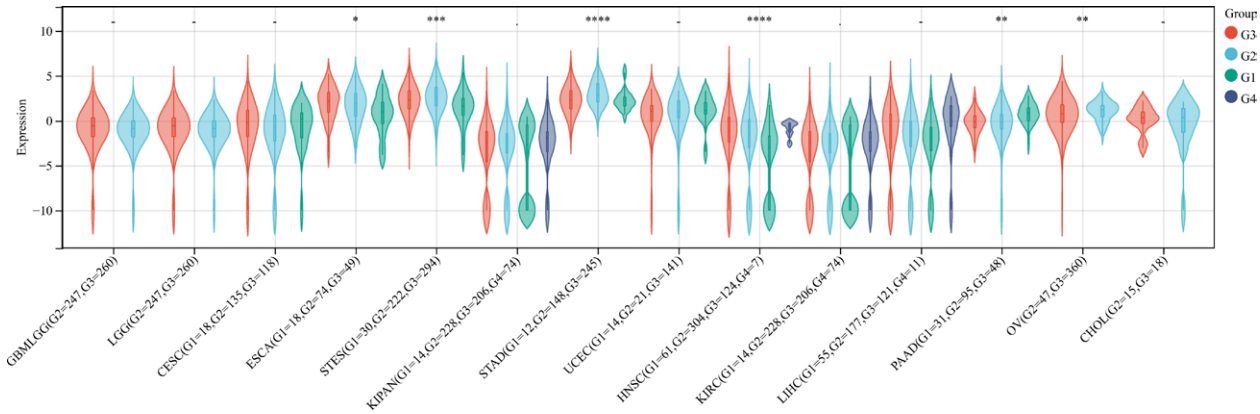

Figure 9. LncRNA FOXP4-AS1 expression in the differentiation grade of human malignancies. FOXP4-AS1 = forkhead box P4 antisense RNA 1, LncRNA = long non-coding RNA.

relatively small number of samples in the literature, it is still necessary to investigate a single tumor type in a larger number of samples, and additional studies are needed to assess DFS and PFS. Due to this, potential publication bias is very likely to exist, despite the lack of evidence from our statistical tests. In the end, the HRs and 95%CIs were extracted by the indirect method, which was inevitably biased. Therefore, it is necessary to increase the number of high quality studies that contain a large number of samples to avoid the various factors in the compound.

5. Conclusions

We conducted the first systematic review and estimation of the relationship between abnormal lncRNA FOXP4-AS1 expression and survival and clinical outcomes in patients with tumors. Based on our results, high expression levels of lncRNA FOXP4-AS1 were associated with poor OS and DFS, making this gene a potential prognostic biomarker. Given the limitations of this study, a more large-scale, high-quality study on a variety of ethnic populations is necessary to assess the value of lncRNA FOXP4-AS1 in tumors.

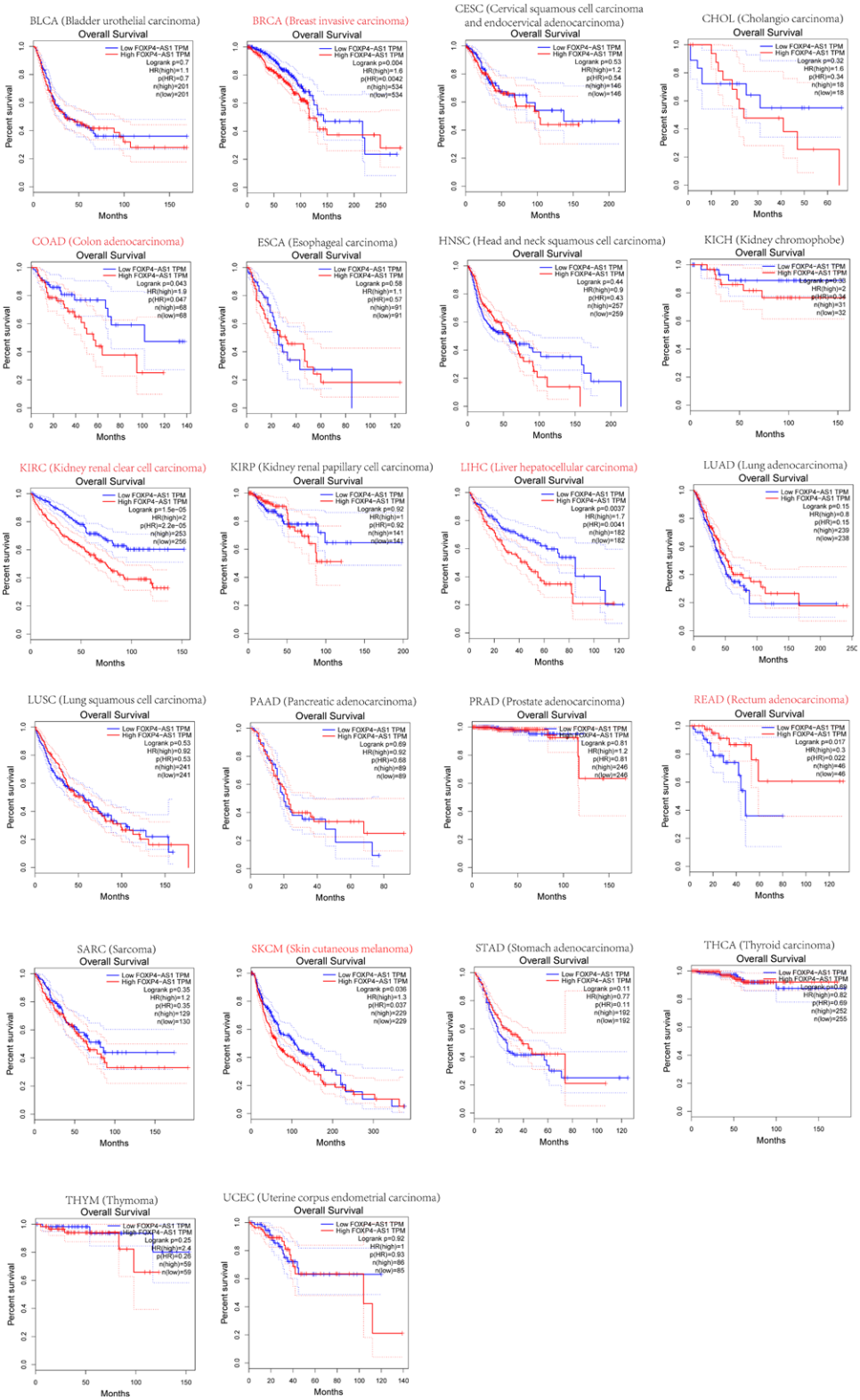

Figure 10. Kaplan–Meier plotter of OS for 22 types of human malignancies. OS = overall survival.

Author contributions

Conceptualization: Qiang Shu, Fei Xie.
Data curation: Xiaoling Liu, Jushu Yang.
Formal analysis: Xiaoling Liu.
Funding acquisition: Fei Xie.
Investigation: Xiaoling Liu, Jushu Yang, Tinggang Mou.
Methodology: Qiang Shu, Xiaoling Liu, Jushu Yang, Tinggang Mou.
Project administration: Qiang Shu, Fei Xie.
Software: Tinggang Mou.
Supervision: Fei Xie.
Writing – original draft: Qiang Shu.
Writing – review & editing: Qiang Shu.

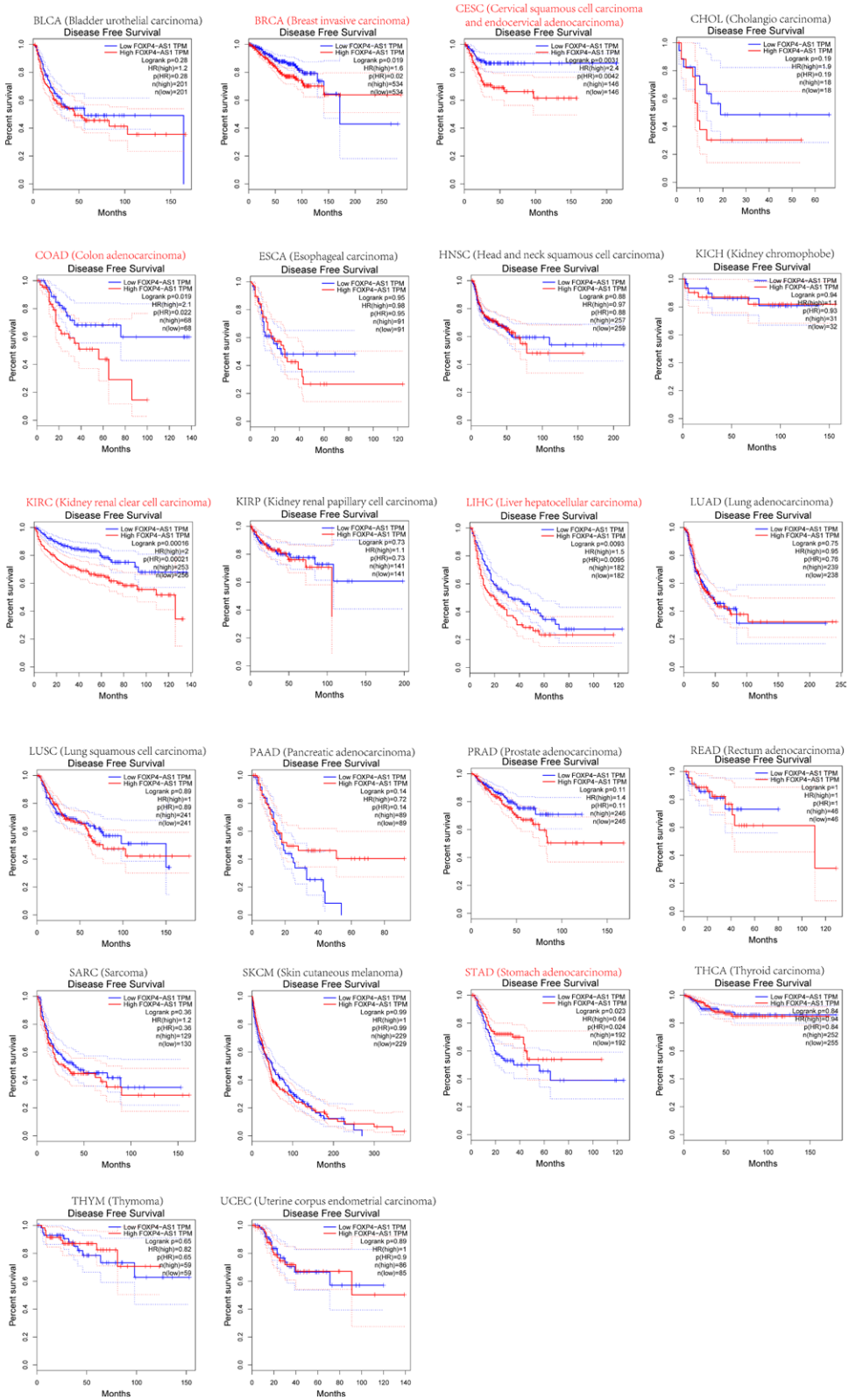

Figure 11. Kaplan–Meier plotter of DFS for 22 types of human malignancies. DFS = disease-free survival.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359–86.

[2] Mattiuzzi C, Lippi G. Current cancer epidemiology. J Epidemiol Glob Health. 2019;9:217–22.

[3] Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem. 2012;81:145–66.

[4] Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs. Nature. 2012;482:339–46.

[5] Ding LJ, Li Y, Wang SD, et al. Long noncoding RNA lncCAMTA1 promotes proliferation and cancer stem cell-like properties of liver cancer by inhibiting CAMTA1. Int J Mol Sci. 2016;17:1617.

[6] Shan Z, An N, Qin J, et al. Long non-coding RNA Linc00675 suppresses cell proliferation and metastasis in colorectal cancer via acting on miR-942 and Wnt/β-catenin signaling. Biomed Pharmacother. 2018;101:769–76.
[7] Li Z, Li Y, Wang Q. LINC00675 is a prognostic factor and regulates cell proliferation, migration and invasion in glioma. Biosci Rep. 2018;38:BSR20181039.
[8] Huo H, Tian J, Wang R, et al. Long non-coding RNA NORAD upregulate SIP1 expression to promote cell proliferation and invasion in cervical cancer. Biomed Pharmacother. 2018;106:1454–60.
[9] Peng W, He D, Shan B, et al. LINC81507 act as a competing endogenous RNA of miR-199b-5p to facilitate NSCLC proliferation and metastasis via regulating the CAV1/STAT3 pathway. Cell Death Dis. 2019;10:533.
[10] Liu FT, Qiu C, Luo HL, et al. The association of HOTAIR expression with clinicopathological features and prognosis in gastric cancer patients. Panminerva Med. 2016;58:167–74. Epub 2016 Mar 10.
[11] Liu FT, Dong Q, Gao H, et al. The prognostic significance of UCA1 for predicting clinical outcome in patients with digestive system malignancies. Oncotarget. 2017;8:40620–32.
[12] Wang D, Bai T, Chen G, et al. Upregulation of long non-coding RNA FOXP4-AS1 and its regulatory network in hepatocellular carcinoma. Onco Targets Ther. 2019;12:7025–38.
[13] Shi ZL, Zhou GQ, Guo J, et al. Identification of a prognostic colorectal cancer model including LncRNA FOXP4-AS1 and LncRNA BBOX1-AS1 based on bioinformatics analysis. Cancer Biother Radiopharm. 2021.
[14] Yao L, Wang T, Wang X. LncRNA FOXP4-AS1 serves as a biomarker for nasopharyngeal carcinoma diagnosis and prognosis. 3 Biotech. 2021;11:25.
[15] Zhao J, Yang T, Li L. LncRNA FOXP4-AS1 is involved in cervical cancer progression via regulating miR-136-5p/CBX4 axis. Onco Targets Ther. 2020;13:2347–55.
[16] Li J, Lian Y, Yan C, et al. Long non-coding RNA FOXP4-AS1 is an unfavourable prognostic factor and regulates proliferation and apoptosis in colorectal cancer. Cell Prolif. 2017;50:e12312.
[17] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
[18] Oremus M, Oremus C, Hall GB, et al. Inter-rater and test-retest reliability of quality assessments by novice student raters using the Jadad and Newcastle-Ottawa Scales. BMJ Open. 2012;2:e001368.
[19] Liang J, Wang D, Qiu G, et al. Long noncoding RNA FOXP4-AS1 predicts unfavourable prognosis and regulates proliferation and invasion in hepatocellular carcinoma. Biomed Res Int. 2021;2021:8850656.
[20] Tao HF, Shen JX, Hou ZW, et al. lncRNA FOXP4-AS1 predicts poor prognosis and accelerates the progression of mantle cell lymphoma through the miR-423-5p/NACC1 pathway. Oncol Rep. 2021;45:469–80.
[21] Yang L, Ge D, Chen X, et al. FOXP4-AS1 participates in the development and progression of osteosarcoma by downregulating LATS1 via binding to LSD1 and EZH2. Biochem Biophys Res Commun. 2018;502:493–500.
[22] Zhong LK, Zhou J, He X, et al. Long non-coding RNA FOXP4-AS1 acts as an adverse prognostic factor and regulates proliferation and apoptosis in nasopharyngeal carcinoma. Eur Rev Med Pharmacol Sci. 2020;24:8008–16.
[23] Wu X, Xiao Y, Zhou Y, et al. LncRNA FOXP4-AS1 is activated by PAX5 and promotes the growth of prostate cancer by sequestering miR-3184-5p to upregulate FOXP4. Cell Death Dis. 2019;10:472.
[24] Niu Y, Wang G, Li Y, et al. LncRNA FOXP4-AS1 promotes the progression of esophageal squamous cell carcinoma by interacting with MLL2/H3K4me3 to upregulate FOXP4. Front Oncol. 2021;11:773864.
[25] Liu XG, Xu H, Chen M, et al. Identify potential clinical significance of long noncoding RNA forkhead box P4 antisense RNA 1 in patients with early stage pancreatic ductal adenocarcinoma. Cancer Med. 2020;9:2062–76.
[26] Luo H, Chen Z, Wang S, et al. c-Myc-miR-29c-REV3L signalling pathway drives the acquisition of temozolomide resistance in glioblastoma. Brain. 2015;138:3654–72.
[27] Huang Y, Ling A, Pareek S, et al. Oncogene or tumor suppressor? Long noncoding RNAs role in patient's prognosis varies depending on disease type. Transl Res. 2021;230:98–110.