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The diagnostic and prognostic significance of long non-coding RNA CRNDE in pan-cancer based on TCGA, GEO and comprehensive meta–analysis

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ABSTRACT

Background: Accumulating evidence has confirmed that CRNDE is significantly expressed in various cancers, suggesting that it may be a potential biomarker for cancer. However, its diagnostic and prognostic values of CRNDE in cancer are not completely clear. Therefore, we conduct a comprehensive study on CRNDE in cancer.

Materials and methods: CRNDE expression data were downloaded from The Cancer Genome Atlas (TCGA). Microarray data were derived from the Gene Expression Omnibus (GEO) database to validate its differential expression. Furthermore, the receiver operator characteristic curve (ROC) and Kaplan-Meier survival analysis were used to evaluate the diagnostic and prognostic values of CRNDE in cancer, respectively. Finally, we carried out a meta-analysis to comprehensively evaluate the diagnostic and prognostic values of CRNDE in cancer.

Results: In TCGA database, CRNDE was overexpressed in nine types of cancer, among which polymorphic glioblastoma and colonic adenocarcinoma are the most highly expressed. The area under curves (AUC) of nine cancer types ranged from 0.855 to 0.984. Additionally, the high expression level of CRNDE was significantly associated with poor overall survival only in hepatocellular carcinoma ($p = 0.032$) among the nine cancers in the Kaplan-Meier survival analysis. Finally, the results of the meta-analysis on the literatures showed that the pooled sensitivity, specificity, summary receiver operator characteristic curve (SROC), and the overall hazard ratio of CRNDE in cancers were 0.77 (95% CI: 0.71–0.82), 0.90 (95% CI: 0.82–0.95), 0.87 (95% CI: 0.84–0.90), and 1.66 (95% CI: 1.37–2.01), respectively.

Conclusion: CRNDE could be a potential biomarker for cancer diagnosis and prognosis.

1. Introduction

Cancer ranks second among human diseases in the United States, and becomes a threat to human life around the world, which has attracted attention from many researchers [1,2]. Scientists try different treatments for cancer such as targeted drug treatment, surgical resection, radiotherapy and chemotherapy. Despite major progresses that has been made in early screening of all types of cancer and the introduction of innovative treatments to reduce cancer mortality, the incidence of cancer still remains worrying [3,4]. Therefore, it is imperative to explore new diagnostic biomarkers for cancer.

With the rapid development of genome-wide sequencing technology, a large number of gene sequencing data can be obtained from online comprehensive platforms such as TCGA, GEO and Oncomine database, which provide researchers easier access to study various diseases [5–7].

With the deepening of human genomics research, 2% of genomic sequences are translated into proteins, most of which are transcribed into long non-coding RNAs (lncRNAs), i.e. RNA molecules with length of 200 nucleotides transcribed in class [8–11]. Previous studies have demonstrated that the regulatory role of lncRNAs affects gene expression activity and then alters cellular biological states to promote tumorigenesis and development [12–18]. Researchers have found that many functional lncRNAs are closely associated with many human diseases [19,20]. For example, our team reported BLACAT1's potential role as a diagnostic marker for many types of cancer and its significant prognostic value in endometrial cancer [21], and MALAT1's possible function as a new biomarker for the diagnosis and prognosis of nasopharyngeal carcinoma [22]. By enhancing miR-218 expression and inhibiting Bmi-1 expression, HOTAIR silencing activates P16Ink4a and

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P14 ARF signaling and leads to inhibition of cancer genesis in hepatocellular carcinoma [23]. LncROR promotes cell proliferation and cell metastasis in bladder cancer, and inhibits apoptosis [24]. Although there are many studies on lncRNAs, the functions of most lncRNAs are still unknown.

Colorectal neoplasia differentially expressed (CRNDE) is located at 16q12.2. Scientists are gradually aware of CRNDE's role in the development of various cancers. It can be translated into multiple transcripts, but the role of each transcript is different from one another [25]. The studies have shown that CRNDE is highly expressed in a variety of diseases at present, including cardiovascular disease, endocrine system disorders, autoimmune diseases and various malignancies [26–28]. But this mechanism has not yet been completely clear in a variety of cancer. Therefore, the purpose of this study is to evaluate the diagnostic and prognostic significance of CRNDE expression in pan-cancer based on data mining and comprehensive literature analysis.

2. Materials and methods

2.1. Data mining based on the TCGA database

The Cancer Genome Atlas (TCGA) is a free and comprehensive database that includes large clusters of human cancer genome sequencing data (https://Cancergenome.nih.gov/). The standard for data inclusion in our study is that the sample size must include both cancer and normal tissues, and that the number of normal tissue controls must be greater than or equal to three. The overall data were downloaded from TCGA database for comprehensively mining the data about CRNDE in cancer.

R3.4.0 software was used to process the data and calculate the difference between normal tissue and cancer groups in each cancer data. The data processing was performed by "edgeR" package. The differentially expressed CRNDE from each cancer was determined on the basis of $p < 0.05$ and logFC > 2. Next, the receiver operator characteristic curve (ROC) was used to evaluate the diagnostic value of CRNDE in each cancer. The "survival" package was utilized to analyze the prognostic value of CRNDE.

2.2. Selection and processing of a qualified microarray in the GEO database

Microarray data were downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) up to September 2017. Then we searched the following keywords: (lncRNA CRNDE) AND (tumor OR cancer OR carcinoma OR neoplasm OR neoplasms malignant). Each data set should meet the following criteria: (1) the data were all obtained from the GPL570 data platform. (2) the samples were all from human, which were divided into cancer tissue group and normal tissue control.(3)for those overlapping microarray arrays, the larger number of cases were employed in our study.(4)the number of the normal tissue was greater than three. We downloaded the original CEL files and used the R3.4.0 software to preprocess the raw data using the RMA method, performed the background correction and normalization, and then collated the platform files. We used "edgeR" package to compare the expression levels between cancer and non-cancerous tissues, and the expression level of CRNDE with $p < 0.05$ and logFC > 2 was considered as statistically significant.

2.3. Diagnostic and prognostic meta-analysis of CRNDE

2.3.1. Literature search

We searched the databases such as PubMed, Web of Science, Embase and Cochrane Library to obtain all relevant articles as of December 31, 2017. The search strategies were as follows:

#1 colorectal neoplasia differentially expressed OR CRNDE OR lncRNA CRNDE

#2 carcinoma OR cancer OR tumor OR tumour

Table 1
Cancer types included in our study from TCGA database.

	Cancer types	Number of samples		
		Total	Normal	Tumor
ACC	Adrenocortical carcinoma	79	0	79
AML	Actue Myeloid	187	2	185
BLCA	Bladder urothelial carcinoma	433	19	414
BRCA	Breast invasive carcinoma	1222	113	1109
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	309	3	306
CHOL	Cholangiocarcinoma	45	9	36
COAD	Colon adenocarcinoma	521	41	480
DLBC	Lymphoid neoplasm diffuse large B-cell lymphoma	48	0	48
ESCA	Esophageal carcinoma	173	11	162
GBM	Glioblastoma multiforme	174	5	169
HNSC	Head and Neck squamous cell carcinoma	546	44	502
KICH	Kidney chromophobe	89	24	65
KIRC	Kidney renal clear cell carcinoma	611	72	539
KIRP	Kidney renal papillary cell carcinoma	321	32	289
LAML	Acute Myeloid Leukemia	151	0	151
LGG	Brain lower grade glioma	529	0	529
LIHC	Liver hepatocellular carcinoma	424	50	374
LUAD	Lung adenocarcinoma	594	59	535
LUSC	Lung squamous cell carcinoma	551	49	502
MESO	Mesothelioma	86	0	86
NBL	nephroblastoma	157	0	157
OV	Ovarian serous cystadenocarcinoma	379	0	379
PAAD	Pancreatic adenocarcinoma	182	4	178
PCPG	Pheochromocytoma and Paraganglioma	186	3	183
PRAD	Prostate adenocarcinoma	551	52	499
READ	Rectum adenocarcinoma	177	10	167
SARC	Sarcoma	265	2	263
SKCM	Skin cutaneous melanoma	472	1	471
STAD	Stomach adenocarcinoma	407	32	375
TGCT	Testicular germ cell tumors	156	0	156
THCA	Thyroid carcinoma	568	58	510
THYM	Thymoma	121	2	119
UCEC	Uterine corpus endometrial carcinoma	587	35	552
UCS	Uterine carcinosarcoma	56	0	56
UVM	Uveal melanoma	80	0	80
WT	high-risk tumor	132	6	126
Total		11574	743	10910

#3 #1 AND #2 AND (accuracy OR sensitivity OR specificity OR prognosis OR prognostic)

2.3.2. Inclusion and exclusion criteria

The included articles should meet the following criteria: (1) patients diagnosed with cancer and the relationship between CRNDE and cancer were investigated; (2) for diagnostic studies, the diagnostic value of CRNDE was evaluated, and the sensitivity and specificity or the true positive (TP), true negative (TN), false positive (FP), false negative (FN) were provided; (3) the literature was written in English. For prognostic studies, the hazard ratio (HR) or risk ratio values with 95% confidence interval(CI)or the survival curve were provided.

Exclusion criteria were as follows: (1) duplicate studies, (2) letters, (3) review articles, (4) case reports, (5) incomplete data, (6) non-human studies, (7) prognostic studies whose value of HR was not within the 95% CI.

2.3.3. Data quality assessment and extraction

For diagnostic studies, the quality of the literature was mainly determined by the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [29]. We evaluated the quality of literature by the questions, which include the types of studies, participants, target conditions, index tests, comparator tests, and so on. For prognostic studies, the Newcastle–Ottawa scale (NOS) was applied to assess the risk of bias and the criteria for reporting observational studies to complete the methodological evaluation.

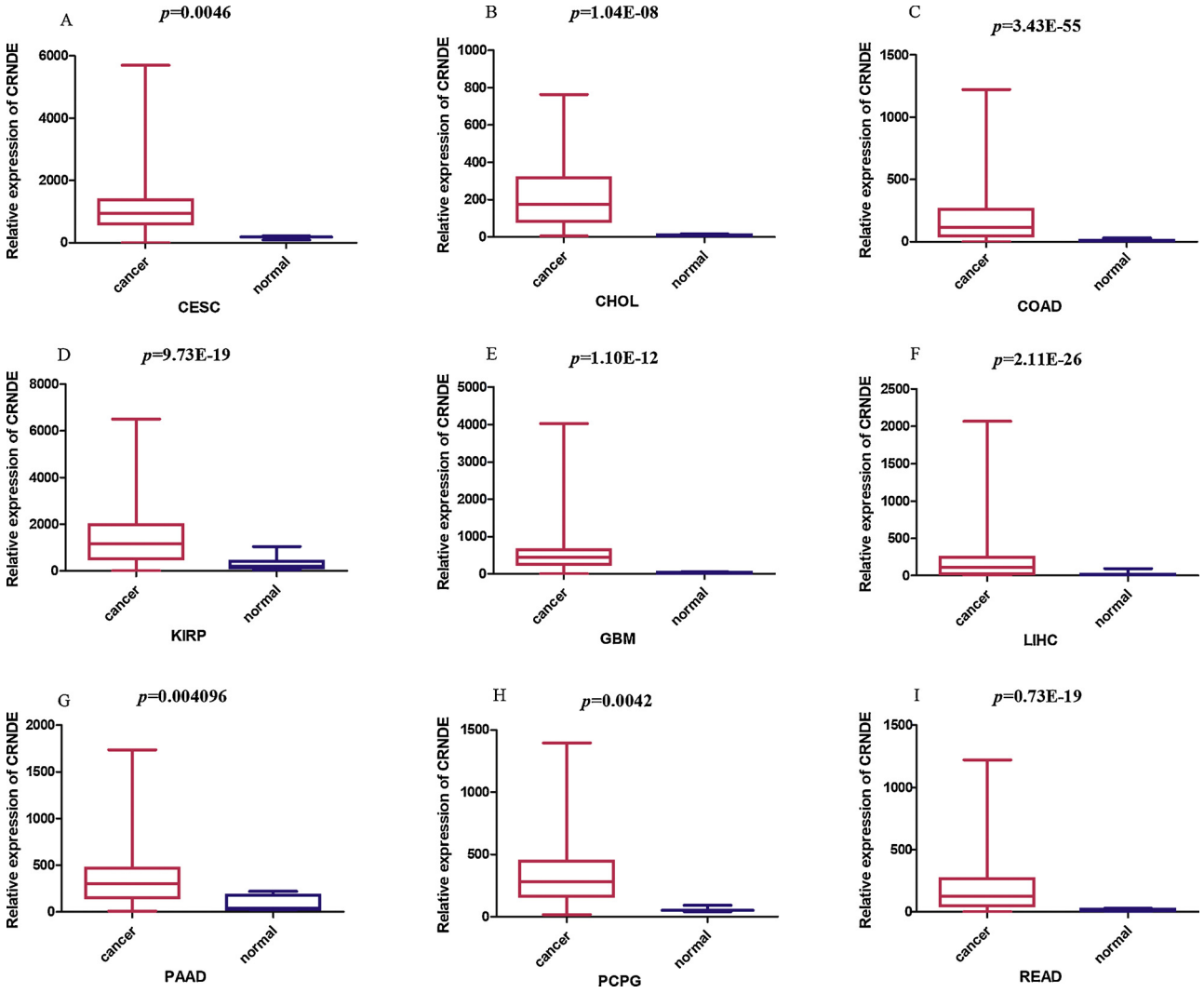

Fig. 1. Expression of CRNDE in 9 kinds of cancer in TCGA database. Red box plot represent the cancer tissue group, and blue box plot represent the normal control tissue. Expression levels in 9 types of cancer were significantly different ($p < 0.05$).(A)CESC; (B) CHOL; (C) COAD; (D) KIRP; (E) GBM; (F) LIHC; (G) PAAD; (H) PCPG; (I) READ.

2.4. Statistical methods

Stata12.0 was used to analyze the data. For diagnostic study, the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), 95% confidence interval (CI), and summary receiver operator characteristic curve (SROC) were analyzed. HR and corresponding 95% CI were used to estimate the correlation between CRNDE expression and prognosis of cancer. The Q test and the I^2 test were used to indicate the degree of heterogeneity. The *p*-value of the Q test < 0.05 or I^2 > 50% suggested significant heterogeneity. In this case, a random-effect model was used. Otherwise, a fixed-effect model was used. Deek's funnel plot or Begg's test was used to evaluate the publication bias. And *p*-value > 0.05 indicated there was no publication bias in these studies. The Kaplan-Meier (K-M) method was utilized for survival analysis. The "survival" package was adopted to extract related gene expression of patients with various cancers and analyze their survival rate.

2.5. Patient and public involvement

All the data were obtained from the public databases such as TCGA, GEO, PubMed, Web of Science, Embase and Cochrane Library, so patients and the public were not involved.

3. Results

3.1. Differentially expressed CRNDE in the TCGA database

Data from a total of 11,574 patients from 37 types of cancer were downloaded from TCGA database. According to our screening criteria, 11 types of cancer were removed from our study (Table 1). After data processing, we found that CRNDE was highly expressed in nine cancers, including colonic adenocarcinoma (COAD), polymorphic glioblastoma (GBM), rectal adenocarcinoma (READ), cholangiocarcinoma (CHOL), hepatocellular carcinoma (LIHC), cervical squamous cell carcinoma (CSCE), pheochromocytoma and paraganglioma (PCPG), renal kidney papillary carcinoma (KIRP), and pancreatic adenocarcinoma (PAAD). Among them, patients with COAD (logFC = 4.80, $p < 0.0001$) and GBM (logFC = 4.75, $p < 0.0001$) showed the most significant difference compared to that in normal individuals. We plotted nine histograms to compare the expression levels of cancer tissues and normal tissues from nine types of cancer (Fig. 1). They are the following nine types of cancer (Fig. 1A) CESC; (Fig. 1B) CHOL; (Fig. 1C) COAD; (Fig. 1D) KIRP; (Fig. 1E) GBM; (Fig. 1F) LIHC; (Fig. 1G) PAAD; (Fig. 1H) PCPG; (Fig.1I) READ. The results showed that the expression of CRNDE in cancer tissues was significantly higher than that in normal tissues.

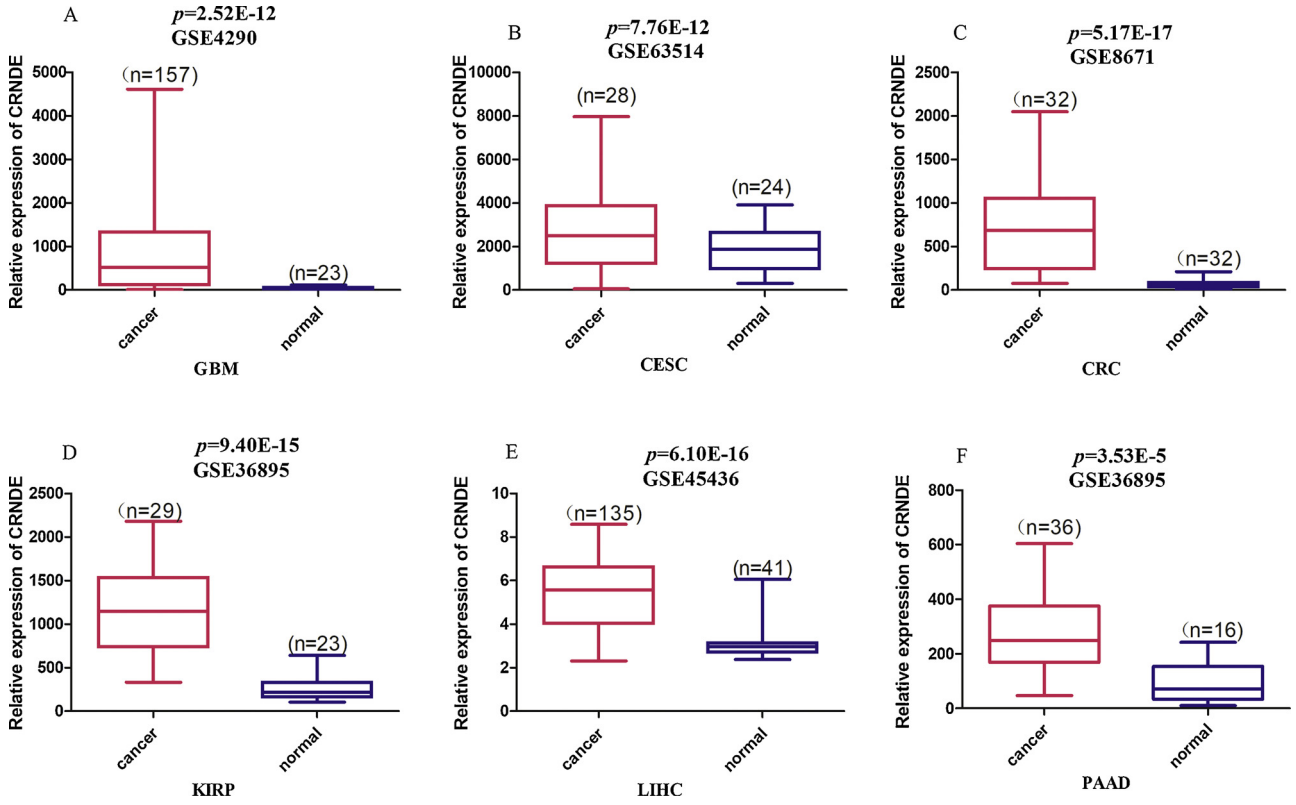

Fig. 2. Based on the GEO database, six microarray data further validated the expression of CRNDE in cancers. (A) GBM = GSE4290, (B) CESC = GSE63514, (C) CRC = GSE8671, (D) KIRP = GSE36895, (E) LIHC = GSE45436, (F) PAAD = GSE16515.

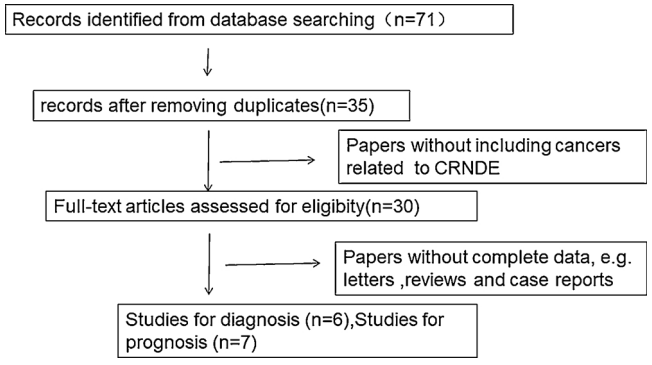

Fig. 3. The flow diagram of this meta-analysis in cancers.

3.2. Validation of differentially CRNDE expression based on the GEO database

The CRNDE expression data were selected from GEO database. Due to the small sample size for CHOL, SARC and PCPG in GEO database, we excluded them in this study. Moreover, the COAD and READ were collectively referred to as colorectal cancer (CRC). With this respect, we finally obtained six sets of microarray data in our study which included both cancer patients and normal controls (GSE4290, GSE45436, GSE8671, GSE63514, GSE16515 and GSE36895). It can be seen from Fig. 2 that CRNDE is overexpressed in six cancers including GBM (Fig. 2A), CESC (Fig. 2B), CRC (Fig. 2C), KIRP (Fig. 2D), LIHC (Fig. 2E) and PAAD (Fig. 2F). The expression levels of CRNDE in cancer tissues

Table 3
Summary of HRs and their 95% CI in the prognostic meta-analysis.

Study	Year	Country	Cancer	OS			NOS
				HR	ll	ul	
Jiang HJ [43]	2017	China	CRC	1.693	1.047	2.738	8
Liu T1 [41]	2016	China	CRC	2.39	1.302	4.386	8
Liu T2 [42]	2016	China	CRC	2.173	1.282	3.684	8
Szafron LM [44]	2015	Poland	OC	6.072	1.814	20.32	7
Dai MY [37]	2017	China	HCC	1.39	1.06	1.82	8
Wang G [25]	2017	China	PC	1.39	0.68	2.88	9
Han P[45]	2017	China	CRC	1.41	0.49	4.09	8

Table 2
Primary characteristics of the adopted articles in the diagnostic meta-analysis.

Study/ Reference	Year	State	Cancer	Case/Con	Sample	method	TP	FP	TN	FN	Sen(%)	Spe(%)	QUADAS-2
Graham1 LD [26]	2011	Australia	CRC	15/15	plasma	PCR	13	1	14	2	93.3	86.7	6
Graham1 LD [26]	2011	Australia	CRC	160/220	tissue	PCR	155	43	177	6	80	96	6
Liu T1 [30]	2016	China	CRC	148/80	serum	PCR	139	24	56	9	70.3	94.4	5
Liu T2 [31]	2016	China	CRC	142/142	tissue	PCR	101	42	100	41	70.4	70.8	6
Dai MY [32]	2017	China	HCC	30/30	Serum	PCR	21	4	9	26	71	87.1	7
Jiang HJ [33]	2017	China	CRC	251/128	tissue	PCR	225	25	103	26	80.5	89.6	5

Notes: TP represents the true positive; FP represents the false positive; TN represents the true negative; FN represents the false negative; Sen represents sensitivity; Spe represents specificity.

Table 4
Diagnostic value of CRNDE overexpression in 9 cancers based on TCGA database.

Cancer	AUC	95%Cl	*p* -value	Sensitivity	Specificity
CESC	0.935	0.904～0.966	< 0.001	92.16	100
CHOL	0.980	0.886～1.000	< 0.001	97.22	100
COAD	0.958	0.942～0.973	< 0.001	86.90	98.04
GBM	0.984	0.952～0.997	< 0.001	94.67	100
KIRP	0.855	0.812～0.892	< 0.001	74.05	90.62
LIHC	0.874	0.838～0.904	< 0.001	69.71	98.00
PAAD	0.880	0.824～0.923	0.009	94.94	75.00
PCPG	0.934	0.888～0.965	< 0.001	89.62	100
READ	0.941	0.896～0.971	< 0.001	85.63	100

was consistent with the TCGA results.

3.3. Literature review of CRNDE expression in various types of cancer

A total of 71 records were retrieved from Pubmed, Web of Science, Embase and Cochrane Library. According to the inclusion and exclusion criteria, finally 6 diagnostic studies and 7 prognostic studies were included (Fig. 3). The primary characteristics were shown in Tables 2 and 3, respectively.

3.4. Diagnostic and prognostic analysis of CRNDE in pan-cancer based on TCGA

The receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of CRNDE in nine cancers. As shown in Table 4, the results showed that the AUCs were 0.935 with 95% CI (0.904-0.966), 0.980 with 95% CI (0.886–1.000), 0.958 with 95% CI 0.942-0.973, 0.984 with 95% CI (0.952-0.997), 0.855 with 95% CI (0.812-0.892), 0.874 with 95% CI (0.838-0.904), 0.880 with 95% CI (0.824-0.923), 0.934 with 95% CI (0.888-0.965), 0.958 with 95% CI (0.896-0.971) respectively for CESC (Fig. 4A), CHOL (Fig. 4B), COAD (Fig. 4C), GBM (Fig. 4D), KIRP (Fig. 4E), LIHC (Fig. 4F), PAAD (Fig. 4G), PCPG (Fig. 4H), READ (Fig. 4I). These AUC values ranged from 0.855 to 0.984, indicating that CRNDE was an effectively

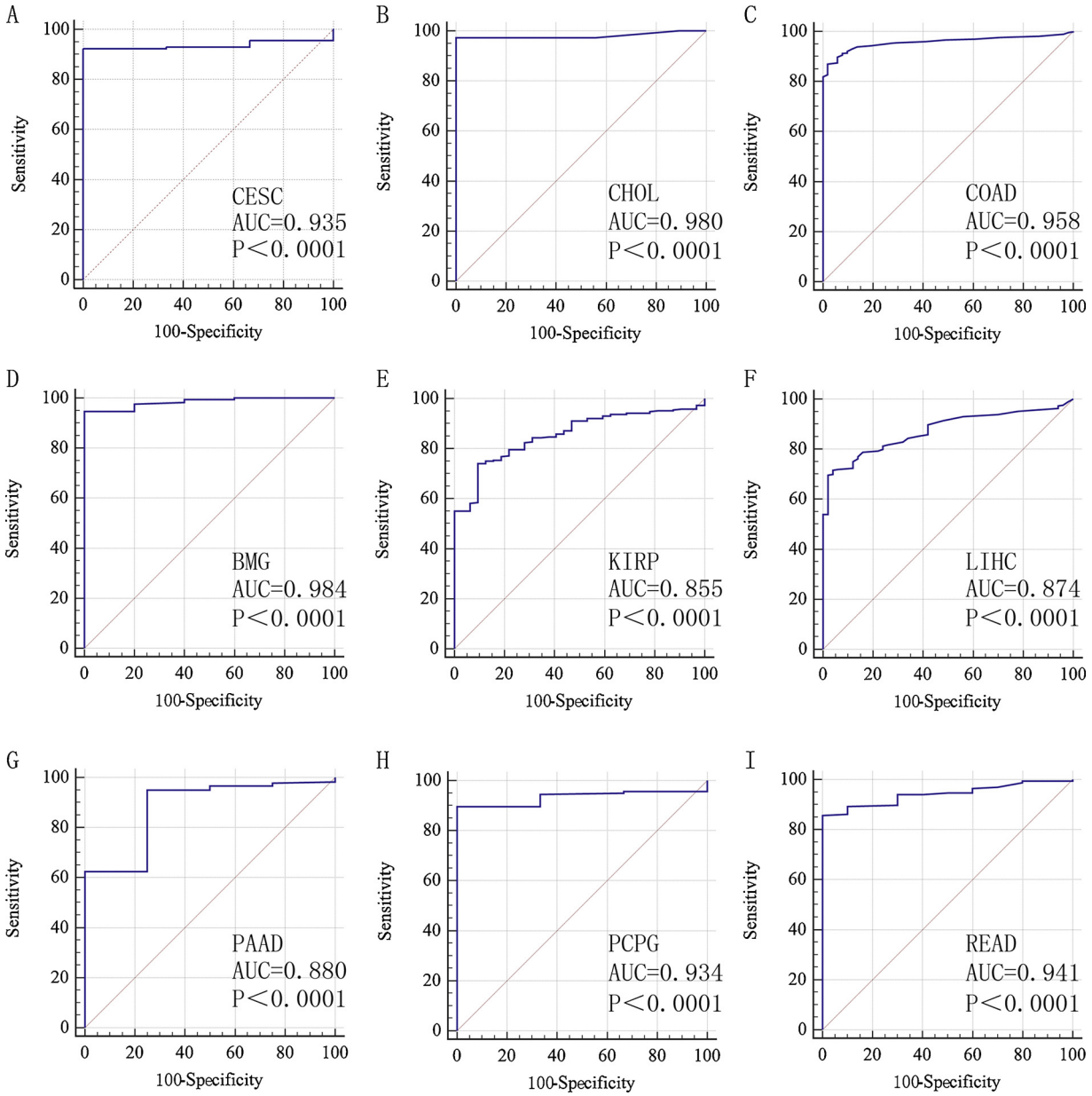

Fig. 4. ROC curve based on TCGA database in 9 types of cancer.(A)CESC; (B) CHOL; (C) COAD; (D) GBM; (E) KIRP; (F) LIHC; (G) PAAD; (H) PCPG; (I) READ.

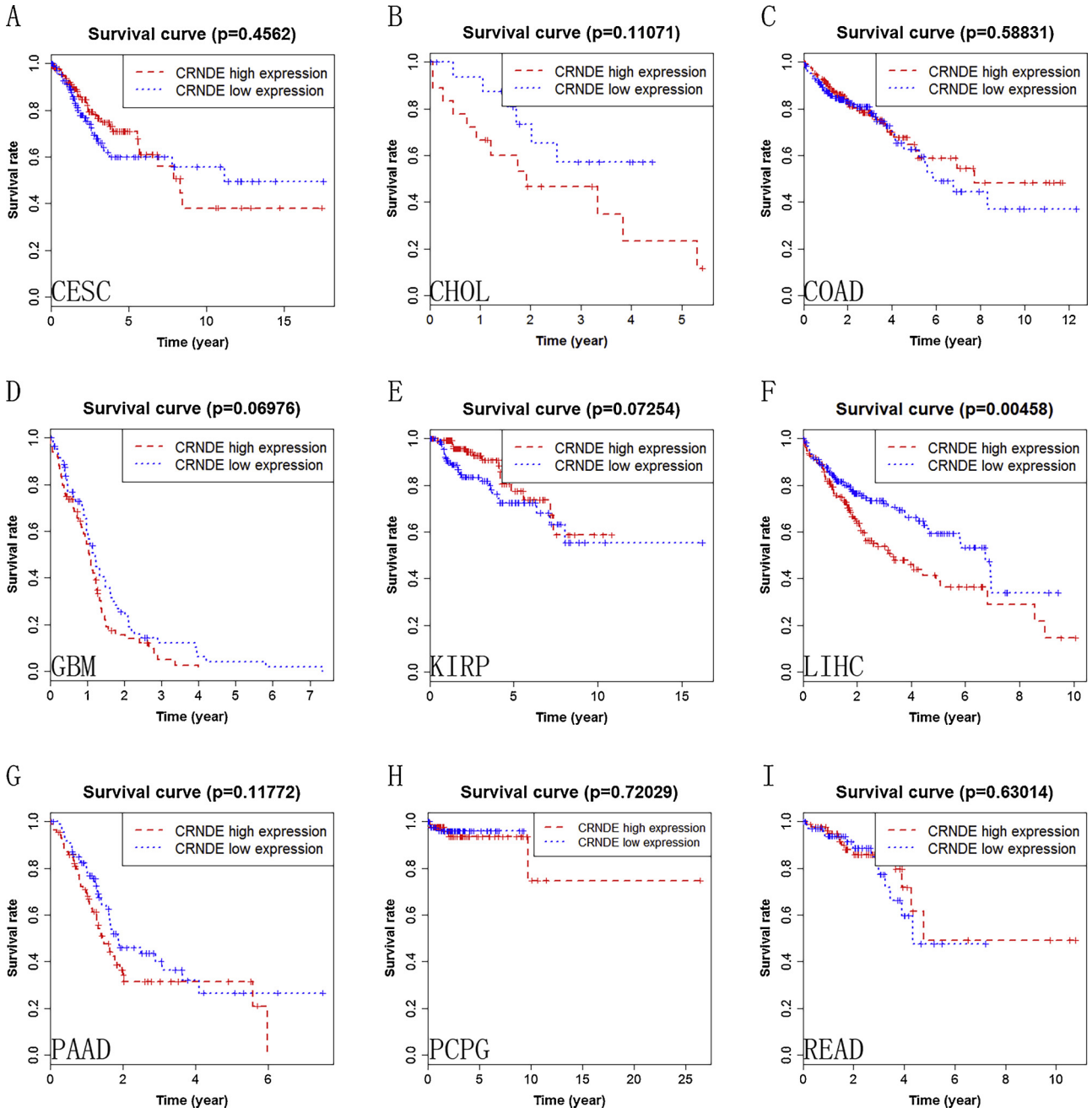

Fig. 5. K–M curves of 9 cases of CRNDE tumors base on TCGA database. The red lines represent the high expression of CRNDE in cancer, and the blue lines represent low expression of CRNDE. The X-axis represents the total survival time (year) and the Y-axis represents the survival rate. Figure (F) showed that the prognostic value of CRNDE in hepatocellular carcinoma was significant, indicating that the survival rate of patients was reduced in the case of high expression of CRNDE. These curves are drawn in the R software through the "survival" package.

Table 5
Primary parameters of the diagnostic value of CRNDE in different cancers.

parameters	value	95%CI
Sen	0.77	0.71-0.82
Spe	0.90	0.82-0.95
PLR	7.6	4.0-14.5
NIR	0.025	0.19-0.33
DOR	30	13-69
SROC	0.87	0.84-0.90

Sen: sensitivity; Spe: specificity; PLR: positive likelihood ratio; NIR: negative likelihood ratio; DOR: diagnostic odd ratio; SROC: summary operating characteristic curve.

diagnostic biomarker in these cancer. We then performed a Kaplan-Meier survival analysis to evaluate the prognostic value of CRNDE in cancer. Unexpectedly, none of the cancer types showed significant association with the overall survival except in LIHC (Fig. 5F) ($p = 0.032$, log-rank test). CESC $p = 0.4562$ (Fig. 5A), CHOL $p = 0.11071$ (Fig. 5B), COAD $p = 0.58831$ (Fig. 5C), GBM $p = 0.08976$ (Fig.5D), KIRP $p = 0.07254$(Fig. 5E), PAAD $p = 0.11772$ (Fig. 5G), PCPG $p = 0.72029$(Fig. 5H), READ $p = 0.63014$ (Fig. 5I).

3.5. Diagnostic value of CRNDE in cancers based on meta-analysis

A total of 1,361 patients from 6 studies were included in the diagnostic meta-analysis. The results showed that there is heterogeneity in

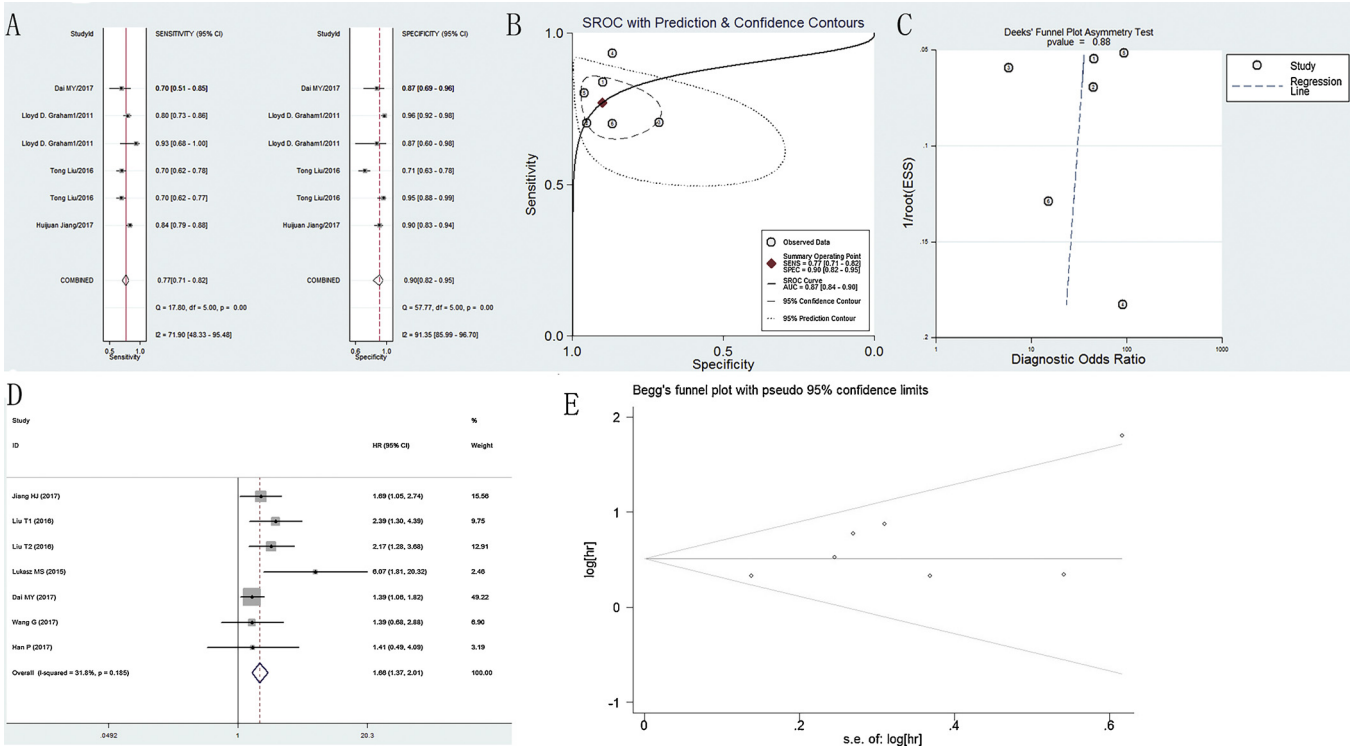

Fig. 6. (A) Pooled sensitivity and specificity of CRNDE in different cancers. (B) SROC of CRNAD in different cancers. (C) Publication bias of the articles about diagnosis. (D) Prognostic value of CRNDE in cancers. (E) Publication bias of the articles about prognosis.

the included studies of diagnosis, for the *p*-value was 13.951 and I^2 was 86%. So the random-effect model was selected. As shown in Table 5, the pooled sensitivity and specificity of CRNDE were 0.77 (95% CI: 0.71-0.82) and 0.90 (95% CI: 0.82-0.95), respectively (Fig. 6A). The AUC of CRNDE for diagnosis of cancer was 0.87 (95% CI: 0.84-0.90) (Fig. 6B). In addition, the PLR and the NLR were 7.6 (95%CI: 4.0–14.5) and 0.25 (95%CI: 0.19-0.33), respectively. The *p*-value of the Deek's test was 0.88, suggesting that there was no publication bias (Fig. 6C).

3.6. Prognostic value of CRNDE in cancers based on meta-analysis

Seven articles were collected to analyze the prognostic value of CRNDE in cancers. Heterogeneity was not found in this meta-analysis ($I^2 = 31.8\%$, $p = 0.185$), so the fixed-effect model was used to calculate the pooled HR and 95% CI. According to the results displayed in Fig. 6D, the pooled HR was 1.66 (95%CI: 1.37–2.01), which showed that the high expression of CRNDE had the poor prognostic value in cancers. The publication biases of these studies for OS were assessed with Begg's test. As shown in Fig. 6E, the funnel plot was nearly symmetric. The *p* for the Begg's test was 0.115, which showed that there was no significant publication bias in these studies. It can be concluded that high CRNDE expression indicated a poor prognosis in cancer patients.

4. Discussion

In this study, we analyzed the differential expression of CRNDE in various types of cancer by literature search and data mining in TCGA and GEO databases. We found that CRNDE was upregulated in 9 out of 37 cancers from the TCGA database, i.e. CESC, CHOL, COAD, GBM, KIRP, LIHC, PAAD, PCPG and READ, six of which has been validated in GEO database, i.e. CESC, CRC, GBM, KIRP, LIHC, and PAAD. Next, the present meta-analysis shows that CRNDE is of significance in the diagnosis and prognosis of cancers. These methods indicated that CRNDE can be an effective biomarker for cancer diagnosis and prognosis.

Several studies have reported abnormal expression in various human solid cancers. CRNDE promotes the development of related cancers through significant genetic control of chromatin, cancer signaling pathways, and cellular metabolism [34–37]. In the previous studies, CRNDE was closely associated with many malignancies and other diseases. CRNDE is a scaffold of the DMBT1 and C-IAP1 complex that activates the PI3K-AKT pathway and promotes carcinogenesis of gallbladder cancer [38]. CRNDE can bind to miR-217 and TCF7L2, and enhances Wnt / protein signaling and thus leading to CRC [39]. Besides, the overexpression of CRNDE may exert a carcinogenic effect on glioma by suppressing miR-384 [40]. In our study, we conducted a large-scale data mining on the original data from 11,574 cancer patients in TCGA database. With help of a series of bioinformatics studies, we found that CRNDE was highly expressed in nine kinds of cancers, among which COAD and GBM had the highest expression. This finding was consistent with the results reported by Graham LD [26] in gliomas and Elils BC [18] in CRC. There were four articles about the role of CRNDE in liver cancer, among which our team have previously reported the diagnosis and prognosis of CRNDE in patients with liver cancer. [32] The AUC of CRNDE in these highly expressed cancers is greater than 0.8, especially in GBM (AUC was 0.984). The results indicated that CRNDE can be a reliable diagnostic marker of cancer. Six sets of microarrays were then downloaded from the GEO database. Further validation of the six sets of microarray data was in good agreement with the results from TCGA. Liang C [41] and Zhang J [35]analyzed and systematically evaluated the prognostic value of CRNDE. Liang C pointed out that the OS of patients with low expression of CRNDE was shorter than that of patients with high expression of CRNDE. The combined results show that CRNDE is associated with lymph node metastasis and TNM staging but is not associated with patient gender and tumor size. Our research is consistent with this conclusion. In addition to their analysis on the prognostic value of CRDNE, our study also assessed the diagnostic value. Our study showed that the pooled sensitivity, specificity, summary receiver operator characteristic curve (SROC), and the overall hazard ratio of CRNDE in cancer were 0.77 (95% CI: 0.71–0.82), 0.90

(95% CI: 0.82–0.95), 0.87 (95% CI: 0.84–0.90), and 1.66 (95% CI: 1.37–2.01), respectively, indicating that CRNDE has good diagnostic performance for CRC. Finally, we further reviewed CRNDE through literature search and then found that our research was somewhat contradictory to the previous results in the published studies. CRNDE is overexpressed in the lung [42], stomach [43] and breast [44] cancer in the literature. However, CRNDE was not highly expressed in our study. This disparity may be attributed to different data sources, research methods and sample sizes. On the other hand, our research still has some limitations. First, the control sample size is so small for most types of cancer in the TCGA database that it may lead to experimental bias. Second, some confounding factors are inevitable due to the large-scale meta-analysis on experimental data. Third, few research on the diagnostic value of CRNDE expression in various types of cancer is included in this study.

Nevertheless, there are some advantages in comprehensive inclusion of various cancer types, multiple research methods and larger selection of sample data for the present study, which demonstrated that CRNDE can be used as a novel diagnostic and prognostic biomarker for cancers. Our study brings a brand new perspective to study the relationship between the CRNDE and cancers on treatment of cancer in future research, but further validations are still needed to find more comprehensive and effective resources for clinical research.

5. Conclusions

In summary, CRNDE overexpression was significantly associated with diagnosis and prognosis in cancers.

Author contribution

ZH and LY were the first authors who drafted the manuscript. CJ designed this study. LX and DM modified the manuscript. CX and GY collected and analyzed the data. All the authors have read and approved the final manuscript. Besides, we owe our special thanks to Huang Yujie for her work in language editing.

Disclosure

No conflict of interest exists.

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