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Prognostic Role of Long Noncoding RNA BANCR in Solid Tumors: A Meta-Analysis

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Abstract

Accumulating studies have reported that long noncoding RNA BRAF-activated nonprotein coding RNA plays vital role in various cancers. However, the prognostic values of BRAF-activated nonprotein coding RNA in solid tumors remain controversial. Thus, we assessed the prognostic values of BRAF-activated nonprotein coding RNA by this meta-analysis. We comprehensively searched PubMed, Web of Science, Medline, China National Knowledge Infrastructure (CNKI), and the Cochrane Library at November 2016. After carefully screening, we ultimately included 14 studies in this meta-analysis. This meta-analysis brought all relevant articles into determining the association of BRAF-activated nonprotein coding RNA expression with overall survival and clinicopathologic features. The results showed that high BRAF-activated nonprotein coding RNA expression significantly shorten the overall survival of solid tumors (pooled hazard ratios 1.66, 95% confidence interval: 1.19-2.32). Moreover, high BRAF-activated nonprotein coding RNA expression was also strongly associated with advanced tumor stage (odds ratios = 2.57, 95% confidence interval: 1.14-5.79), differentiation grade (odds ratio = 1.71, 95% confidence interval: 1.26-2.31), lymph node metastasis (odds ratio = 2.67, 95% confidence interval: 1.93-3.70, $P < .001$), and distant metastasis (odds ratio = 2.98, 95% confidence interval: 1.76-5.07, $P = .02$). In conclusion, this meta-analysis demonstrated that high BRAF-activated nonprotein coding RNA expression may be a potential novel biomarker for indicating a poor prognosis and progression in human solid tumors.

Keywords

lncRNA, BANCR, prognosis, clinicopathologic features, solid tumors

Abbreviations

BANCR, BRAF-activated nonprotein coding RNA; CI, confidence interval; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; lncRNA, long noncoding RNA; OR, odds ratio; OS, overall survival

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Introduction

Cancer is one of the major public health problems worldwide.[1] Many patients with cancer are diagnosed at a later stage, significantly reducing the survival rate of patients.[2] Since early diagnosis and accurate prognosis analysis are the fundamental premise to improve the survival rate of patients, it is urgent to find more effective prognostic biomarkers to predict prognosis and provide better and more suitable therapy for patients with cancer.

Long noncoding RNAs (lncRNAs) are a class of noncoding transcripts longer than 200 nucleotides.[3] Accumulating evidences indicate that lncRNAs play tremendous roles in epigenetics and biological processes, including cell proliferation, differentiation, apoptosis, and migration.[4-6] Long noncoding RNAs are abnormally expressed in the various cancers, functioning as oncogenes or tumor suppressors.[7] Moreover, recent studies show that lncRNA plays a vital role in prognosis and metastasis of patients with cancer.[8,9] Zhou *et al* reported lncRNA signatures had important clinical implications to

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predict prognosis for patients with glioblastoma and diffuse large B-cell lymphoma.[10,11] Besides, Liu *et al* reported that high expression of lncRNA H19 was positively correlated with poor prognosis and metastasis.[12]

BRAF-activated noncoding RNA (BANCR), located at chromosome 9, was originally found in melanoma cells.[13] Li *et al* confirmed that BANCR could promote proliferation in malignant melanoma by regulating mitogen-activated protein kinase (MAPK) pathway activation.[14] Subsequent studies reported that BANCR was aberrantly expressed in various solid tumors, such as lung cancer,[15-17] hepatocellular carcinoma (HCC),[18] gastric cancer (GC),[19,20] papillary thyroid carcinoma,[21] and colorectal cancer (CRC).[22] Although most studies indicated that high BANCR expression had an association with poor prognosis of patients with cancer, 1 study reported that low BANCR expression was associated with worse prognosis for patients with lung cancer.[16] The precise prognostic role of BANCR in solid tumors remains controversial. Moreover, these studies investigating the prognostic role of BANCR are limited by small sample size. Therefore, we performed this meta-analysis to investigate the prognostic value and clinical significance of BANCR in human solid tumors.

Materials and Methods

Search Strategy

PubMed, Web of Science, Medline, CNKI, and the Cochrane Library were systematically searched. The search strategy used both Medical Subject Headings (MeSH) terms and free-text words to increase sensitivity. The following search terms were used: "BRAF-activated non-protein coding RNA," "BANCR," and "LINC00586." Additionally, we screened the references of retrieved relevant articles to identify potentially eligible literatures.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) the BANCR expression was evaluated in human cancer tissues, (2) the relationship between the expression of BANCR and clinicopathologic features or prognosis was described; and (3) the articles must provide sufficient data to calculate the hazard ratios (HR) and 95% confidence interval (CI) for prognosis or odds ratios (OR) and 95% CI for clinicopathologic features. Exclusion criteria were as follows: (1) studies of letters, editorials, expert opinions, case reports, and reviews; (2) duplicate publications.

Data Extraction

Two investigators extracted the data independently by the same standard and the following information were extracted: first author, publication year, country of origin, cancer type, total number of patients, correlation between BANCR expression and clinicopathologic characteristics, and the HR and the corresponding 95% CI or survival curve for overall survival (OS).

Quality Assessment

The quality assessment is an important component of a thorough meta-analysis. Two investigators independently performed this quality assessment. The NOS criteria included 3 aspects of studies: (1) selection: 0 to 4; (2) comparability: 0 to 2; and (3) outcome: 0 to 3.[23] The total Newcastle-Ottawa Scale (NOS) scores were ranged from 0 to 9.

Statistical Analysis

All analyses were performed using the STATA software version 11.0 and Cochrane Collaboration Review Manager Version 5.2. The HRs and 95% CI were used to evaluate the association between BANCR expression and OS. The ORs and 95% CI were used to evaluate the relationship between BANCR expression and clinicopathologic features. We extracted the HRs and 95% CI according to the following methods: (1) the HRs and 95% CI were obtained directly from the articles; (2) the HRs and 95% CI were calculated by the total number of events or survival rate and the *P* value in the articles; and (3) we estimated the HRs and 95% CI by extracting several survival rates at specified times from the Kaplan-Meier survival curves.[24] The observed HR > 1 implied a poorer survival for the group with high expression of BANCR, and the observed HR < 1 implied a better survival for the group with high expression of BANCR.

To investigate the heterogeneity among studies, I^2 statistics and χ^2 Q test were used. When I^2 value more than 50% and a P value less than.05 for Q test, heterogeneity was regarded as significant. Fixed-effects model was used when there was no significant heterogeneity between studies. Otherwise, the random-effects model was used. The meta-regression and subgroup analysis were performed by cancer type, number of patients, survival analysis method, and NOS scores. We also performed sensitivity analysis to test the stability of the pooled results. Begg test and funnel plot were applied for assessing the publication bias.[25] Statistical significance was defined when a P value is less than .05.

Results

Study Selection and Characteristics

As shown in the flow diagram (Figure 1), the electronic search acquired 158 records from PubMed, Web of Science, Medline, CNKI, and the Cochrane Library. A total of 125 irrelevant studies or duplicates were excluded by screening titles and abstracts. Then, after assessing the full text, we ultimately included 14 studies in the final analysis.[14,16,18,19,21,26-34] Among the included studies, 9 studies were enrolled to analyze the prognostic role of BANCR in human solid tumors, and 11 studies were employed to evaluate the association of high BANCR expression with clinicopathologic features.

The main characteristics of studies were included in Table 1. The 14 studies included a total of 1383 patients, with sample sizes ranging from 54 to 184 patients. Ten different types of

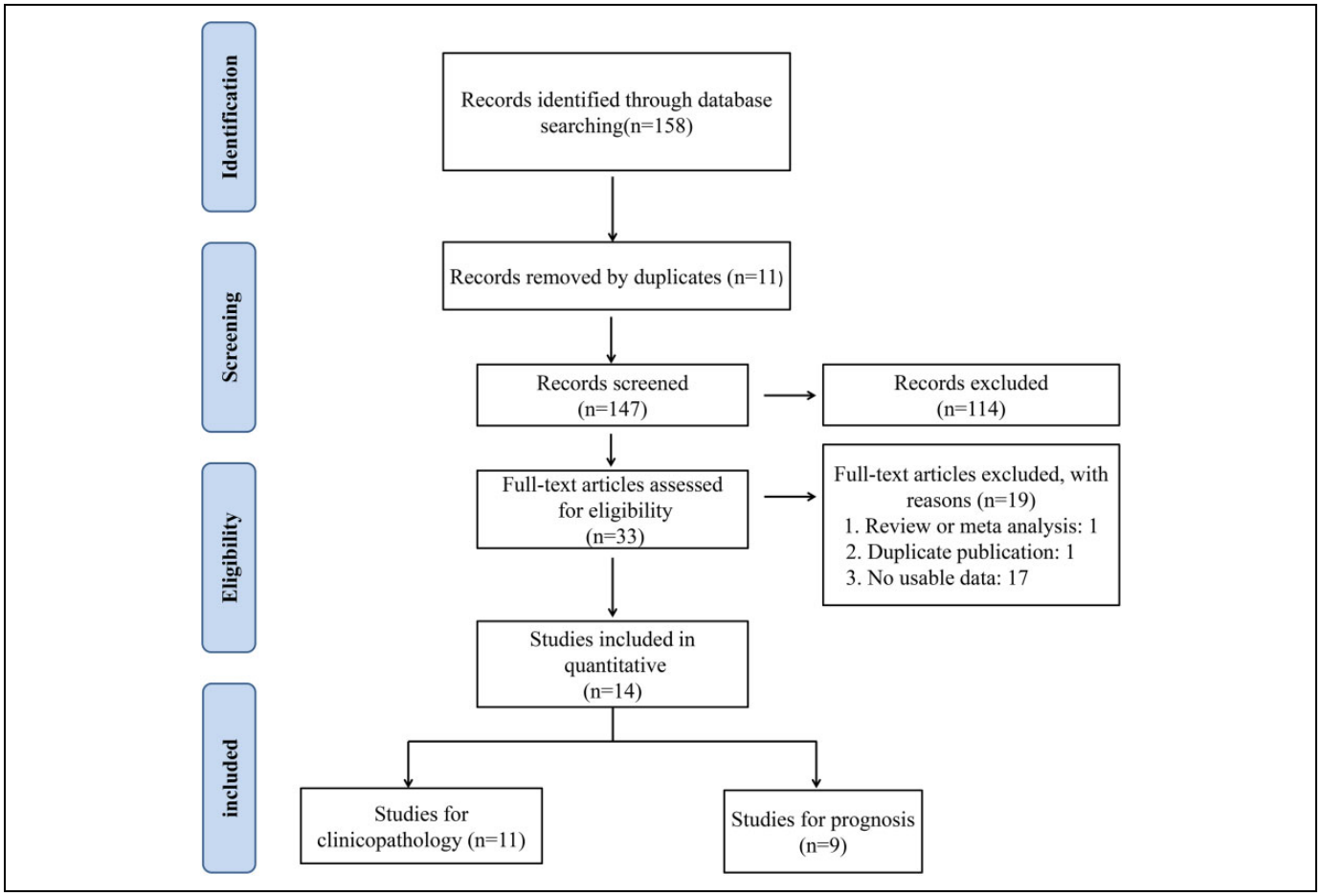

Figure 1. The flow diagram of this meta-analysis.

Table 1. Characteristics of Studies in This Meta-Analysis.

Author	Year	Country	Cancer Type	Sample	High Expression	Low Expression	Method	Cutoff	Outcome	Survival Analysis	HR	NOS Score
Li	2014	China	Melanoma	72	36	36	qRT-PCR	Median	OS	Univariate	Calculated	6
Sun	2014	China	NSCLC	113	53	60	qRT-PCR	Fold change = 4	OS	Multivariate	Reported	7
Zhou	2016	China	HCC	109	54	55	qRT-PCR	Median	OS	Multivariate	Reported	8
Li	2015	China	GC	184	92	92	qRT-PCR	Median	OS	Multivariate	Reported	8
Liao	2016	China	PTC	92	29	63	qRT-PCR	Mean	-	-	-	7
He	2016	China	BC	54	19	35	qRT-PCR	Fold change = 1	-	-	-	6
Liu	2016	China	ESCC	142	-	-	qRT-PCR	Median	OS	Univariate	Survival curve	6
Su	2015	China	Rb	60	30	30	qRT-PCR	Median	OS	Multivariate	Reported	8
Guo	2014	China	CRC	60	18	42	qRT-PCR	Mean	-	-	-	8
Zi	2016	China	ESCC	142	71	71	qRT-PCR	Median	OS	Multivariate	Reported	8
Peng	2016	China	Osteosarcoma	84	42	42	qRT-PCR	Median	OS	Multivariate	Reported	7
Qin	2014	China	CRC	56	28	28	qRT-PCR	Median	-	-	-	7
Wang	2016	China	HCC	108	43	65	qRT-PCR	Mean	-	-	-	8
Wang	2016	China	CRC	107	-	-	qRT-PCR	-	OS	Univariate	Reported	7

Abbreviations: BC, bladder cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PTC, papillary thyroid carcinoma; qRT-PCR, quantitative real-time polymerase chain reaction; Rb, retinoblastoma.

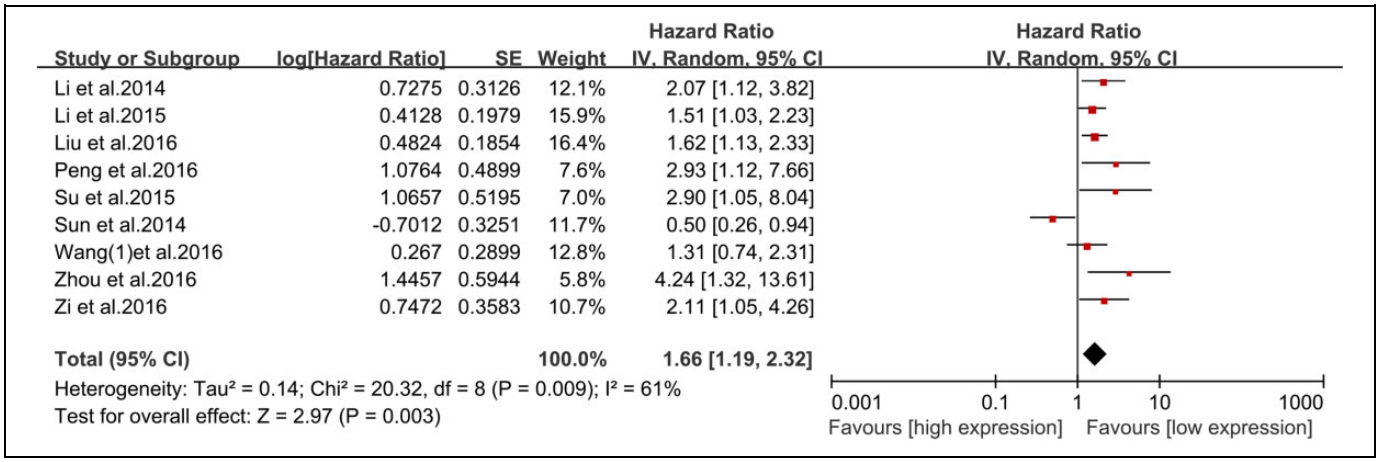

Figure 2. Forest plot for the association between BANCR expression and overall survival in solid tumors. BANCR indicates BRAF-activated nonprotein coding RNA.

Table 2. Subgroup Analysis and Meta-Regression of the Studies Reporting the Association of High BANCR Expression and Overall Survival of Cancer.

Stratified Analysis	No. of Studies	No. of Patients	Pooled HR (Random Effect Model)	95% CI of Pooled HR	Meta-Regression, *P* Value	Heterogeneity	
						I^2 (%)	*P* Value
Tumor type					.768		
Digestive system cancers	5	684	1.63	1.30-2.04		0	.43
Nondigestive system cancers	4	329	1.64	0.67-4.04		81	.001
No. of patients					.213		
>100	6	797	1.43	1.16-1.77		68	.008
<100	3	216	2.40	1.52-3.81		0	.77
Survival analysis					.857		
Multivariate	6	692	1.79	0.99-3.22		74	.002
Univariate	3	321	1.62	1.23-2.13		0	.56
NOS score					.881		
≥7	7	799	1.66	1.03-2.68		69	.004
<7	2	214	1.73	1.26-2.36		0	.50

Abbreviations: BANCR, BRAF-activated noncoding RNA; CI, confidence interval; HR, hazard ratio.

cancer were included in this analysis. In all of included studies, the patients were divided into high-expression group and low-expression group according to the expression of BANCR. The NOS scores were from 6 to 8. All studies used qRT-PCR to measure the expression of BANCR. All diagnoses were based on pathology.

Associations Between BANCR Expression and Prognosis

Nine studies investigated the association between BANCR expression and OS in a total of 1013 patients. The random-effects model was used as the significant heterogeneity ($I^2 = 61\%$, $P = .009$). The meta-analysis showed that the HR, expressed as the high BANCR expression group versus the low BANCR expression group, was 1.66 (95% CI: 1.19-2.32, $P = .003$, Figure 2). The result indicated high BANCR expression was associated with worse prognosis for human solid tumors.

Aiming to investigate the source of heterogeneity, subgroup analysis and meta-regression were performed by cancer type, number of patients, survival analysis method, and NOS scores (Table 2).The significant relationship between high BANCR expression and poor prognosis were also observed in digestive system cancers (HR = 1.63, 95% CI: 1.30-2.04, $P < .001$), whereas the result in nondigestive system cancers indicated no statistical significance. Subgroup analysis on other factors including number of patients and NOS scores did not alter the significant prognostic impact of high BANCR expression. However, the subgroup analysis and meta-regression did not remove the significant heterogeneity, the source of heterogeneity were failed to determined.

Associations Between BANCR Expression and Clinicopathologic Features

Eleven studies reported the association between BANCR expression and clinicopathologic features in a total of 1062 patients. According to the heterogeneity, random-effects model or fixed-effects model were used, respectively, to analyze the

Table 3. Meta-Analysis Results of the Associations of High BANCR Expression With Clinicopathological Parameters.

Clinicopathological Parameters	No. of Studies	No. of Patients	Pooled HR (95% CI)	*P* Value	Heterogeneity *I2* (%)	Heterogeneity *P* Value	Model
Gender (male vs female)	11	1062	0.99 (0.66-1.49)	.96	56	.01	Random effects
TNM stage (advanced stage vs early stage)	9	948	2.57 (1.14-5.79)	.02	86	<.001	Random effects
Differentiation grade (poorly vs well/moderately)	8	773	1.71 (1.26-2.31)	.0005	47	.07	Fixed effects
Lymph node metastasis (yes vs no)	7	696	2.67 (1.93-3.70)	<.001	46	.09	Fixed effects
Distant metastasis (yes vs no)	3	410	2.98 (1.76-5.07)	.02	45	.16	Fixed effects

Abbreviations: BANCR, BRAF-activated nonprotein coding RNA; CI, confidence interval; HR, hazard ratio; TNM, Tumor-Node-Metastases.

association between BANCR expression and clinicopathologic features. The results showed that high BANCR expression was significantly associated with advanced tumor stage (OR = 2.57, 95% CI: 1.14-5.79, $P = .02$), differentiation grade (OR = 1.71, 95% CI: 1.26-2.31), lymph node metastasis (OR = 2.67, 95% CI: 1.93-3.70, $P < .001$), and distant metastasis (OR = 2.98, 95% CI: 1.76-5.07, $P = .02$). However, there was no significant association between BANCR and gender (Table 3).

Publication Bias and Sensitivity Analysis

The sensitivity analysis was conducted by omitting any single study in turn from the pooled analysis. The results showed that the pooled HRs had no significant change after removing each study (Figure 3). Thus, this sensitivity analysis confirmed the reliability of our results. When we removed Sun *et al*'s study, the heterogeneity was significantly decreased ($I^2 = 0\%$, $P = .47$).

Publication bias of this meta-analysis was assessed by the Begg test, and the result indicated no significant publication bias ($P > .05$, Figure 4). As shown in the funnel plot, there was no obvious asymmetry.

Discussion

Long noncoding RNAs were previously described to be transcriptional noise or garbage.[35] Recently, increasing studies have reported that lncRNAs were involved in the initiation and progression of cancers.[36] BRAF-activated noncoding RNA is mainly induced by BRAFV600E and could regulate melanoma cell migration by regulating expression of CXCL.[13] Subsequently, many studies focused on the role of BANCR in human solid tumors.[37-39] However, the prognostic role of BANCR in solid tumor still remains controversial. A number of studies reported that high expression of BANCR was associated with poor prognosis of patients with cancer. These studies consistently suggest that BANCR serves as an oncogene, but few studies in suggested BANCR acts as tumor suppressor gene in lung cancer. BRAF-activated noncoding RNA expression was significantly downregulated in lung cancer tissues, and low BANCR expression was associated with worse prognosis in patients with lung cancer. The difference in BANCR between lung cancer and other solid tumors may be attributed to tumor heterogeneity. Moreover, some studies investigating the clinical implications of BANCR are limited by small sample size. The results may be inaccurate due to small sample size. Therefore, we performed this meta-analysis to explore the precise prognostic role and clinical significance of BANCR in human solid tumors.

Most of the included studies come from China. Cancer statistics in China reported that with increasing incidence and mortality, cancer is the leading cause of death in China and a major public health problem.[40] Besides, the 5-year survival rate of patients with cancer in China is still frustrating. The prognosis of patients with cancer in China have been an important health problem. This current status could explain why most of studies were found in China.

In the present study, we combined 9 studies in a total of 1013 patients to investigate the prognosis role of BANCR. The result showed that high BANCR expression was associated with poor prognosis for human solid tumors (HR = 1.66, 95% CI: 1.19-2.32, $P = .003$). Subgroup analysis indicated a similar result was also found in digestive system cancers (HR = 1.63, 95% CI: 1.30-2.04, $P < .001$). Accumulating studies reported that BANCR could promote cell growth, differentiation, and migration in digestive system cancer, such as HCC, GC, CRC, and esophageal squamous cell carcinoma.[18,19,27,29] Our results also confirmed the role of BANCR in digestive system cancer. In addition, high BANCR expression was significantly correlated with advanced tumor stage (OR = 2.57, 95% CI: 1.14-5.79), differentiation grade (OR = 1.71, 95% CI: 1.26-2.31), lymph node metastasis (OR = 2.67, 95% CI: 1.93-3.70), and distant metastasis (OR = 2.98, 95% CI: 1.76-5.07). However, there was no significant association between BANCR and gender. Once the expression of BANCR was remarkably increased, the balance between oncogene and suppressor would be broken. The oncogenes were stirred up and promote tumor cell proliferation, angiogenesis, invasion, and migration. The aggressive behavior would promote progression of patients with cancer, which could explain why high BANCR expression was significantly associated with advanced tumor stage, metastasis, and differentiation grade.

All included studies were nonrandomized studies. The quality assessment by the NOS criteria is an important component of a thorough meta-analysis of nonrandomized studies. We found that the quality scores of included studies were all more

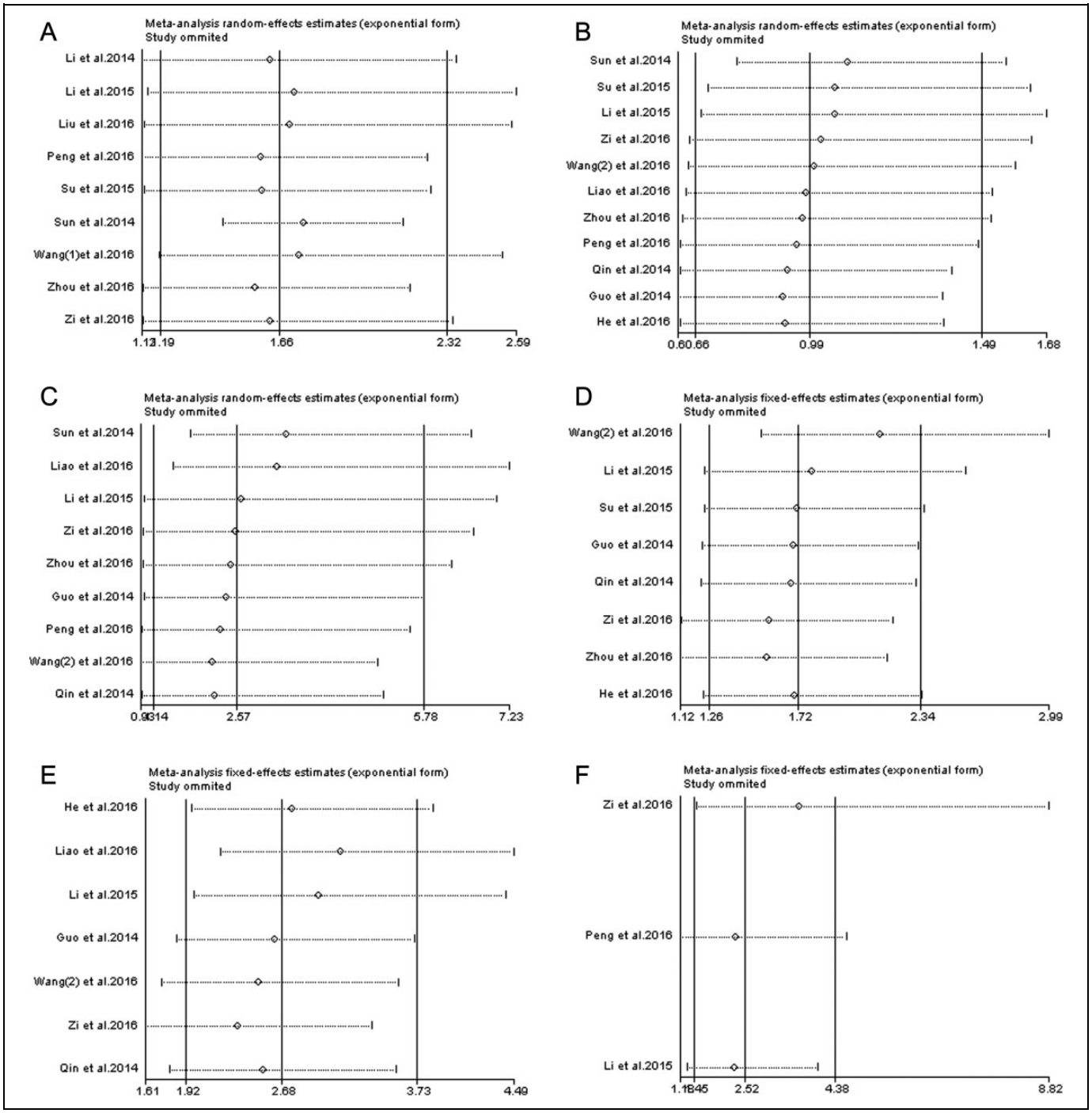

Figure 3. Sensitivity analyses of included studies. A, Prognosis, (B) gender, (C) TNM stage, (D) differentiation grade, (E) lymph node metastasis, and (F) distant metastasis. TNM, Tumor-Node-Metastases.

than 6 scores. The quality assessment suggested indicate that the results of included studies were reliable.

The heterogeneity of included studies in this meta-analysis was significant, but the subgroup analysis and meta-regression was failed to determine the source of heterogeneity. We further performed sensitivity analysis by omitting any single study in turn from the pooled analysis. When we removed Sun *et al*'s study, the heterogeneity was significantly decreased. Thus, we could presume that the main source of heterogeneity derived from Sun *et al*'s study. But when we remove any single study, the results of the pooled analysis remain stable. The sensitivity analysis confirmed the reliability of our results. Besides, no publication bias was observed in this meta-analysis, which indicated the actual results may be obtained.

Nevertheless, the present study still has some limitations. First, the pooled analysis included different types of cancers

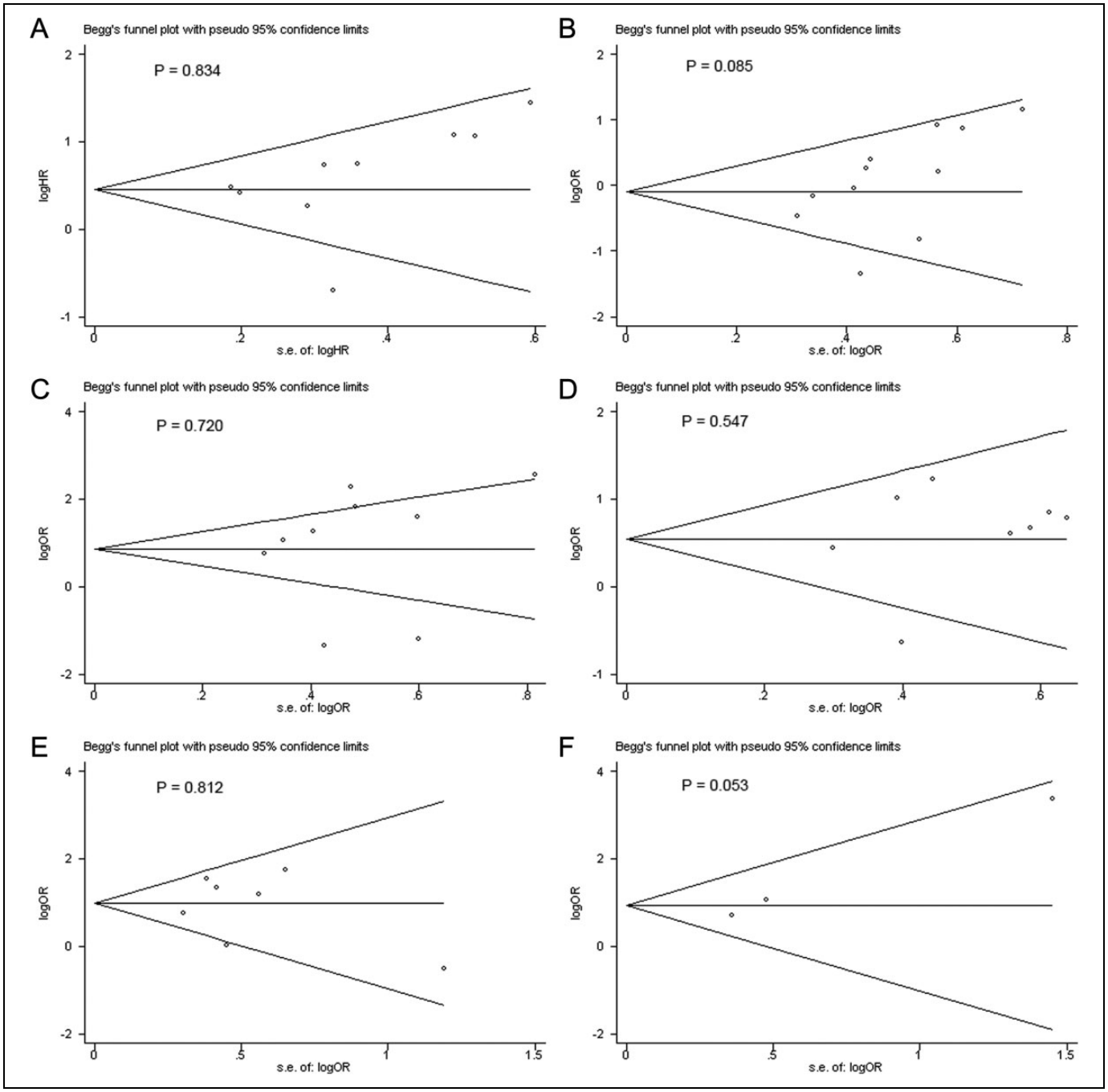

Figure 4. Funnel plot for the evaluation of potential publication bias. A, Prognosis, (B) gender, (C) TNM stage, (D) differentiation grade, (E) lymph node metastasis, and (F) distant metastasis.

which may increase heterogeneity. Second, the HRs and 95% CI were estimated by Kaplan-Meier survival curves in 2 studies. This method may generate some potential deviations. Third, different methods were employed to divide high- and low-expression group. Fourth, lacking of adequate studies in different cancer types is one of the limitations in this meta-analysis.

In conclusion, this meta-analysis indicated that high BANCR expression was associated with poor prognosis for human solid tumors. Moreover, high BANCR expression has an association with advanced tumor stage, lymph node metastasis, and distant metastasis. Thus, BANCR may be a potential novel biomarker to predict prognosis and progression of human solid tumors.

Declaration of Conflicting Interests

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