

Research Paper

Prognostic Value of Long Noncoding RNA CRNDE as a Novel Biomarker in Solid Cancers: An Updated Systematic Review and Meta-Analysis

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Abstract

Background: Long noncoding RNA colorectal neoplasia differentially expressed (CRNDE) has been reported to exhibit a potential oncogenic role in the development of human cancers. However, the clinical value of CRNDE expression in various cancers still remains unclear. Herein, we conducted a meta-analysis to investigate the association between CRNDE and clinical outcomes in solid cancers.

Methods: A systematic search was performed through the PubMed, EMBASE, Web of Science, Ovid, Cochrane library, CNKI and WanFang databases for eligible studies on clinical values of CRNDE in solid cancers. The pooled hazard ratios (HRs) or odd ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the link between CRNDE and clinical outcomes.

Results: A total of 3690 patients from 20 studies (including 2 studies have 2 cohorts, respectively) were included. The results suggested that elevated CRNDE expression predicted a poor overall survival (OS) for in 13 types of solid cancers (HR=1.46, 95% CI: 1.33-1.58, $P<0.001$) with no heterogeneity ($I^2=21.8\%$, $P=0.19$). Subgroup analysis indicated a significant association between high CRNDE expression and shorter OS in the studies with digestive system cancers (HR=1.42, 95% CI: 1.28-1.55, $P<0.001$), qRT-PCR method (HR=1.45, 95% CI: 1.30-1.59, $P<0.001$), sample size >100 (HR=1.44, 95% CI: 1.32-1.57, $P<0.001$), and NOS>7 (HR= 1.50, 95% CI: 1.23-1.78, $P<0.001$). Furthermore, the pooled results showed that CRNDE was an independent prognostic factor for OS in cancer patients (HR=1.37, 95% CI: 1.22-1.52, $P<0.001$). In addition, we also revealed that CRNDE was positively related to tumor size (OR=2.10, 95%CI: 1.68-2.63, $P<0.001$), TNM stage (OR=2.86, 95%CI: 2.29-3.56, $P<0.001$), lymph node metastasis (LNM) (OR=3.21, 95%CI: 2.01-5.13, $P<0.001$), and distant metastasis (OR=4.36, 95%CI: 2.36-8.07, $P<0.001$). Although the probable evidences of publication bias were found in the studies with OS, tumor size, TNM stage or LNM, the trim and fill analysis confirmed the reliability of these results was not affected.

Conclusion: Elevated CRNDE expression was associated with larger tumor size, advanced TNM stage, worse LNM and distant metastasis, and shorter OS, suggesting that CRNDE may act as an independent prognostic biomarker in solid cancers.

Key words: long noncoding RNA, CRNDE, cancer, prognosis, meta-analysis

Introduction

Cancer has already become one of the major public health issues worldwide. Recently, cancer becomes the second leading cause of death in the

United States [1]. Unfortunately, with increasing incidence and mortality in China, cancer has been the leading cause of death since 2010 [2]. Cancer is a

complex human disease associated with a variety of chromosomal translocations, deletions and amplification, epigenetic alterations and genetic mutations. Despite recent advances in the diagnosis and treatment of human cancer, clinical prognosis still remains poor. However, one of the main reasons is the lack of effective biomarker to early diagnose cancer and predict clinical prognosis of cancer patients.

Long noncoding RNAs (lncRNAs), which are longer than 200 nucleotides in length, are an emerging class of evolutionarily conserved non-protein coding RNAs [3]. Although most lncRNAs cannot translate into any functional proteins, they are involved in most aspects of cellular and physiologic processes through acting as transcriptional modulators, posttranscriptional processors, enhancers, splicing regulators, chromatin remodelers, molecular decoys for miRNAs, or as guides for protein-DNA, protein-RNA and protein-protein interactions [4-8]. Notably, increasing evidences suggest that lncRNAs are aberrantly expressed in a broad spectrum of human cancers, and may play crucial roles in promoting and maintaining cancer initiation and progression, demonstrating their clinical potential as biomarkers and therapeutic targets [9-12]. Among these cancer-related lncRNAs, a new discovered lncRNA termed as 'colorectal neoplasia differentially expressed' (CRNDE) has drawn increasing attentions [13, 14].

CRNDE was originally discovered to be upregulated in colorectal cancer (CRC), and located on the long arm of chromosome 16 on the strand opposite to the adjacent IRX5 gene [15, 16]. CRNDE contains a total of six exons, five of which are core exons (E1, E2, E4, E5 and E6) and one of which is less mentioned exon (E3). Till now, 14 splice variants of CRNDE have been identified and named as CRNDE 201-214 [15, 16]. Recent studies demonstrated that CRNDE is not only overexpressed in CRC tissues [17-19], but also abnormally expressed in different types of cancers, including hepatocellular carcinoma (HCC) [20, 21], non-small cell lung cancer (NSCLC) [22, 23], glioma [24, 25], renal cell carcinoma (RCC) [26], breast cancer [27, 28], gastric cancer (GC) [29], intrahepatic cholangiocarcinoma (IHCC) [30], pancreatic cancer (PC) [31], papillary thyroid cancer (PTC) [32], bladder cancer [33], ovarian cancer (OC) [34], and cervical cancer (CC) [35]. It has been demonstrated that CRNDE may play an important role in tumorigenesis. CRNDE could function as a crucial molecular switch for diverse cancer-related pathways including cell proliferation, differentiation, apoptosis, cytoskeletal dynamism, angiogenesis, invasion and metastasis [19, 36-40].

As a cancer-related lncRNA, elevated CRNDE expression is closely related to poor prognosis as well

as aggressive clinicopathologic features for cancer patients. Increasing evidences demonstrated that CRNDE may server as a negative prognostic biomarker in various cancers, and high CRNDE expression markedly correlated with larger tumor size, advanced TNM stage, worse lymph node metastasis and distant metastasis [29]. However, most studies reported about the prognostic role of CRNDE expression are limited by sample size and discrete clinical outcomes. Therefore, we conducted a systematic review and quantitative meta-analysis to investigate the clinicopathological and prognostic value of CRNDE as a potential biomarker in human solid cancers.

Materials and Methods

Search strategy and study selection

We searched though the PubMed, EMBASE, Web of Science, Ovid, Cochrane library, CNKI and WanFang databases for potentially eligible studies on clinical values of CRNDE expression in human solid cancers from inception up to October 24, 2018. The search terms were included: "CRNDE", "colorectal neoplasia differentially expressed", "lncRNA", "long noncoding RNA", "cancer", "carcinoma", "neoplasm", "prognosis" and "survival". The reference lists of the retrieved articles were searched manually, and the literature search was performed by two independent researchers (Yu Zhou and Tian Xu).

The studies were considered eligible if they met the following criteria: any type of human cancer was studied; the studies investigated the prognostic value of CRNDE expression in cancers; the levels of CRNDE expression in cancerous tissues were detected; patients were grouped according to the levels of CRNDE expression; the studies included an association between CRNDE and clinicopathologic parameters; the studies provided sufficient data to estimate the HRs with corresponding 95% CI for OS; and the studies were published in English. The exclusion criteria were as follows: letters, editorials, expert opinions, case reports and reviews; the studies only investigated the molecular structure and functions of CRNDE; the studies did not include the usable data for further analysis; and duplicate publications.

Data extraction and quality assessment

Two investigators (Yu Zhou and Tian Xu) independently evaluated and extracted the data from each eligible study, and a consensus was achieved for disagreements by a third investigator (Shikai Zhu). According to the above inclusion and exclusion criteria, the following elements were extracted: first author, publication date, country, tumor type, TNM stage, sample size, cut-off value, follow-up period,

detection method, adjuvant therapy before the surgery, survival analysis methodology, HRs with corresponding 95% CIs for OS, disease-free survival (DFS) and progression-free survival (PFS), and other clinicopathologic parameters including age, gender, tumor size, tumor differentiation, TNM stage, lymph node metastasis and distant metastasis. HRs with corresponding 95% CIs were preferentially extracted from univariate or multivariate analyses. If these were not available, the HR estimates were calculated from Kaplan-Meier survival curves using Engauge Digitizer V4.1 software according to the method of Tierney et al [41].

The quality of included studies was assessed based on the Newcastle-Ottawa scale (NOS) criteria. The NOS criteria apply a "star" rating system ranges from 0 to 9 stars for the judgment of methodological quality, which was based on selection (0-4 stars), comparability (0-2 stars) and outcome (0-3 stars) [42]. Based on previous recommendations, studies with 5 points were considered to be of high quality. The two aforementioned investigators independently evaluated the quality of each study. Conflicting evaluations or inconsistent data from the included studies were resolved through discussion with a third investigator (Shikai Zhu).

Statistical analyses

All data analyses were performed with STATA statistical software version 14.0 (Stata Corporation, College Station, TX, USA). Pooled HRs with 95% CIs were used to estimate the prognostic value of CRNDE on OS, DFS and PFS in solid cancers. Pooled ORs with 95% CIs were used to estimate the association

between CRNDE and clinicopathological characteristics such as age, gender, tumor size, tumor differentiation, TNM stage, lymph node metastasis and distant metastasis. X^2 -based Cochran Q test and Higgins I^2 statistic were utilized to determine the heterogeneity among those studies. P -value <0.05 in combination with I^2 -value $>50\%$ was considered significant heterogeneity. Random-effects models were applied in cases with significant heterogeneity. Subgroup analysis and sensitivity analysis were performed to dissect the heterogeneity. In addition, publication bias was determined using Begg's funnel plots and Egger's linear regression tests. If there were the probable evidence of publication bias, the trim and fill analysis was performed. P -value <0.05 was considered statistically significant.

Results

Study Selection and Characteristics

A total of 325 potentially relevant articles were identified in this meta-analysis. To yield relevant articles, we evaluated the titles, abstract and author information of all collected articles, and 204 duplicate articles were excluded. After screening the titles and abstract carefully, 92 irrelevant articles were excluded such as letters, editorials, expert opinions, case reports, reviews and other type uninvolved publications for the analysis and full text review. For evaluated the eligibility of full-text articles, nine articles without the sufficient data or dividing into high and low expression groups were excluded. Finally, 20 eligible studies were included in this meta-analysis (Figure 1).

A total of 3690 patients from 20 studies (2 studies included 2 cohorts, respectively) between 2015 and 2018 were included (Table 1). A total of 17 studies were published in English and 3 in Chinese. The regions of those studies were from China (n=19), Poland (n=1) and USA (n=2). Among these studies, the sample size ranged between 54 and 512 patients, and 14 studies enrolled more than 100 patients. 14 types of solid cancers were recorded including CRC (n=4), glioma (n=3), RCC (n=2), breast cancer (n=2), GC (n=1), HCC (n=2), IHCC (n=1), PC (n=1), NSCLC (n=2), PTC (n=1), bladder cancer (n=1), OC (n=1) and CC (n=1). The levels of CRNDE expression were detected by quantitative real-time polymerase chain reaction (qRT-PCR) (n=16), microarray (n=3) and RNA-seq (n=3). None of patients received adjuvant therapy before the surgery were conformed in 12

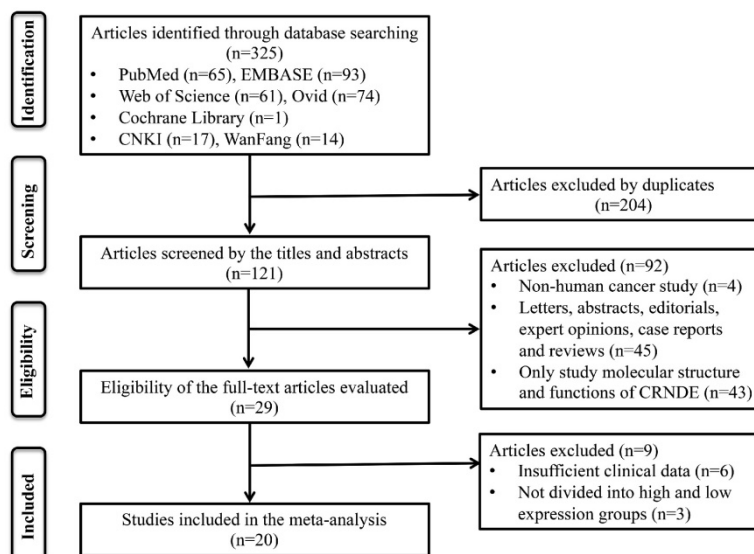


Figure 1. The flow diagram of this meta-analysis.

studies. Multivariate analyze was included in 10 studies. Clinical outcomes were recoded including 19 studies for OS, 2 for DFS, and 2 for PFS. HRs with the corresponding 95% CIs for OS were extracted from the original data in 10 studies, and calculated from Kaplan-Meier Curves in other 10 studies (Supplement Table 1). Clinicopathologic parameters were also recoded in 15 studies including age, gender, tumor size, tumor differentiation, TNM stages, lymph node metastasis (LNM) and distant metastasis (Supplement Table 2). Additionally, all studies were more than 6 according to the NOS score criteria and thus were considered high quality (Supplement Table 3).

Prognostic value of CRNDE expression in solid cancers

A total of 19 studies including 3496 patients were recruited to assess the effects of CRNDE expression on OS in solid cancers. The pooled results suggested that elevated CRNDE expression predicted a poor OS for in 13 types of solid cancers (HR=1.46, 95% CI: 1.33-1.58, $P<0.001$) with no heterogeneity ($I^2=21.8\%$, $P=0.190$) (Figure 2A). Furthermore, subgroup analysis was also conducted to investigate the association between HRs and these variables including cancer type, detection method, sample size and NOS. Stratified analysis indicated that there was a negatively relationship between CRNDE and OS in the studies with digestive system cancers (HR=1.42, 95% CI: 1.28-1.55, $P<0.001$), gynecologic cancers (HR=4.52, 95% CI: 1.49-7.56, $P<0.001$), and glioma

(HR=1.83, 95% CI: 1.23-2.44, $P<0.001$) (Figure 3A). And we also found that upregulation of CRNDE expression significantly related to short OS in the studies using qRT-PCR method (HR=1.45, 95% CI: 1.30-1.59, $P<0.001$) as well as microarray/RNA-seq method (HR=1.49, 95% CI: 1.26-1.72, $P<0.001$) (Figure 3B). Higher CRNDE expression predicted shorter OS in the studies with sample size >100 (HR=1.44, 95% CI: 1.32-1.57, $P<0.001$) as well as those with sample size <100 (HR=1.96, 95% CI: 1.23-2.69, $P<0.001$) (Figure 3C). In addition, the effect of CRNDE overexpression on predicting poor OS was found in the studies with NOS <7 (HR=1.45, 95% CI: 1.31-1.58, $P<0.001$) as well as those with NOS >7 (HR= 1.50, 95% CI: 1.23-1.78, $P<0.001$) (Figure 3D).

The independent prognostic value of CRNDE expression in different cancers were also evaluated based on the multivariate analysis in 10 studies with 1766 patients (Figure 2B). The pooled HRs showed that CRNDE expression was an independent prognostic factor for OS in cancer patients (HR=1.37, 95% CI: 1.22-1.52, $P<0.001$). In addition, the prognostic value of CRNDE expression for DFS or PFS were also evaluated in 4 studies including 1355 patients (Figure 2C). The pooled data suggested that elevated CRNDE expression predicted a poor DFS for in hepatocellular carcinoma and ovarian cancer (HR=1.46, 95% CI: 1.06-1.87, $P<0.001$). However, there was no significant association between CRNDE and PFS, maybe due to small sample size.

Table 1. The main characteristics of the included studies in this meta-analysis

Author	Year	Country	Tumor Type	TNM Stage	Sample Size	Cut-off Value	Follow-up (months)	Detection Method	Adjuvant therapy	Survival Analysis	Outcome Measure	NOS	
Szafron LM	2015	Poland	OC	Ib-IV	135	Mean	38(median)	qRT-PCR	None	M	OS	DFS	9
Han Y	2015	China	CC	I-IV	87	2- $\Delta\Delta Ct=1$	60(total)	qRT-PCR	None	U/M	OS		9
Liu T	2016	China	CRC	I-IV	142	Median	92 (total)	qRT-PCR	None	U/M	OS		8
Jing SY	2016	China	Glioma	I-IV	164	Median	70 (total)	qRT-PCR	None	U/M	OS		8
Du DX	2017	China	GC	I-IV	118	Median	60 (total)	qRT-PCR	None	U/M	OS		9
Dai MY	2017	China	HCC	I-IV	373	Median	120 (total)	Microarray	NA	U	OS		8
Wang G	2017	China	PC	I-IV	58	NA	50 (total)	qRT-PCR	NA	U	OS		8
Huan JL	2017	China	BrC	I-IV	103	Mean	60 (total)	qRT-PCR	None	U	OS		8
Jiang HJ	2017	China	CRC	I-IV	251	NA	57(median)	qRT-PCR	NA	U/M	OS		9
Luo YH	2017	China	PTC	I-IV	502	NA	200 (total)	RNA-seq	NA	M	OS		6
Kiang KM ¹	2017	China	Glioma	I-IV	68	Median	200 (total)	Microarray	NA	U	OS		6
Kiang KM ²	2017	China	Glioma	I-IV	101	Median	200 (total)	Microarray	NA	U	OS		6
Han P	2017	China	CRC	NA	64	Median	50 (total)	qRT-PCR	None	U	OS		8
Ding J	2017	China	CRC	I-IV	80	NA	NA	qRT-PCR	None	NA	NA		6
Li XH	2017	China	NSCLC	I-IV	137	Mean	60 (total)	qRT-PCR	None	U/M	OS	PFS	9
Zhang M	2017	China	NSCLC	I-IIIa	66	NA	60 (total)	qRT-PCR	NA	U	OS		8
Xia XL	2017	China	IHCC	I-IV	118	Mean	60 (total)	qRT-PCR	None	U/M	OS	PFS	8
Tang QL	2018	USA	HCC	NA	369	Median	120 (total)	RNA-seq	NA	U	OS	DFS	6
Cheng JL	2018	China	BIC	I-IV	54	N/T=1	NA	qRT-PCR	NA	NA	NA		6
Li ZB	2018	China	BrC	I-IV	76	2- $\Delta\Delta Ct=1$	NA	qRT-PCR	None	NA	NA		6
Ding CG ¹	2018	China	RCC	I-IV	112	Median	96 (total)	qRT-PCR	None	U/M	OS		9
Ding CG ²	2018	USA	RCC	NA	512	Median	150(total)	RNA-seq	NA	U	OS		6

Abbreviations: OC, ovarian cancer; CC, cervical cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; PC, pancreatic cancer; BrC, breast cancer; PTC, papillary thyroid cancer; NSCLC, non-small cell lung cancer; IHCC, intrahepatic cholangiocarcinoma; BIC, bladder cancer; RCC, renal cell carcinoma; NA, not available; T, tumor; N, normal; qRT-PCR quantitative real-time PCR; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

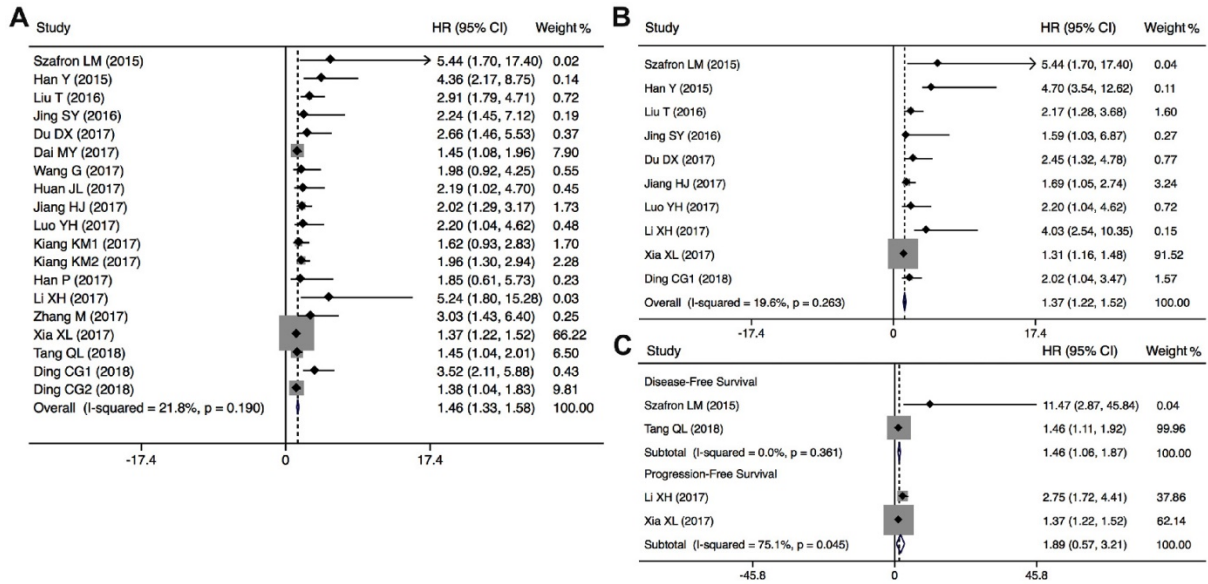


Figure 2. Forest plots of the HRs for the association between CRNDE expression and OS (A), independent predictive factor for OS (B), and DFS/PFS (C).

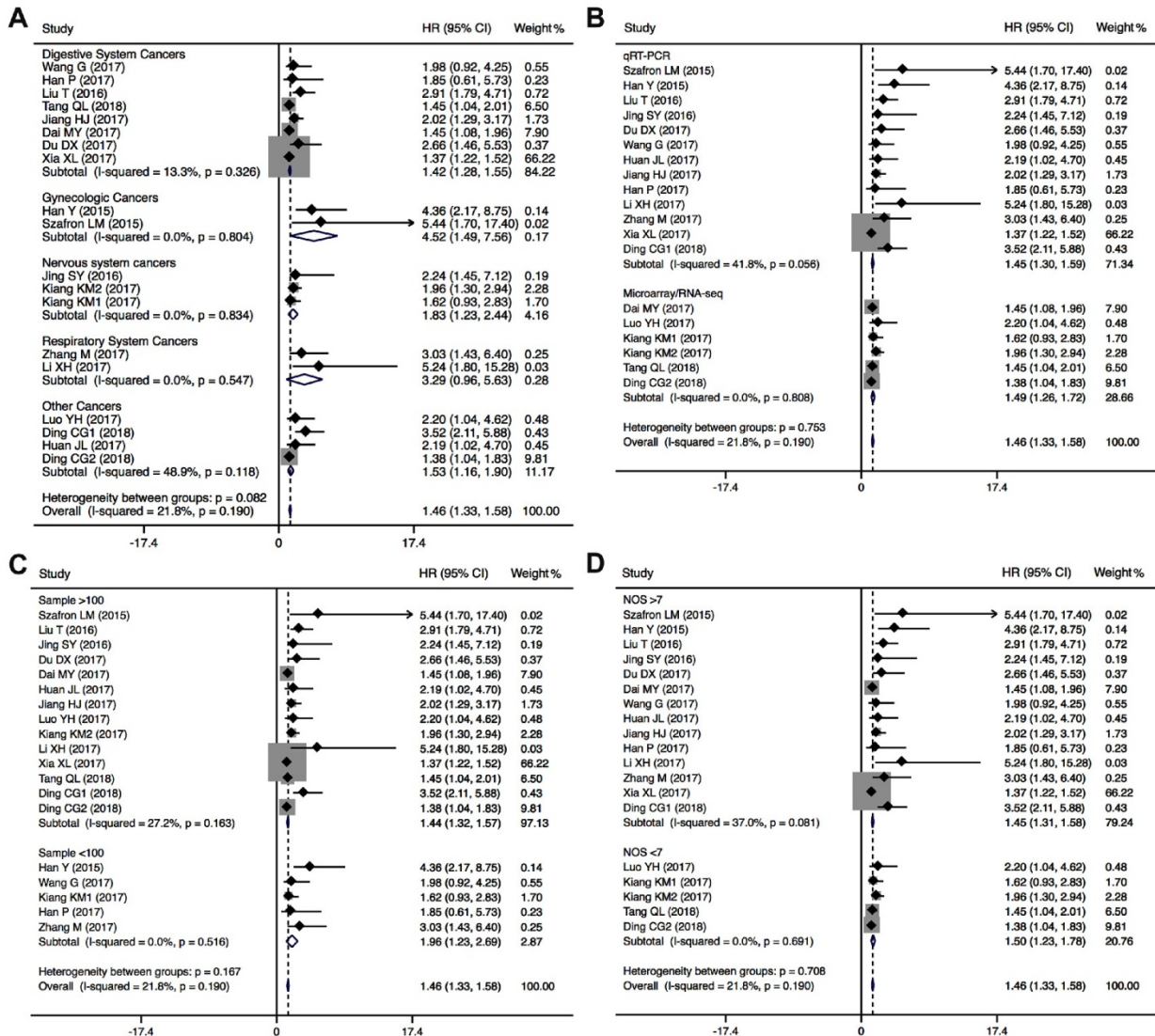


Figure 3. Forest plots of subgroup analysis for the HRs of OS by (A) cancer type, (B) detection method, sample size (C), and NOS (D).

Association between CRNDE expression and clinicopathological characteristics of solid cancers

The association between CRNDE expression and clinicopathological characteristics are examined in 15 studies with 1861 cancer patients (Table 2). 12 studies with 1346 cancer patients were included to analysis the link between CRNDE and tumor size, and the pooled data found an obviously association between CRNDE and tumor size (OR=2.10, 95%CI: 1.68-2.63, $P<0.001$) (Figure 4A). According to the association between CRNDE and TNM stage, the analysis results of 13 studies with 1546 cancer patients showed that there was a significant relationship between CRNDE and TNM stage (OR=2.86, 95%CI: 2.29-3.56, $P<0.001$) (Figure 4B). As indicated in Figure 4C, 1141 cancer patients from 12 studies were included to assess the association between CRNDE and LNM, and the results demonstrated that the patients with high CRNDE expression were more susceptibility to develop LNM (OR=3.21, 95%CI: 2.01-5.13, $P<0.001$). In addition, 5 studies with 682 cancer patients were included to analysis the link between CRNDE and distant metastasis, and the results found an obviously association between CRNDE expression and distant metastasis (OR=4.36, 95%CI: 2.36-8.07, $P<0.001$). However, there was no significantly correlation between CRNDE and other clinicopathological features, including age ($Z=1.63$, $P=0.103$), gender ($Z=0.75$, $P=0.451$), and tumor differentiation ($Z=1.27$, $P=0.203$).

Publication bias and sensitivity analysis

To evaluate the publication bias, the Begg's funnel plots and Egger's linear regression tests were applied in this meta-analysis. In the analysis of evaluating the association between CRNDE expression on OS, visual inspection of the Begg's funnel plot revealed asymmetry (Figure 5A), and Egger's test suggested the probable evidence of publication bias ($t=2.61$, $P=0.018$). Furthermore, to assess the impact of potential publication bias, the trim and fill analysis was performed with the fixed-effects model. Ten which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry. The imputed studies produce a symmetrical funnel plot (Figure 5A). The pooled analysis incorporation the hypothetical studies continued to show a statistically significant association between CRNDE expression on OS in solid cancers (corrected HR=1.44, 95% CI: 1.33-1.55, $P<0.001$). According to evaluating the independent prognostic value of CRNDE expression for OS in cancers, visual inspection of the Begg's funnel plot revealed symmetry (Figure 5B), and Egger's linear regression test revealed no publication bias for the analysis of OS ($t=1.24$, $P=0.253$). Due to the small number of studies, the publication bias was not analyzed in the DFS and PFS groups.

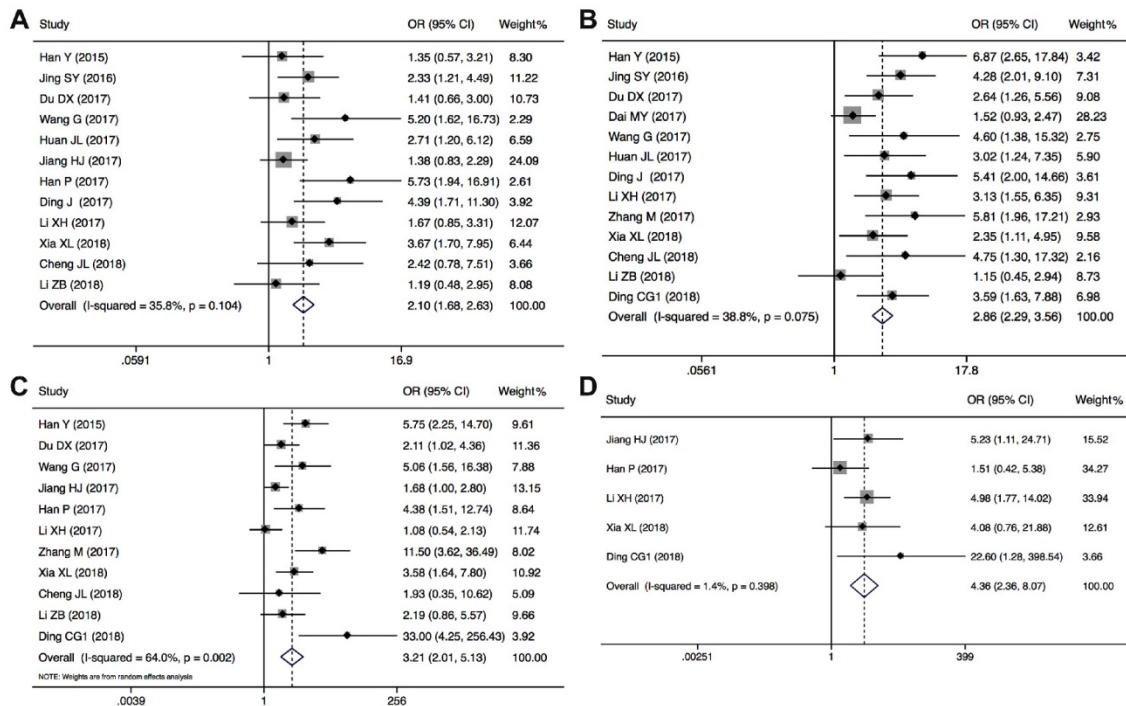


Figure 4. Forest plots of the included studies evaluating the correlation between CRNDE expression and clinicopathological characteristics. (A) tumor size; (B) TNM stages; (C) LNM; (D) distant metastases.

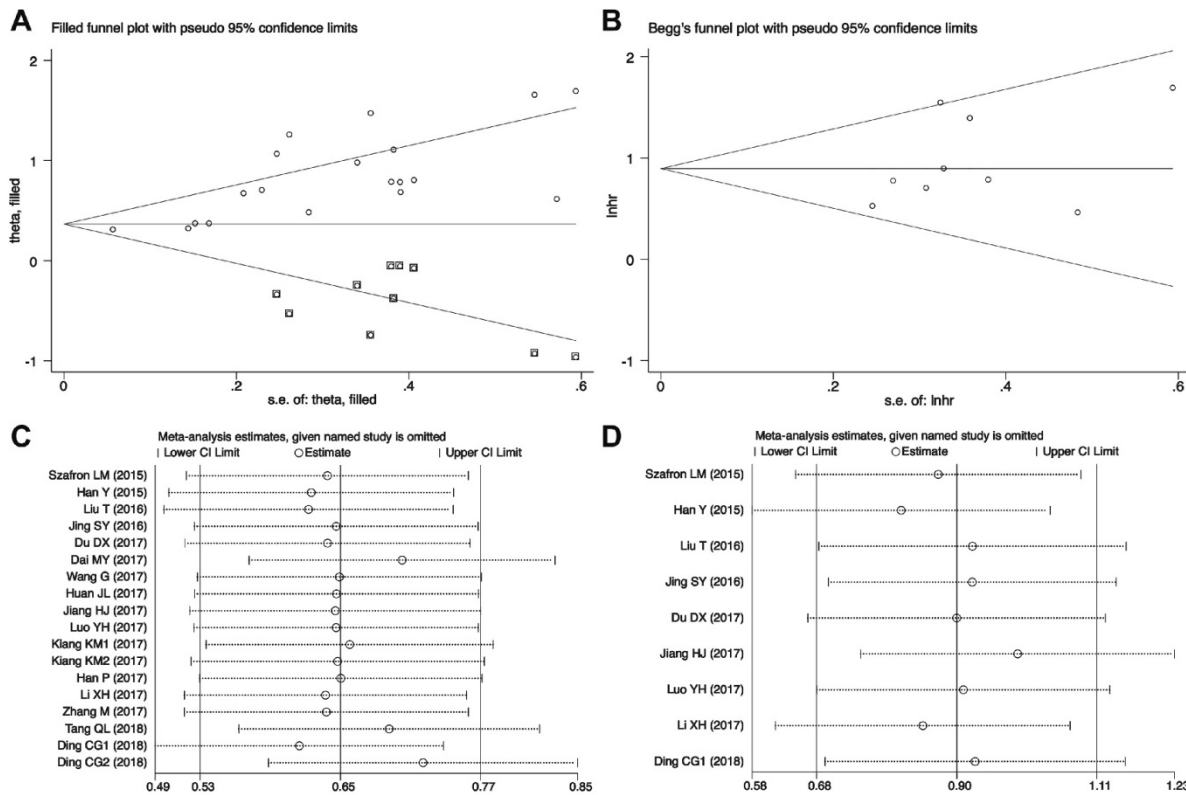


Figure 5. Publication bias and sensitivity analysis for OS in this meta-analysis. (A) Begg's funnel plots of the included studies for OS; (B) Begg's funnel plots of the included studies for independent predictive factor for OS; (C) Sensitivity analysis of the included studies for OS; (D) Sensitivity analysis of the included studies for independent predictive factor for OS. HR, hazard ratios; CI, confidence interval; SE, standard error.

Table 2. Correlation between CRNDE expression and clinicopathological characteristics of cancers

Clinical parameters	No. of studies	No. of patients	OR (95% CI)	P-value	Heterogeneity	
					I ²	P-value
Age (elder vs. younger)	15	1861	1.17(0.97-1.40)	0.103	9.6%	0.346
Gender (male vs. female)	12	1595	1.02(0.83-1.25)	0.876	0.0%	0.594
Tumor size (larger vs. smaller)	12	1346	2.10(1.68-2.63)	<0.001	35.8%	0.104
Tumor differentiation (poor vs. well)	11	1168	1.41(0.83-2.39)	0.203	74.0%	<0.001
TNM stage (III+IV vs. I+II)	13	1546	2.86(2.29-3.56)	<0.001	38.8%	0.075
Lymph node metastasis (present vs. absent)	12	1141	3.21(2.01-5.13)	<0.001	64.0%	0.002
Distant metastasis (present vs. absent)	5	682	4.36(2.36-8.07)	<0.001	1.4%	0.398

Sensitivity analyses demonstrated that the study by Xia XL et al.[30] was the top one with heterogeneity in the OS group, and their removal changed the results into more significant ones with no heterogeneity (HR=1.64, 95% CI: 1.43-1.85; I²=9.5%, P=0.341) (Figure 5C). And as indicated in Figure 5D, the pooled HR for the independent prognostic value of CRNDE in cancers was not significantly affected by the exclusion of any of the studies.

In addition, we also evaluated the association between CRNDE and tumor size, TNM stages, LNM or distant metastases. Visual inspection of the Begg's funnel plots revealed obvious asymmetry in the studies investigating CRNDE on tumor size (t=2.30, P=0.045, Figure 6A), TNM stages (t=2.99, P=0.012, Figure 6B), and LNM (t=3.04, P=0.014, Figure 6C). The corrected OR regarding the association between

CRNDE and tumor size (corrected OR=1.92, 95% CI: 1.54-2.39, P<0.001), TNM stages (corrected OR=2.38, 95% CI: 1.94-2.91, P<0.001), and LNM (corrected OR=2.31, 95% CI: 1.40-3.80, P=0.001), which showed that the correction for potential publication bias had an influence on the stability of the result. And Begg's funnel plots suggested that there was no evidence of publication bias among the studies investigating CRNDE on distant metastases (t=0.99, P=0.397) (Figure 6D).

Discussion

Long noncoding RNAs (lncRNAs), which are encoded by a vast less explored region of the human genome, may hold missing drivers of cancer and have gained attention recently as a potentially crucial layer of carcinogenesis and cancer development. Recently,

more evidence has emerged that lncRNAs are dysregulated in various types of human cancers, and has led to pioneering efforts to develop lncRNA-based clinical applications such as diagnostic, therapeutic, or prognostic biomarkers, drug sensitizers, and therapeutic targets.

As a newly characterized oncogene, CRNDE is an important lncRNA in human malignancies. Recent studies have revealed the multilayered biological function of CRNDE involve in cell proliferation, chemo-resistance, invasion and metastasis, which result in the cancer initialization and development [43-45]. Collective evidence has indicated that dysregulation of CRNDE is associated with adverse clinical characteristics such as tumor size, tumor differentiation, TNM stage, lymph node metastasis and distant metastasis, and poor prognosis in many solid cancers [46]. However, the perplexity and inconsistency arise from a wide range of studies due to heterogeneity. In this present study, we found that elevated CRNDE expression predicted a shorter OS in thirteen types of solid cancers, and served as an independent predictive factor for patients' prognosis. Furthermore, CRNDE was positively associated with tumor size, TNM stage, lymph node metastasis, and distant metastasis. To sum up, our findings provided convincing evidences to support CRNDE as a

negative, unfavorable prognostic biomarker for human solid cancers.

Although CRNDE has been suggested to serve as oncogenic lncRNA, the underlying molecular mechanisms involved in CRNDE interactions are complex and diverse (Table 3). Recent discoveries have revealed that CRNDE could provide specific functional scaffolds for regulatory complexes, such as the polycomb repressive complex 2 (PRC2) and CoREST chromatin-modifying complexes. CRNDE functions as an oncogene to interact with PRC2 to repress p21 transcription, contributing to the radio-resistant phenotype formation of lung cancer cells [47]. Furthermore, CRNDE was also discovered to act as a scaffold of deleted in malignant brain tumors 1 (DMBT1) and cellular inhibitor of apoptosis protein 1 (C-IAP1) complexes, which could accelerate cancer development by promoting the PI3K/AKT pathway [39, 48]. CRNDE can epigenetically silence dual-specificity phosphatase 5 (DUSP5) and CDKN1A expression through binding to EZH2 [19]. CRNDE also modulate the levels of CDK4/6 and CCNE1 expression, contributing to the cell cycle transition from G0/G1 stage to S stage[48]. In addition, CRNDE could promote tumorigenesis through the EGFR, mTOR, Notch1, Ras/MAPK and toll-like receptor pathway [17, 25, 38, 49-52].

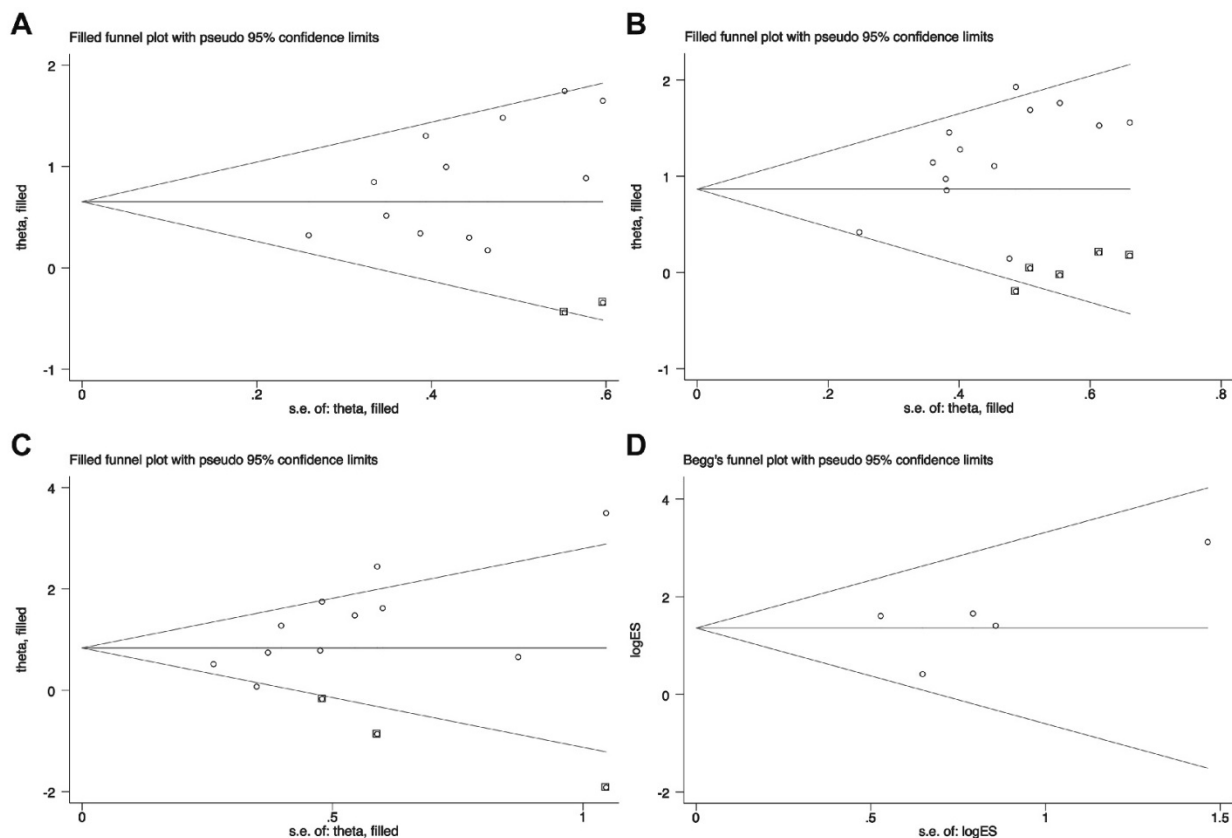


Figure 6. Begg's funnel plots of the included studies for clinicopathological characteristics. (A) tumor size; (B) TNM stages; (C) LNM; (D) distant metastases.

Table 3. Roles of CRNDE in cancer initiation and progression

Cancer type	Molecular Mechanisms	Functions	Reference
Ovarian Cancer	decrease accumulation of TP53 protein	prognostic biomarker	[34]
Cervical Cancer	NA	prognostic biomarker and correlate with FIGO stage, invasion depth and LNM, promote cell growth and metastasis	[35, 43]
Colorectal Cancer	epigenetically silence DUSP5/CDKN1A, downregulate E2F1 by targeting miR-136, upregulated by insulin/IGF pathway, activate Ras/MAPK pathway by binding to hnRNPUL2, regulate Wnt/ β -catenin pathway by suppressing miR-181a-5p or binding to miR-217 with TCF7L2	prognostic biomarker and correlate with tumor size, TNM stage, LNM and distant metastasis, promote cell proliferation, cell cycling, metastasis and chemo-resistance, and inhibit cell apoptosis	[16-19, 40, 54, 55]
Glioma	upregulated by EGFR and mTOR pathway, downregulate miR-136-5p to increase Bcl-2 and Wnt2, inhibit miR-384/PIWIL4/STAT3 axis, downregulate XIAP and PAK7 by binding to miR-186	prognostic biomarker and correlate with tumor size, WHO grade and recurrence, promote cell growth, proliferation, migration and invasion, and inhibit cell apoptosis	[24, 25, 49, 51, 57, 58]
Gastric Cancer	activate PI3K/AKT pathway, downregulate E2F3 by targeting miR-145	prognostic biomarker and correlate with invasion depth, TNM stage and LNM, promote cell proliferation, migration and invasion	[29, 59]
HCC	activate PI3K/Akt-Wnt/ β -catenin pathway, regulate miR-203/BCAT1 axis, regulate NF- κ B and p-AKT by inhibition of miR-384	diagnostic and prognostic biomarker, promotes HCC cell proliferation, growth and metastasis, and inhibit cell apoptosis	[20, 21, 45, 56]
Pancreatic Cancer	upregulate IRS1 by sponging miR-384	prognostic biomarker and correlate with tumor size, TNM stage, differentiation and LNM, promote cell proliferation, migration and invasion	[31]
Breast Cancer	activate Wnt/ β -catenin pathway by directly repressing miR-136	diagnostic and prognostic biomarker and correlate with tumor size and TNM stage, promote cell proliferation, migration and invasion	[27, 28]
PTC	increase PTN expression by competitively binding miR-384	prognostic biomarker, promotes cell proliferation, invasion and migration	[32, 60]
NSCLC	downregulate p21 by interacting with PRC2/ EZH2, regulate CDK4/6 and CCNE1 expression, activate PI3K/AKT pathway	prognostic biomarker and correlate with cancer type, TNM stage and distant metastasis, promote cell proliferation and growth	[22, 23, 48]
IHCC	NA	prognostic biomarker and correlate with tumor size, TNM stage, differentiation and LNM, promote cell proliferation, migration, invasion and EMT	[30]
Bladder Cancer	NA	correlate with TNM stage, promote cell proliferation and migration, inhibit apoptosis	[33]
RCC	upregulate Vimentin, ZEB1/2 expression, downregulate E-cadherin expression, activate Wnt/ β -catenin pathway	prognostic biomarker and correlate with tumor size, TNM stage, LNM, pathological grade and metastasis, promote cell migration and invasion	[26, 53]
TSCC	upregulate Kras, CDC42 and IRS1 by inhibiting miR-384	promote cell proliferation and invasion	[61]
Osteosarcoma	activate Notch1 pathway	correlate with advanced stage and metastasis, promote cell growth, proliferation, invasion and migration	[52]
Multiple Myeloma	suppressing miR-451 expression	correlate with tumor progression and poor survival, promote cell proliferation, inhibit cell cycle arrest in the G0/G1 phase and apoptosis	[44]
Gallbladder Cancer	activate PI3K/AKT pathway by recruiting DMBT1 and c-IAP1	promote gallbladder cancer carcinogenesis	[39]

Recent studies have indicated that CRNDE can act as competitive endogenous RNA (ceRNA) to regulate miRNAs, and play key roles in the occurrence and development of human cancers. CRNDE functions as a ceRNA to promote malignant progression of several cancers through competitive sponging of microRNA-136, miR-181a-5p and miR-217 to activate Wnt/ β -catenin pathway [18, 28, 53-55]. CRNDE also has ability to upregulate IRS1, piwi-like RNA-mediated gene silencing 4 (PIWIL4), NF- κ B, p-AKT, Bcl-2, Wnt2 and E2F3 expression by sponging miR-384, miR-145, miR-136-5p [31, 56-61]. To fully appreciate the functions of CRNDE, further studies are required to construct complete functional cell type-specific lncRNA expression maps in different steps of cancer progression.

Some limitations of this meta-analysis should be acknowledged due to the discrete data across these clinical studies. The criteria for calculating the cut-off

value were not the same in different studies. The inclusion of only studies that reported HR or survival curves might have resulted in the potential for selection bias. Furthermore, some of the HRs were calculated by reconstructing survival curves rather than directly obtained from the primary studies, thus a calculation bias might be present. In addition, the inclusion of a relatively larger number of studies in China might have decreased the applicability of our results across different ethnicities. The data collection may be incomplete because data from non-English and non-Chinese language papers were not included. The publication bias of meta-analysis about the relationship between CRNDE and clinicopathological features was significant, which might be caused by some unpublished studies with negative results. In this meta-analysis, only summarized data rather than individual patient data were used. Therefore, it is possible that our results might overestimate the

prognostic effects of abnormal CRNDE expression on survival in different types of cancers. We believed that more clinical studies should be conducted to evaluate potential prognostic role of CRNDE expression in other types of cancer that have not been included.

In conclusion, this meta-analysis showed that elevated CRNDE expression was significantly associated with shorter overall survival in patients with solid cancers, and might act as a novel effective prognostic biomarker and therapeutic target for solid cancers. Furthermore, CRNDE could promote cancer cell proliferation, invasion and metastasis, and suppresses apoptosis through various complicated mechanisms. Thus, CRNDE may potentially be used as a novel biomarker for predicting poor prognosis of patients with solid cancers. More clinical studies on other different types of human cancers that have not yet been investigated needed to be conducted. In the near future, the lncRNA profile of each human cancer type should be systematically investigated to improve clinical outcomes for cancer patients by engendering a personalized approach to medicine.

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Competing Interests

The authors have declared that no competing interest exists.

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