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REVIEW

Prognostic value of long non-coding RNA CRNDE in gastrointestinal cancers: a meta-analysis

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Purpose: Numerous studies have reported that the long non-coding RNA colorectal neoplasia differentially expressed (CRNDE) plays important roles in the tumorigenesis, progression, and prognosis of various types of cancer. However, thus far, a systematic analysis of CRNDE in cancers of the digestive system has not been conducted. Thus, the aim of this meta-analysis was to explore the relationship between CRNDE expression and survival or the clinicopathological features of gastrointestinal cancer.

Methods: Eligible studies were collected from nine databases (ie, PubMed, Medline, Embase, Cochrane Library, Ovid, Science Citation Index Expanded, China Biology Medicine, Chinese National Knowledge Infrastructure, and Wanfang). The meta-analysis was conducted using the Stata SE.12 Software. The pooled hazard ratio (HR) or odds ratio (OR) with a 95% confidence interval (Cl) was used to assess the clinical value of CRNDE expression in gastrointestinal cancers.

Results: A total of 1,053 patients from nine articles were selected. The analysis provided evidence suggesting a significant negative correlation between high CRNDE expression and the rate of overall survival [HR=1.92, 95% CI (1.40–2.64), $p<0.001$] in patients with malignancies of the digestive system. A positive correlation was observed between high CRNDE expression and lymph node metastasis [OR=2.82, 95% CI (1.85–4.31), $p<0.001$], distant metastasis [OR=2.72, 95% CI (1.16–6.35), $p=0.021$], more advanced tumor-node-metastasis stage [OR=3.13, 95% CI (2.03–4.83), $p<0.001$], and tumor size >5 cm [OR=2.81, 95% CI (1.62–4.88), $p<0.001$]. In the non-colorectal cancer subgroup, high CRNDE expression predicted worse histopathological grade [OR=2.21, 95% CI (1.37–3.57), $p=0.001$] and depth of tumor invasion [OR=2.54, 95% CI (1.46–4.41), $p=0.001$].

Conclusion: This meta-analysis revealed that CRNDE may be an unfavorable risk factor of survival and predict advanced clinicopathological features of patients with gastrointestinal cancer. These findings emphasize the usefulness of CRNDE as a predictor of prognosis and pathological biomarker in this type of tumors.

Keywords: colorectal neoplasia differentially expressed, long non-coding RNA, gastrointestinal cancers, prognosis, clinical pathological features

Introduction

Gastrointestinal malignancies mainly comprise colorectal cancer (CRC), gastric cancer (GC), hepatocellular carcinoma (HCC), esophageal cancer, pancreatic cancer (PC), and gallbladder cancer.[1,2] In 2018, it was estimated that 4,930,000 new cases (27% of the total number of cases) and 3,530,000 new cancer-related deaths (37% of the total cancer deaths) were assigned to malignancies of the digestive system.[1,2] Digestible system cancers seriously threaten psychological and physical health worldwide. Although marked progress and developments have been achieved in

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the screening, diagnosis, treatment, and prognostic evaluation of digestive system cancers, the rate of long-term survival rate of patients remains unsatisfactory.[3–7] Thus, it is clinically necessary and urgent to identify reliable biomarkers which can contribute to the screening, diagnosis, and evaluation of prognosis in gastrointestinal tumors.

Long non-coding RNA (lncRNA) is a class of non-coding RNA molecules (length >200 nucleotides) without protein-coding potential.[8] Previously, lncRNA is regarded as a "transcriptional noise". More recently, numerous studies revealed that lncRNAs act as regulators of gene expression and are involved in carcinogenesis, cell proliferation and invasion, or metastasis.[9,10] Currently, LncRNAs have become a research hotspot in the field of cancer. LncRNA colorectal neoplasia differentially expressed (CRNDE), which is located on chromosome 16, exhibits high levels of expression in CRC,[11] GC,[12] glioma,[13] HCC,[14] etc. This high expression suggests that CRNDE may be involved in cancer cell proliferation, migration, and invasion, metabolism, angiogenesis, suppression of apoptosis, and tumor occurrence/development. Tissue- or serum-derived CRNDE acts as a biomarker with outstanding sensitivity and specificity.

Numerous studies have demonstrated that the elevated expression of CRNDE in gastrointestinal cancer was associated with poor prognosis, more advanced tumor-node-metastasis (TNM) stage, and lymph node metastasis.[11,15–22] In addition, several research studies investigating the association between CRNDE expression and clinicopathological characteristics (ie, distant metastasis, histopathological grade, tumor invasion depth, and tumor size) yielded contradictory results. Jiang et al and Liu et al suggested that high CRNDE expression was associated with a higher risk of distant metastasis; however, Han et al and Xia et al did not report a significant association.[11,15,17,22] These studies were mostly single-center clinical studies with small sample sizes, investigating the mechanism of a single pathway mechanism. Consequently, the results obtained from individual studies were inconclusive. The objective of this quantitative meta-analysis was to summarize the results of published research studies, aiming to elucidate the relationship between CRNDE expression and survival prognosis of survival or clinicopathological features in patients with digestive system gastrointestinal cancer.

Materials and methods

Search strategy

Eligible articles for this meta-analysis (until 3 October 2018) were retrieved from nine databases (ie, PubMed, Medline, Embase, Cochrane Library, Ovid, China Biology Medicine, Science Citation Index Expanded, China National Knowledge Infrastructure, and WanFang). The terms used in this search were "CRNDE" or "lncRNA CRNDE" or "colorectal neoplasia differentially expressed" and "neoplasm" or "carcinoma" or "tumor" or "cancer". Moreover, the reference lists of relevant articles were manually investigated during retrieval, to avoid missing any potentially eligible studies. The full-text articles published in English and Chinese were included in this meta-analysis.

Inclusion and exclusion criteria

Inclusion criteria were as follows: [1] patients diagnosed with histologically confirmed gastrointestinal cancer; [2] studies evaluating the relationship between the expression level of CRNDE in tissue or serum specimens and overall survival (OS) or clinicopathological parameters of any type of gastrointestinal cancer; [3] ability to directly or indirectly extract the hazard ratio (HR) with 95% confidence interval (CI) from survival curves. Exclusion criteria were as follows: [1] unavailability of data regarding survival or clinicopathological features; [2] duplicate or similar studies; [3] reviews, meta-analyses, case reports, and letters not published in English or Chinese; [4] cell or animal laboratory studies.

Data extraction

The following information was collected from each of the eligible articles: name of first author, year of publication, country, type of cancer, sample source, test method, case number, follow-up time, survival end-point, HR with 95% CI, and clinicopathological parameters such as age, sex, histopathological grade, tumor invasion depth (T stage), lymph node metastasis (N stage), distant metastasis (M stage), TNM stage, and tumor size. For studies in which the results of both univariate and multivariate analyses were provided, only the latter data were selected because of the higher precision regarding the interpretation of confounding factors. For research studies providing only Kaplan–Meier curve data, the HRs with 95% CIs were calculated using the Engauge Digitizer version 10.10.[23,24] Two investigators independently extracted all the essential data from the selected literature. Discrepancies or disagreements were discussed and overcome in consultation with a third investigator.

Quality assessment

The quality of all included studies was assessed using the Newcastle–Ottawa Scale. Those with a Newcastle–Ottawa Scale score ≥6 were regarded as high-quality studies.

Statistical methods

This meta-analysis was performed using the Stata SE12.0 software (StataCorp, College Station, Texas). A $P<0.05$ denoted statistical significance. HRs with 95% CIs were calculated to assess the relationship between CRNDE expression and survival risk. Odds ratios (ORs) with 95% CIs were calculated to assess the relationship between CRNDE expression and clinicopathological features (ie, age, sex, histopathological grade, T stage, N stage, M stage, TNM stage, and tumor size). The heterogeneity among studies was evaluated using the chi-squared-based Q test and I^2 statistics. In cases of extreme heterogeneity (ie, $I^2>50\%$ or $P<0.10$ for Q test), we used the random-effects model. Otherwise, the fixed effects model was applied. The subgroup analysis was performed based on different items. The sensitivity analysis was performed to evaluate the accuracy and robustness of the results. Publication bias analysis was performed using the Begg's funnel plot and Egger's test. A two-sided $P<0.1$ denoted statistical significance, for which the Duval and Tweedie's trim and fill method was applied.

Results

Characteristics of eligible studies

According to the inclusion and exclusion criteria, a total of nine eligible studies were finally included in the current meta-analysis. These included eight and seven studies of prognosis and clinicopathological characteristics. A total of 1,053 patients were included in these studies, with a minimum and maximum sample size of 58 and 251 patients, respectively. Notably, eight and one studies were published in English and Chinese, respectively. Four tumor types were evaluated, including CRC (6),[11,15–19] GC (1),[20] PC (1),[21] and intrahepatic cholangiocarcinoma (1).[22] All studies were performed in China, and all participants were Asian. The detailed process of literature search and selection is presented in Figure 1. The relevant information of the research studies included for the analysis of prognosis and clinicopathological parameters is shown in Tables 1 and 2, respectively.

Association between CRNDE and prognosis

A total of 973 patients from nine studies were included in this meta-analysis.[11,15–17,19–22] The heterogeneity test revealed high heterogeneity ($I^2=61.5\%$, $p=0.011$). The random effects model was used to analyze the pooled HRs with 95% CI. The results revealed a significant association between high CRNDE expression and poor OS [HR=1.92, 95% CI (1.40–2.64), $p<0.001$] in gastrointestinal cancer (Figure 2A).

A meta-analysis of the subgroups was further performed based on the type of cancer, sample source, sample size,

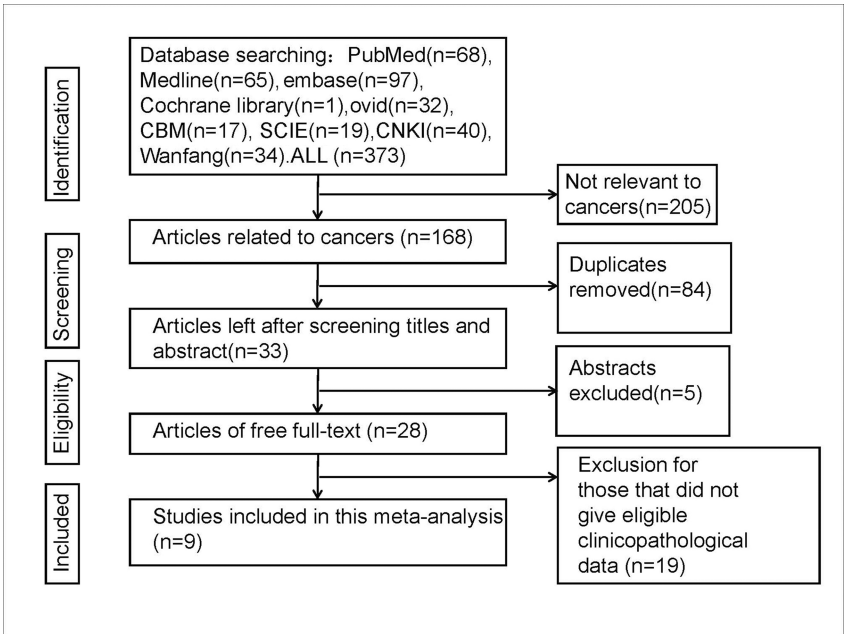

Figure 1 Flowchart of the current meta-analysis.

Table 1 Survival data of studies included

Author	Year	Country	Type	Source	Method	Cut-off	Sample size	Survival analysis	Analysis type	Follow-up months	HR availability	Quality score
Liu-148[15]	2016	China	CRC	Tissue	RT-qPCR	Youden index	148	OS	Multivariate	44.9 (mean)	Yes	8
Liu-142[16]	2016	China	CRC	Serum	RT-qPCR	Median	142	OS	Multivariate	55 (median)	Yes	8
Jiang[11]	2017	China	CRC	Tissue	RT-qPCR	Mean	251	OS	Multivariate	117 (total)	Yes	8
Du[20]	2017	China	GC	Tissue	RT-qPCR	Median	118	OS	Multivariate	60 (total)	Yes	8
Han[17]	2017	China	CRC	Tissue	RT-qPCR	Median	64	OS	Kaplan–Meier	50 (total)	Yes	8
Wang[21]	2017	China	PC	Tissue	RT-qPCR	N/A	58	OS	Kaplan–Meier	40 (total)	Yes	8
Ding[18]	2017	China	CRC	Tissue	RT-qPCR	X-tile algorithm	80	NA	NA	NA	No	6
Xia[22]	2018	China	ICC	Tissue	RT-qPCR	Mean	118	OS	Multivariate	60 (total)	Yes	8
Li[19]	2018	China	CRC	Serum	RT-qPCR	X-tile algorithm	74	OS	Kaplan-Meier	72 (total)	Yes	8

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; PC, pancreatic cancer; ICC, intrahepatic cholangiocarcinoma; NA, none available.

Table 2 Clinicopathological features of studies included in the meta-analysis

Author	Year	Case number	LncRNA CRNDE expression																	
			High									Low								
			Total	VA	M	LD	T3–4	LNM	DM	HTS	TS≥5	Total	VA	M	LD	T3–4	LNM	DM	HTS	TS≥5
Liu-148[15]	2016	148	104	NA	NA	NA	NA	NA	NA	NA	NA	44	NA	NA	NA	NA	NA	NA	NA	NA
Liu-142[16]	2016	142	71	NA	NA	NA	NA	NA	NA	NA	NA	71	NA	NA	NA	NA	NA	NA	NA	NA
Jiang[11]	2017	251	120	73	73	19	96	53	9	NA	77	131	65	77	37	96	42	2	NA	74
Du[20]	2017	118	61	34	21	39	40	35	NA	37	24	57	33	27	27	23	18	NA	21	18
Han[17]	2017	64	32	24	23	12	NA	24	7	NA	24	32	17	16	1	NA	13	5	NA	11
Wang[21]	2017	58	38	22	24	20	NA	26	NA	23	28	20	11	12	5	NA	6	NA	5	7
Ding[18]	2017	80	40	16	25	13	NA	NA	NA	23	25	40	21	20	19	NA	NA	NA	8	11
Xia[22]	2018	118	51	23	32	30	19	28	5	32	35	67	37	48	27	14	17	2	28	24
Li[19]	2018	74	8	5	4	NA	NA	NA	NA	NA	NA	66	42	48	NA	NA	NA	NA	NA	NA

Abbreviations: VA, venerable age, ≥50 y[11], ≥58 y[15], ≥60 y[16–22]; M, male; LD, low differentiation; T3–4, depth of infiltration (T3–4); LNM, lymph node metastasis positive; DM, distant metastasis; HTS, high TNM stage (III–IV); T ≥5, tumor size ≥5 cm.

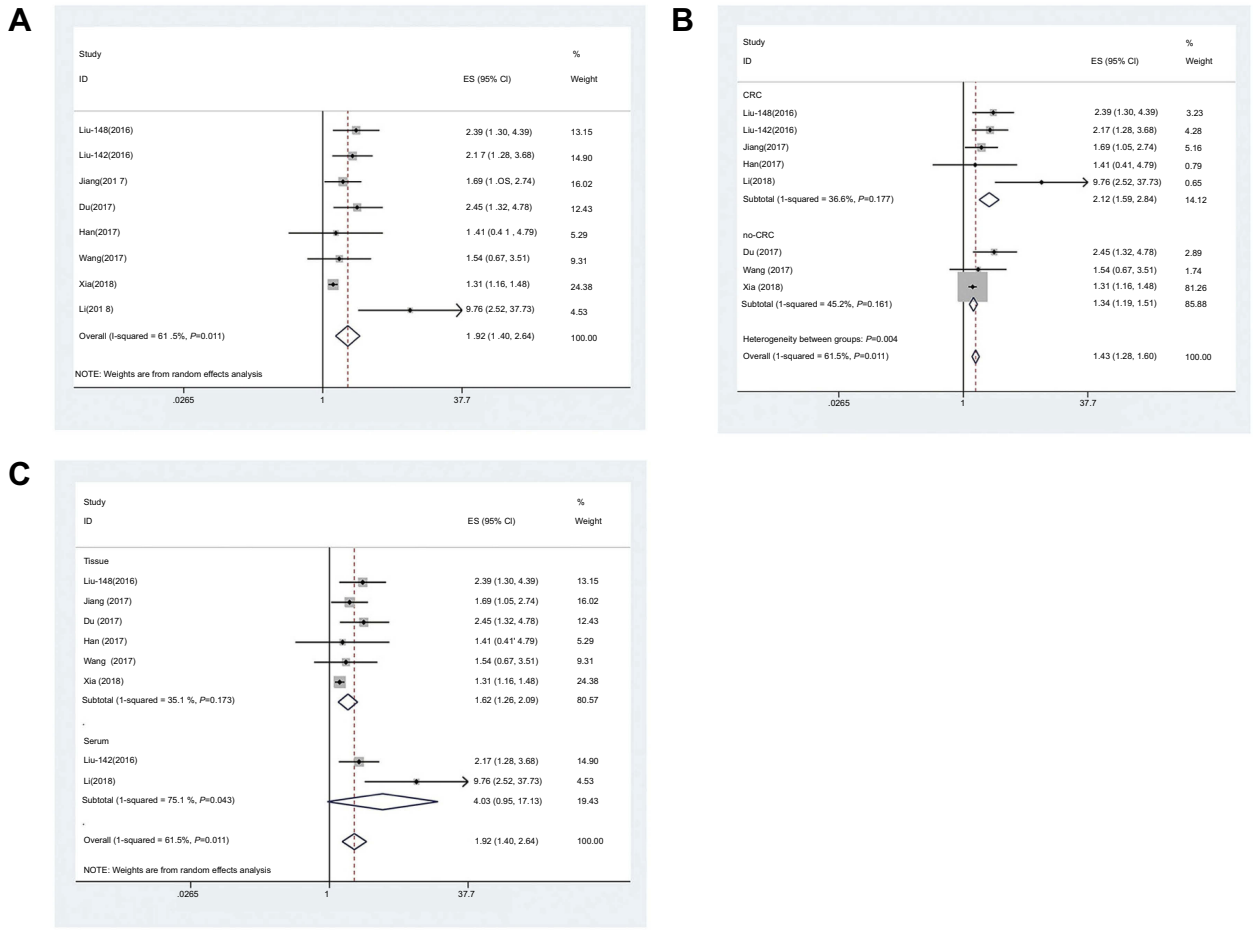

Figure 2 Meta-analysis of the pooled HRs of OS in different types of cancer with high CRNDE expression. (**A**) Forest plot of the correlation between CRNDE expression and OS. (**B**) Subgroup analysis of HRs of OS according to the factor of type of cancer. (**C**) Subgroup analysis of HRs of OS according to the factor of sample source.
Abbreviations: CRC, colorectal cancer; no-CRC, non-colorectal cancer; ES, effect size.

follow-up times, and type of analysis (Table 3). A negative correlation was observed between high CRNDE expression and OS, in patients with both CRC [HR=2.12, 95% CI (1.59–2.84), p<0.001] and non-CRC [HR=1.34, 95% CI (1.19–1.51), p=0.024] (Figure 2B). In addition, a negative correlation was observed between high CRNDE expression and OS in samples derived from tissue [HR=1.62, 95% CI (1.26–2.09), p<0.001] (Figure 2C). Moreover, a negative correlation was observed between high CRNDE expression and OS in the sample size ≥100 subgroup [HR=1.80, 95% CI (1.32–2.46), p<0.001] (Figure S1A). A negative correlation was also observed between high CRNDE expression and OS in patients with follow-up times <5 years [HR=2.04, 95% CI (1.45–2.88), p<0.001] and ≥5 years [HR=2.02, 95% CI (1.21–3.39), p=0.008] (Figure S1B). In studies in which a multivariate analysis was reported, the association between high CRNDE expression and OS of patients was significant [HR=1.80, 95% CI (1.32–2.46), p<0.001] (Figure S1C). There was no significant association observed in other subgroups.

The sensitivity analysis suggested that the pooled HR was not significantly affected by any individual study. Therefore, the conclusions derived from the present analysis were accurate and robust (Figure 3).

Association between CRNDE and clinicopathological features

Seven studies, including a total of 763 patients, provided data regarding clinicopathological parameters.[11,17–22] The fixed effects or random models were used to analyze the relationship between the CRNDE expression levels and clinicopathological parameters (Table 4). The pooled effect estimates of the N stage [OR=2.82, 95% CI (1.85–4.31), p<0.001] (Figure 4A), M stage [OR=2.72, 95% CI (1.16–6.35), p=0.021] (Figure 4B), more advanced TNM stage [OR=3.13, 95% CI (2.03–4.83), p<0.001] (Figure 4C), tumor size ≥5 cm [OR=2.81, 95% CI (1.62–4.88), p<0.001] (Figure 4D) were in favor of the high CRNDE expression group.

Table 3 Subgroup analysis of overall survival

Subgroups	Studies(n)	Number of patients	HR	95% CI	*P*	Heterogeneity		
						I^2(%)	*P*	Model
Total	8	793	1.92	1.40–2.64	<0.001	61.5%	0.011	Random
Cancer type								
CRC	5	679	2.12	1.59–2.84	<0.001	36.6%	0.177	Fixed
Non-CRC	3	294	1.34	1.19–1.51	0.024	45.2%	0.161	Fixed
Source								
Tissue	6	757	1.62	1.26–2.09	<0.001	35.1%	0.173	Random
Serum	2	216	4.03	0.95–17.13	0.059	75.7%	0.043	Random
Sample size								
≥100	5	777	1.80	1.32–2.46	<0.001	61.3%	0.035	Random
<100	3	196	2.56	0.84–7.78	0.098	65.9%	0.053	Random
Follow-up								
<5	4	412	2.04	1.45–2.88	<0.001	0.0%	0.776	Random
≥5	4	561	2.02	1.21–3.39	0.008	76.1%	0.006	Random
Analysis type								
Multivariate analysis	5	777	1.80	1.32–2.46	<0.001	61.3%	0.035	Random
Kaplan–Meier	3	196	2.56	0.84–7.78	0.098	65.9%	0.053	Random

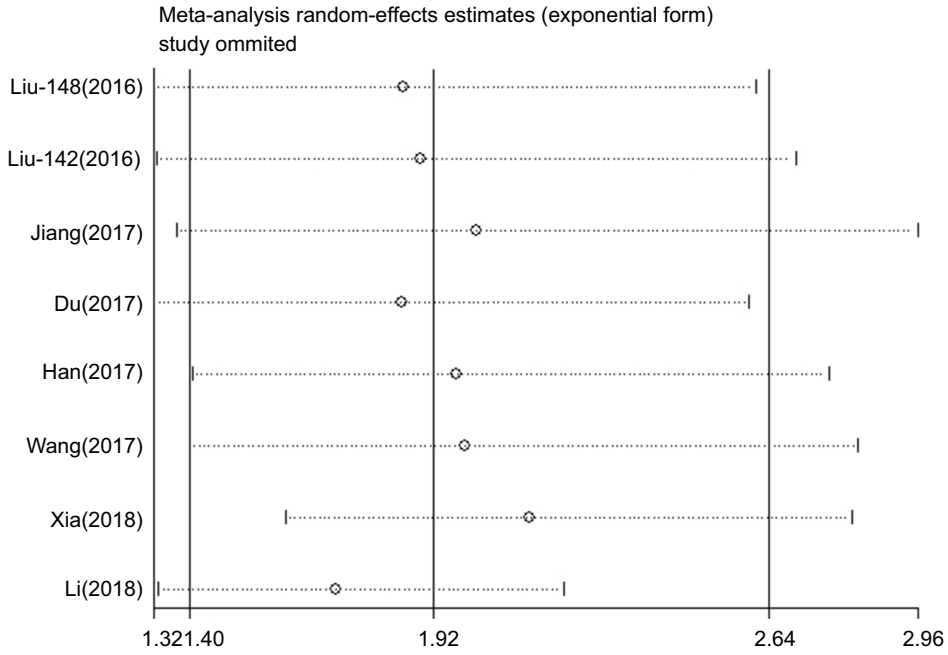

Figure 3 Sensitivity of CRNDE expression for overall survival.

In the non-CRC group, a significant association between high CRNDE expression and high T stage [OR=2.54, 95% CI (1.46–4.41), *p*=0.001] (Figure 4E) or worse histopathological grade [OR=2.21, 95% CI (1.37–3.57), *p*=0.001] (Figure 4F) was observed. Nevertheless, there was no association observed with age (Figure S2A) or sex (Figure S2B).

Table 4 Subgroup analysis of pooled odds ratios for the relationship between CRNDE expression levels and clinicopathological parameters by factor of cancer type

Category	Studies (n)	Number of patients	OR	95% CI	*P*	Heterogeneity		
						I^2 (%)	*P*	Model
Age (venerable age vs no)	7	763	1.11	0.83–1.50	0.486	29.1%	0.206	**Fixed**
CRC	4	469	1.36	0.92–2.01	0.124	43.5%	0.151	Fixed
Non-CRC	3	294	0.84	0.52–1.33	0.451	0.0%	0.699	Fixed
Sex (female vs male)	7	763	1.00	0.74–1.36	0.997	29.5%	0.203	Fixed
CRC	4	469	0.79	0.54–1.77	0.240	24.9%	0.262	Fixed
Non-CRC	3	294	1.43	0.88–2.32	0.144	0.0%	0.608	Fixed
Differentiation (poor vs well-morderate)	5	609	2.03	0.79–5.20	0.140	81.2%	0.000	Random
CRC	2	315	2.56	0.07–92.17	0.140	90.6%	0.001	Random
Non-CRC	3	294	2.21	1.37–3.57	0.001	0.0%	0.756	Random
Depth of infiltration (T3–4 vs T1–2)	4	567	1.53	0.81–2.91	0.191	65.2%	0.035	Random
CRC	2	331	0.94	0.35–2.50	0.895	70.0%	0.068	Random
Non-CRC	2	236	2.54	1.46–4.41	0.001	0.0%	0.690	Random
Lymph node metastasis (positive vs negative)	5	609	2.82	1.85–4.31	$p<0.001$	29.7%	0.224	Random
CRC	2	315	2.41	0.97–6.01	0.059	60.5%	0.111	Random
Non-CRC	3	294	3.49	2.13–5.70	$p<0.001$	0.0%	0.740	Random
Distant metastasis (yes vs no)	3	433	2.72	1.16–6.35	0.021	0.0%	0.450	Fixed
CRC	2	315	2.49	0.93–6.64	0.069	32.0%	0.225	Fixed
Non-CRC	1	118	3.53	0.66–19.0	0.141	–	–	Fixed
TNM stage (III-IV vs I-II)	4	374	3.13	2.03–4.83	$p<0.001$	0.0%	0.508	Fixed
CRC	1	80	5.41	2.00–14.66	0.001	–	–	Fixed
Non-CRC	3	294	2.75	1.70–4.46	$p<0.001$	0.0%	0.642	Fixed
Tumor size (≥5 vs <5 cm)	6	689	2.81	1.62–4.88	$p<0.001$	62.5%	0.020	Random
CRC	3	395	2.99	1.13–7.93	$p<0.001$	75.8%	0.016	Random
Non-CRC	3	294	2.79	1.29–6.05	$p<0.001$	57.0%	0.098	Random

The sensitivity analysis revealed that the pooled ORs were not significantly affected by any individual study. Therefore, the conclusions derived from this analysis in both the whole group and subgroups were accurate and robust (Figure S3A–H).

Publication bias

Begg's funnel plot and Egger's regression test suggested that there was no publication bias across the clinicopathological features, except for N stage (Begg's test: $p=0.027$, Egger's test: $p=0.011$). For the subgroups (Begg's test: $p<0.05$, Egger's test: $p<0.05$), the Duval and Tweedie's trim and fill method was applied. The results showed that the adjusted values were similar to the observed ones (Table 5).

Discussion

The incidence and mortality associated with gastrointestinal tumors is constantly increasing. Gastrointestinal cancers account for 27% and 37% of the total number of new cases and cancer-related death, respectively. Among them, CRC contributes 10% and 9% of the total number of new cases and cancer deaths, respectively, ranking third in terms of incidence and second in terms of mortality.[1] Therefore, it is particularly important to identify highly sensitive and specific biomarkers for the accurate diagnosis, treatment, and evaluation of prognosis in patients with gastrointestinal tumors.

Via interaction with DNA, RNA, proteins, lipids, or other molecules, lncRNAs act as key signal transduction mediators in cancer signaling pathways, and exert an effect

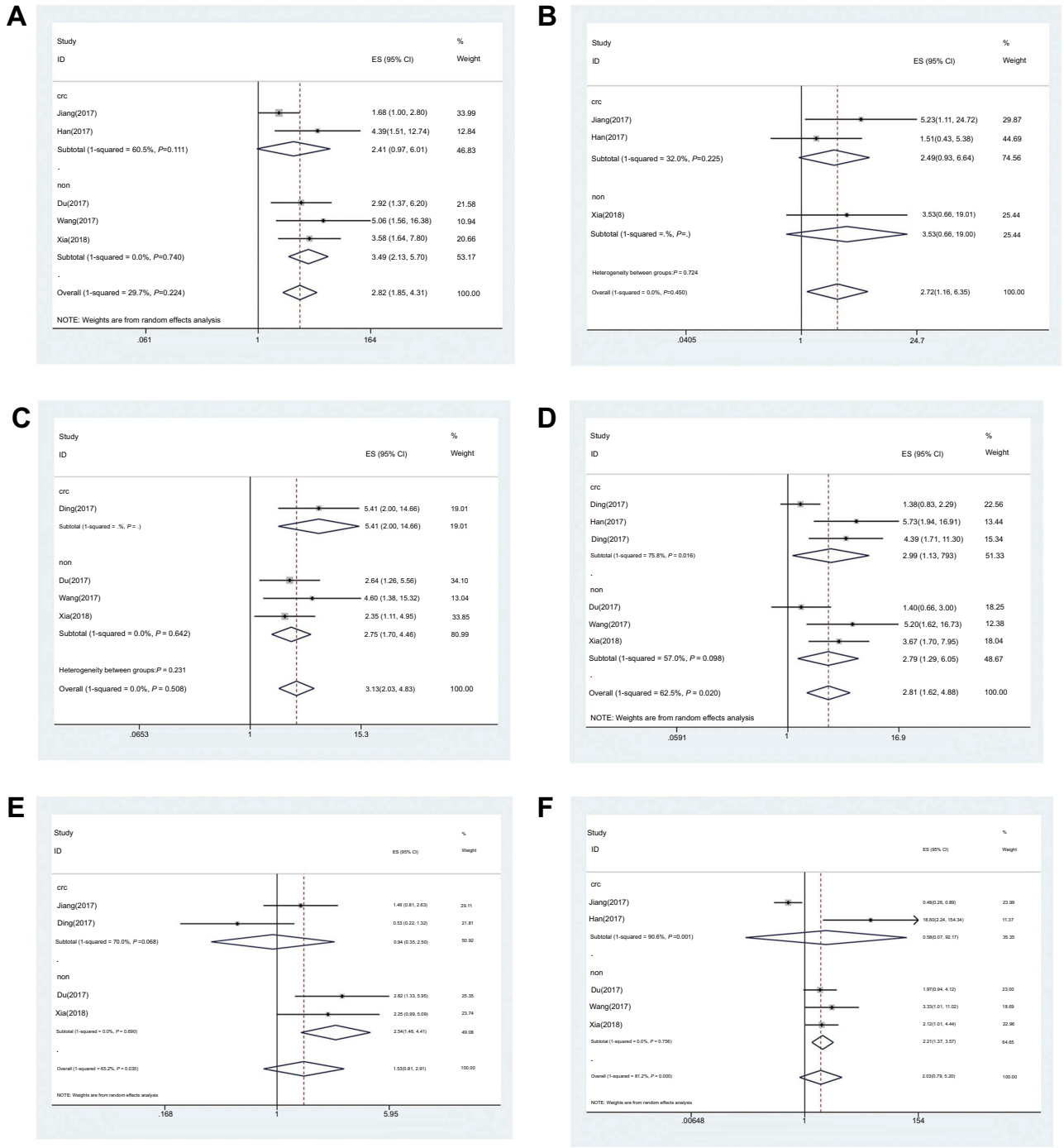

Figure 4 Forest plot of the correlation between CRNDE expression and clinicopathological characteristics. (**A**) Lymph node metastasis (positive vs negative). (**B**) Distant metastasis (yes vs no). (**C**) TNM stage (III–IV vs I–II). (**D**) Tumor size (≥5 vs <5 cm). (**E**) Depth of infiltration (T3–4 vs T1–2). (**F**) Differentiation (poor vs well-moderate). **Abbreviations:** CRC, colorectal cancer; non, non-colorectal cancer; ES, effect size.

on proliferation, metabolism, invasion, radioresistance, and chemoresistance.[25–27] Recent discoveries have revealed lncRNAs contributed to the diagnosis, treatments, and prognosis of cancer patients. For example, Liu et al suggested that the combination of CRNDE and carcino-embryonic antigen (CEA) expression showed improved diagnostic value versus each expression alone.[15] Zhang et al suggested that CRNDE contributed to the formation of the radioresistant phenotype of lung adenocarcinoma cells as an oncogene by modulating p21.[26] Qu et al suggested that activated in RCC with sunitinib resistance (ARSR) enhanced resistance to sunitinib by competitively binding miR-34/miR-449 in renal cell cancer.[27]

Table 5 The results of Begg's and Egger's tests for the publication bias

	Begg's test		Duval and Tweedie's trim and fill			Egger's test	
	Z	P	Trimmed studies	Observed values (CI)	Adjusted values (CI)	Intercept	P
HR analysis	0.870	0.386	5	1.92 (1.40–2.64)	1.33 (1.00–1.76)	1.734	0.013
Age	0.000	1.000	–	–	–	−0.652	0.685
Sex	0.300	0.764	–	–	–	−0.164	0.921
Differentiation	2.200	0.027	2	2.03 (0.79–5.20)	1.24 (0.52–2.97)	4.684	0.119
Depth of infiltration	0.340	0.734	–	–	–	−2.573	0.716
Lymph node metastasis	2.200	0.027	2	2.82 (1.85–4.31)	2.42 (1.63–3.58)	3.507	0.011
Distant metastasis	0.000	1.000	–	–	–	5.711	0.277
TNM stage	0.340	0.734	–	–	–	3.469	0.127
Tumor size	1.880	0.060	0	2.81 (1.62–4.88)	2.81 (1.62–4.88)	4.537	0.024

The results of this meta-analysis confirmed that high CRNDE expression may serve as a negative risk factor of survival, and predict advanced clinicopathological characteristics of patients with gastrointestinal tumors. According to the cancer type subgroup analysis, CRNDE could predict worse prognosis in CRC, but not in non-CRC. Based on the sample source subgroup analysis, CRNDE could predict poor prognosis in the tissue group; however, this ability was inconsistent in the serum group. This result may be attributed to the lack of relevant research on serum samples. Additional clinical trials are warranted to address the lack of data. Furthermore, the relationship between the expression of CRNDE and clinicopathological characteristics was investigated in patients. The pooled results revealed that high CRNDE expression was positively correlated with more advanced TNM stage and tumor size ≥5 cm. This correlation was stronger in CRC patients. High CRNDE expression was positively correlated with lymph node metastases. This correlation was stronger in non-CRC patients. Collectively, a positive correlation was observed between high CRNDE expression and M stage and N stage. However, this relationship was not observed in the cancer type subgroup analysis. This discrepancy may be attributed to the limited number of studies included in this analysis. Considering the high OR value recorded in the overall analysis, the high expression of CRNDE exhibits a great potential for the prediction of distant metastasis. Of note, in the CRC group, there was no significant correlation between CRNDE expression and worse histopathological grade or T-stage. However, in the non-CRC group, a positive correlation was observed between these factors. There was no significant association observed between CRNDE expression and age and sex.

Thus far, all published studies confirmed that high CRNDE expression was associated with a shorter OS in patients. These findings are consistent with the results observed in the present meta-analysis. The HRs reported by Li et al were higher than those of other studies. An explanation may be that patients in the study reported by Li et al exhibited a more advanced TNM stage and received FOLFOX chemotherapy versus patients in other studies (TNM stage I–IV).[19] Inter-study heterogeneity mainly originated from this difference. It is suggested that CRNDE expression has a higher prognostic value in patients with more advanced TNM stage. Two meta-analyses investigated the relationship between CRNDE and survival or clinicopathological features in patients with solid cancer. Consistent with the present findings, Xie et al and Liang et al confirmed that high CRNDE expression predicts poor OS.[28,29] Moreover, both studies suggested that high CRNDE expression is related to more advanced TNM stage and N stage in patients with solid tumors – a finding which is also consistent with the conclusions of our meta-analysis. Liang et al also suggested that there was no correlation between CRNDE expression and tumor size or histopathological grade.[29] This observation was different from our results. In their studies, other clinicopathological features (eg, M stage and T stage) were not evaluated. We included more studies, detailed subgroups [cancer type (CRC vs other gastrointestinal cancers), follow-up (<5 years vs ≥5 years), source (tissue vs serum), etc.], and clinicopathological features (age, differentiation, distant metastasis, etc.). In addition, we conducted a more comprehensive and detailed investigation of the relevance of CRNDE to prognosis and clinicopathological characteristics.

In gastrointestinal tumors, high CRNDE expression is often related to poor OS and more advanced clinicopathological features. Recent research provided novel insights into the functions of CRNDE in cancer pathogenesis and clinicopathological processes. In CRC, CRNDE enhanced cell proliferation and chemoresistance via modulation of Wnt/β-catenin through competitively binding miR-217 and miR-181a-5p.[17,30] CRNDE functioned as a competing endogenous RNA for miR-136, led to the derepression of its endogenous target, E2F transcription factor 1 (E2F1).[31] Several studies demonstrated that CRNDE regulates tumor progression through interaction with proteins. Jiang demonstrated that CRNDE stabilized by heterogeneous nuclear ribonucleoprotein U-like 2 protein (hnRNPUL2) enhanced cell proliferation and migration by activating the Ras/MAPK signaling pathways.[11] The results of the present study suggested that CRNDE is involved in cell carcinogenesis and inhibition of apoptosis by binding enhancer of zeste homolog 2 (EZH2).[18] In GC, the present research confirmed that CRNDE enhanced cellular proliferation by increasing the expression of downstream molecules of E2F transcription factor 3 (E2F3) through derepression of miR-145.[12] Du et al indicated that CRNDE accelerated cell migration and invasion via the activation of the PI3K/Akt signaling pathways.[20] In PC, CRNDE sponges miR-384 to enhance cellular proliferation and metastasis via upregulation of insulin receptor substrate 1 (IRS1).[21] In HCC, CRNDE suppressed miR-384 to promote cellular migration, invasion, and proliferation via the upregulation of NF-κB and p-AKT.[32] Wang found that CRNDE increased the expression levels of mitogen-activated protein kinase 1 (MAPK1) through inhibition of miR-217 in the process of cell proliferation, migration, and invasion.[33] Xia et al demonstrated that CRNDE played a key role in epithelial-mesenchymal transition and metastasis.[22]

The present meta-analysis was characterized by limitations. Firstly, all studies were conducted in China, which may limit the representativeness of other ethnic populations. Thus, international studies with larger sample sizes are necessary to verify the results obtained in this meta-analysis. Secondly, our analysis included only studies published in English or Chinese. This may cause publication bias. Thirdly, partial HRs were calculated or extracted from reconstructed survival curves rather than being directly extracted from the primary studies. Fourthly, the inclusion of research studies without a consistent CRNDE cut-off value was one of the sources of heterogeneity. Finally, owing to the lack of relevant data, it is not possible to analyze the relationship between CRNDE expression and several clinicopathological features, such as CEA expression and tumor location.

Conclusion

This meta-analysis revealed that CRNDE might act as an unfavorable risk factor of survival and contribute to the elucidation of the relationship between CRNDE and clinicopathological features in gastrointestinal cancer. Collectively, CRNDE may act as a putative cancer biomarker and can be potentially applied for early diagnosis, targeted therapy, and evaluation of prognosis in patients with gastrointestinal cancer. Further studies are warranted to confirm these findings. Future research may determine the appropriate CRNDE cut-off value, develop an efficient and accurate method for serum testing, and elucidate the molecular mechanisms of CRNDE involvement in the promotion of tumorigenesis.

Abbreviation list

lncRNA, long noncoding RNA; CRNDE, colorectal neoplasia differentially expressed; HR, hazard ratio; OR, odds ratios; OS, overall survival; 95% CI, 95% confidence intervals; NOS, the Newcastle–Ottawa Quality Assessment Scale; qRT-PCR, quantitative real-time PCR; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; EC, esophageal cancer; PC, pancreatic cancer; GCa, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; CEA, carcino-embryonic antigen; ARSR, activated in RCC with Sunitinib Resistance; E2F1, E2F Transcription Factor 1; E2F3, E2F transcription factor 3; hnRNPUL2, heterogeneous nuclear ribonucleoprotein U-like 2 protein; EZH2, enhancer of zeste homolog 2; IRS1, insulin receptor substrate 1; NF-κB, nuclear factor-κB; p-AKT, phospho-AKT; MAPK1, mitogen-activated protein kinase 1; EMT, epithelial-mesenchymal transition.

Ethics approval and informed consent

Patients or clinical samples were not investigated in this study; hence, ethical approval was not required.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

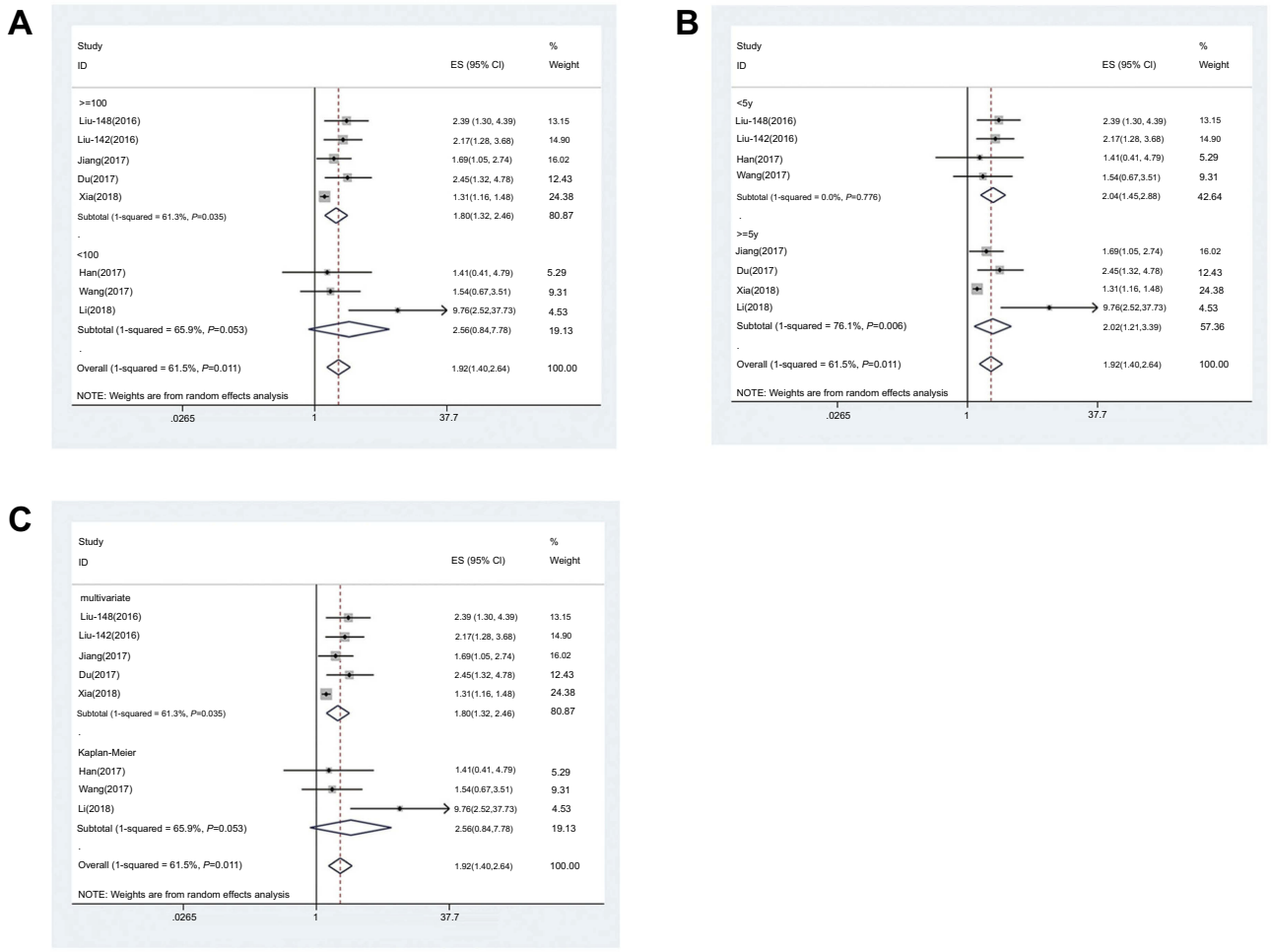


Figure S1 Meta-analysis of the pooled HRs of OS in different types of cancer with high CRNDE expression. (**A**) Subgroup analysis of HRs of OS according to the factor of sample size. (**B**) Subgroup analysis of HRs of OS according to the factor of follow-up time. (**C**) Subgroup analysis of HRs of OS according to the factor of analysis type.
Abbreviation: ES, effect size.

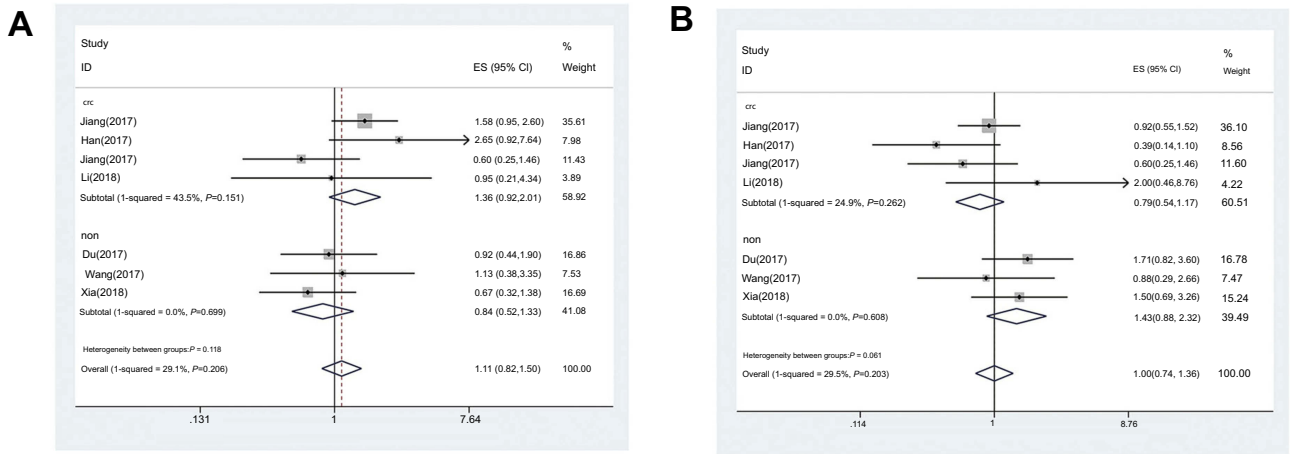
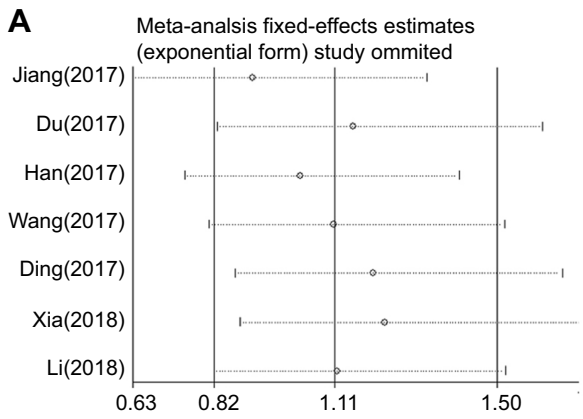


Figure S2 Forest plot of the correlation between CRNDE expression and clinicopathological characteristics. (**A**) Age (venerable age vs no). (**B**) Sex (female vs male).
Abbreviations: CRC, colorectal cancer; non, non-colorectal cancer; ES, effect size.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(exponential form) study ommited
Jiang(2017)
Du(2017)
Han(2017)
Wang(2017)
Ding(2017)
Xia(2018)
Li(2018)
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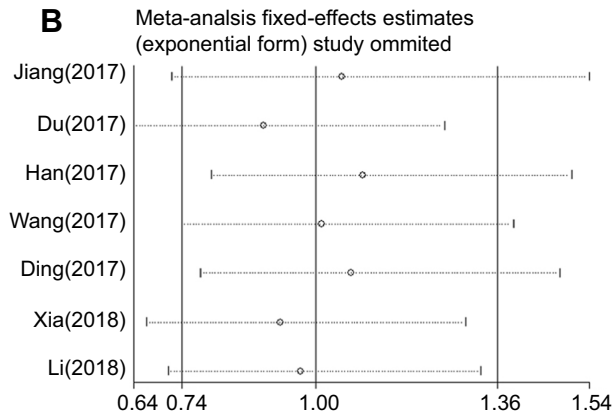
0.82
1.11
1.50


B
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Jiang(2017)
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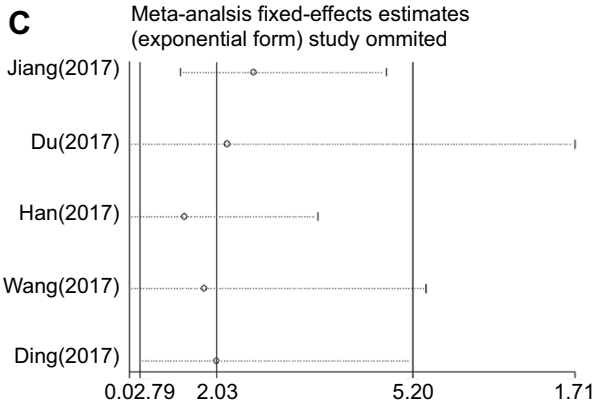
1.36
1.54


C
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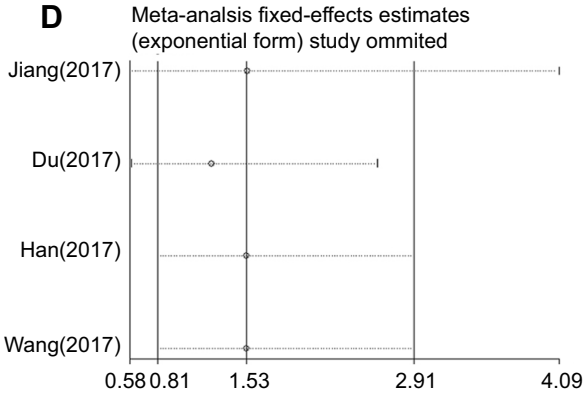
2.03
5.20
1.71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4.09

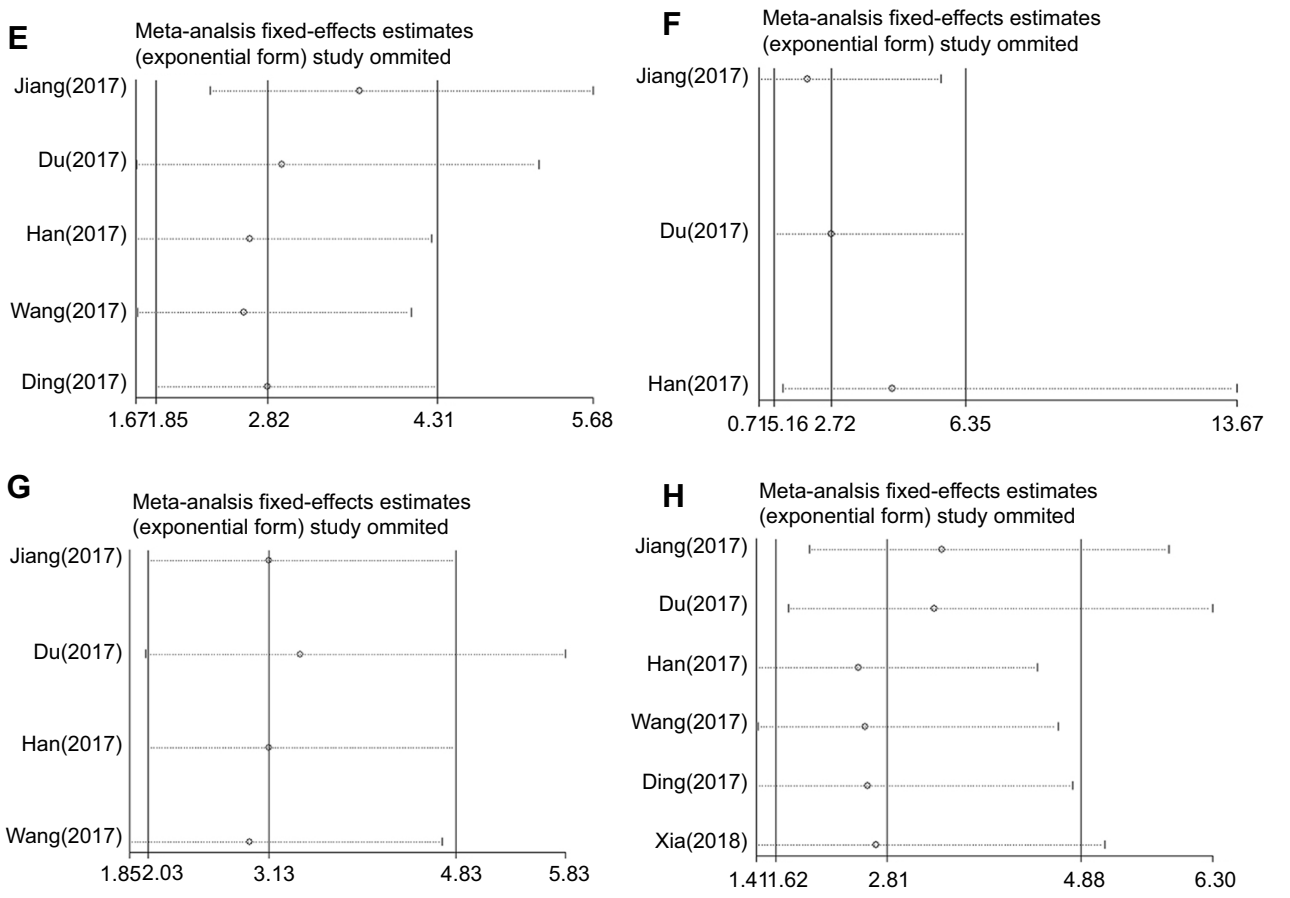

Figure S3 Sensitivity of CRNDE expression for the ORs of clinicopathological characteristics. (**A**) Age. (**B**) Sex. (**C**) Differentiation. (**D**) Depth of invasion. (**E**) Lymph node metastasis. (**F**) Distant metastasis. (**G**) TNM stage. (**H**) Tumor size.