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Expression and Prognostic Significance of Cadherin 4 (CDH4) in Renal Cell Carcinoma

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Aberrant expression of cadherin family members and their possible biological function have been widely studied in renal cell carcinoma (RCC). However, the expression of cadherin 4 (CDH4) and its value in RCC diagnosis and prognosis remains elusive.

Material/Methods: The TCGA database was used to analyze the expression of CDH4 and its clinical parameters and prognosis in 891 RCC patients. In addition, real-time PCR was used to verify the transcription of CDH4 in renal clear cell carcinoma tissue, and the distribution of protein was observed by immunohistochemical staining.

Results: We found that the mRNA level of CDH4 was elevated in primary RCC in contrast with normal kidney samples using bioinformatics analysis based on the TCGA database. Among the 3 main subtypes of RCC, transcriptional CDH4 was significantly increased in KIRC and KIRP, while it was downregulated in KICH. Interestingly, CDH4 mRNA gradually decreased with the progression of KIRC and KIRP. The transcription of CDH4 in the primary tumor of KIRP patients at T3-T4 stages and KIRC patients with lymph node and distant metastasis were decreased significantly. Overall survival (OS) showed that KIRC and KICH patients with lower expression of CDH4 had worse outcomes.

Conclusions: The transcriptional level of CDH4 may serve as an effective diagnostic and prognostic biomarker for RCC patients.

MeSH Keywords: **Biological Markers • Cadherins • Carcinoma, Renal Cell • Prognosis**

Abbreviations: **CDH4** – cadherin 4; **RCC** – renal cell carcinoma; **KIRC** – kidney clear cell carcinoma; **KICH** – kidney papillary cell carcinoma; **KIRP** – kidney chromophobe

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Background

Renal cell carcinoma (RCC) arises from the renal epithelium and is the most common type of kidney cancer. In 2018, RCC ranked sixth among all types of tumors in males and eighth in females, based on the incidence of new cases [1]. RCC is estimated to have resulted in 14 000 deaths in 2012. The incidence of RCC varies geographically, being higher in Europe and America, and lower in Southeast Asia and Africa [2,3]. Histologically, the most common histologic subtypes of RCC are clear renal cell carcinoma (KIRC, 85%), papillary renal cell carcinoma (KIRP, 10%), and chromophobe renal cell carcinoma (KICH, 5%) [4].

Approximately 70% of RCC is localized or locally advanced at diagnosis, while 30% of patients present with disseminated disease upon first diagnosis [5]. Localized RCC can be completely removed by surgery [6], but follow-up studies show that it commonly recurs. Among patients with localized RCC who undergo resection, 30–35% will eventually develop distant metastases [7]. Patients with metastasized RCC respond poorly to chemotherapy or radiotherapy. Although the introduction of targeted therapies has improved the prognosis for these patients, the 5-year survival rate is only 10% due to the adverse effects and intrinsic or acquired resistance [8]. Therefore, it is necessary to identify genes associated with RCC invasion and metastasis and to clarify their functions.

Cadherins are transmembrane glycoproteins that mediate calcium-dependence homophilic cellular adhesion and cellular recognition, playing a crucial role in cellular proliferation, differentiation, and transformation [9]. They are also essential for building higher organizational structures of tissues [10]. To date, more than 100 different molecules of the classic human cadherins have been identified, which are divided into 3 subgroups – major cadherins, protocadherins, and cadherin-related proteins [11] – based on their structural features and functional organization [12]. Dysregulation of cadherins has been frequently demonstrated, thereby contributing to tumorigenesis and tumor metastasis [13–15]. The founding member of the superfamily is E-cadherin (CDH1), a common epithelial marker, the functional loss of which has frequently been associated with poor prognosis and survival in patients with various cancers [16].

CDH4 encodes retinal cadherin (R-cadherin) and is a type I cadherin. It plays a crucial role in the development of various organs, including the retina, brain, gastrointestinal tract, pancreas, and kidney [17–21]. Dysregulation of CDH4 has long been considered to be associated with several human cancers [22]. However, it functions in tumors remains controversial. In gastric cancer, downregulation of CDH4 is associated with unfavorable outcomes of patients [23]. The formation of adherence junctions by CDH4 facilitates a mesenchymal to epithelial-like transition in breast cancer cells [24], and inducing autophagy in glioblastoma cells leads to mesenchymal-epithelial transition, accompanied by upregulation of CDH4 [25,26]. On the contrary, CDH4 was suggested to possess an oncogenic function in osteosarcoma and rhabdomyosarcoma [27,28]. In glioma, CDH4 is necessary for promoting the cell-cell contact inhibition of proliferation and migration [25]. Silencing CDH4 hinders the cellular metastatic capacity [29]. To date, the expression of CDH4 and its possible role in the pathogenesis of RCC remains elusive.

In the present study, we assessed the expression characteristics of CDH4 in RCC in contrast to normal kidney tissues and evaluated their utility in RCC diagnosis and prognosis.

Material and Methods

Bioinformatic analysis using The Cancer Genome Atlas (TCGA) database

The Cancer Genome Atlas (TCGA) database was used to analyze the expression of CDH4 in 891 cases of RCC and 129 cases of normal tissues and the clinical-pathological characteristics of RCC patients. Data were downloaded using UCSC Xena (*https://xena.ucsc.edu/*), which provides the RNA sequencing data of original RCC and normal patient samples and the clinical-pathological parameters. The correlation between CDH4 mRNA level and clinicopathological parameters, such as age, sex, and TMN stages of RCC patients were also analyzed.

Real-time quantitative reverse transcription polymerase chain reaction

A KIRC cDNA microarray chips (Cat no: MecDNA-HKidE030CS01) containing 15 pairs of KIRC tissue samples and matched adjacent tissue samples were purchased from Shanghai OUTDO Biotech Co. (Shanghai, China). We used the QuantStudio 6 Real-Time PCR System (Applied Biosystem, USA) and Power SYBR green PCR master mix (Applied Biosystem, USA) to assess the relative expression of CDH4. The [ΔΔC(T)] method was used to calculate the CDH4 expression in each sample. The primer sequences were as follows:
CDH4-Forward, 5'-CAACCTGAACGCCATCAACATC-3',
CDH4-Reverse, 5'-CGCAAGCTGAGTTGGGCATAG-3';
GAPDH-Forward, 5'-AAGCTCACTGGCATGGCCTT-3',
GAPDH-Reverse, 5'-CTCTCTTCCTCTTGTGCTCTTG-3'.

Immunohistochemical staining assay

For immunohistochemical analysis, a tissue microarray (TMA, n=164) including 82 pairs of KIRC tissue samples matched

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Table 1. mRNA expression of CDH4 and its correlation with clinicopathological parameters of patients with RCC.

Clinicopathological parameters		Relevant expression of CDH4			
		n	Mean±SD	t	p-Value
Tissue	Normal	129	2.79±1.33	14.697	<0.001*
	RCC	891	5.10±3.11		
Age	<60	414	5.17±3.14	0.571	0.568
	≥60	474	5.05±3.07		
Gender	Male	599	4.96±3.06	–1.838	0.066
	Female	292	5.37±3.20		
T	T1–T2	616	5.21±3.16	1.680	0.093
	T3–T4	273	4.83±2.99		
LN	No	330	5.02±3.21	2.713	0.007*
	Yes	49	3.70±2.81		
M	No	551	5.47±3.22	2.566	0.011*
	Yes	90	4.66±2.70		
Pathologic stage	I–II	565	5.28±3.20	2.056	0.040*
	III–IV	353	4.83±2.92		

SD – standard deviation; RCC – renal cell carcinoma; T – tumor; LN – lymph node; M – metastasis. * p<0.05 was considered statistically significant.

to their adjacent tissue samples were purchased from Shanghai OUTDO Biotech Co. (Shanghai, China; Cat no: HKidCRC180Sur-01). The expression of CDH4 protein in kidney tissue was detected using the Universal SP kit (SP-9000, ZSGB-BIO, Beijing, China). Sections were incubated with anti-CDH4 antibodies (AP1401A, ABGENT, 1: 100 dilution) as described previously [30]. Images were acquired using an Olympus microscope. Liver tissue was used as a positive control.

The immunostaining was independently evaluated by 2 pathologists blinded to both the sample origins and the subject outcomes. We counted the numbers of all cells in 5 microscopic fields and calculated the percentage of positive cells. Tumor specimens were scored in a semi-quantitative manner because of the heterogeneity of CDH4 staining. Protein levels were determined by the percentage of staining (no positive cells for 0, ≤25% positive cells for 1, 26~50% positive cells for 2, 51~75% positive cells for 3, and >75% positive cells for 4) and the extent of cell staining (negative for 0, faint yellow for 1, yellow or deep yellow for 2, tan or brown for 3) in each tumor sample. The score for each tissue sample was obtained by multiplying the intensity level for each tumor sample and the percentage of positive cells.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software. The relevance between the relative expression of CDH4 and clinicopathological parameters in RCC patients was assessed by independent-samples testing. Differences in pathological stages were examined by analysis of variance (ANOVA). The paired *t* test was applied to the score of immunohistochemical staining and real-time RT-PCR data. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficacy of CDH4 in RCC. The association of CDH4 mRNA levels with survival of RCC patients was analyzed using GraphPad Prism 7.0. P≤0.05 was considered statistically significant.

Results

Dysregulation of CDH4 in primary RCC.

Based on the RNA-seq data from the TCGA database, overexpression of CDH4 was found in 891 RCC tissues (5.10±3.11) compared with 129 normal kidney tissues (2.79±1.33, p<0.001; Table 1). We further analyzed the mRNA level of CDH4 in different pathological types of RCC, including 534 cases of KIRC, 66 cases of KICH, and 291 cases of KIRP. Interestingly, compared with the normal control group, the transcription level of CDH4 in KIRC was significantly higher (Tables 2–4).

Next, we performed real-time PCR to identify the transcription of CDH4 in KIRC primary tumors samples and matched adjacent tissue samples. Compared with normal kidney tissue (0.86±0.97), the relative expression of CDH4 in RCC (21.58±25.21) was

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Table 2. mRNA expression of CDH4 and its correlation with clinicopathological parameters of patients with KIRC.

Clinicopathological parameters		Relevant expression of CDH4			
		n	Mean±SD	t	p-Value
Tissue	Normal	72	2.91±1.36	15.661	<0.001*
	KIRC	534	5.91±2.97		
Age	<60	246	5.93±2.97	0.097	0.923
	≥60	288	5.90±2.98		
Gender	Male	346	5.74±2.97	–1.849	0.065
	Female	188	6.23±2.95		
T	T1–T2	343	6.09±3.03	1.875	0.061
	T3–T4	191	5.59±2.83		
LN	No	240	5.84±3.06	1.025	0.306
	Yes	16	5.03±2.74		
M	No	422	6.09±3.01	3.206	0.001*
	Yes	79	4.92±2.67		
Pathologic stage	I	268	6.23±3.10	F=3.913[a]	0.009*
	II	57	5.97±2.78		
	III	123	5.88±2.85		
	IV	84	4.97±2.61		

SD – standard deviation; KIRC – kidney clear cell carcinoma; T – tumor; LN – lymph node; M – Metastasis. [a] Analysis of variance (ANOVA) was used. * p<0.05 was considered statistically significant.

Table 3. mRNA expression of CDH4 and its correlation with clinicopathological parameters of patients with KICH.

Clinicopathological parameters		Relevant expression of CDH4			
		n	Mean±SD	t	p-Value
Tissue	Normal	25	2.90±1.23	–5.092	0.000*
	KICH	66	1.33±1.34		
Age	<60	47	1.39±1.48	0.539	0.592
	≥60	19	1.19±0.97		
Gender	Male	39	1.43±1.41	0.725	0.471
	Female	27	1.19±1.26		
T	T1–T2	46	1.29±1.15	–0.391	0.697
	T3–T4	20	1.43±1.74		
LN	No	40	1.42±1.20	–0.168	0.874
	Yes	5	1.64±2.96		
M	No	34	1.24±1.17	0.703	0.487
	Yes	2	0.65±0.29		
Pathologic stage	I	21	1.52±1.36		0.657
	II	25	1.10±0.92		
	III	14	1.30±1.36		
	IV	6	1.75±2.57		

SD – standard deviation; KICH – kidney papillary cell carcinoma; T – tumor; LN – lymph node; M – metastasis. * p<0.05 was considered statistically significant.

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Table 4. mRNA expression of CDH4 and its correlation with clinicopathological parameters of patients with KIRP.

Clinicopathological parameters		Relevant expression of CDH4			
		n	Mean±SD	t	p-Value
Tissue	Normal	32	2.91±1.36	5.229	<0.001*
	KIRP	291	4.45±2.87		
Age	<60	121	5.09±2.89	3.221	0.001*
	≥60	167	4.01±2.73		
Gender	Male	214	4.35±2.84	–0.982	0.327
	Female	77	4.73±2.94		
T	T1–T2	227	4.67±2.89	2.685	0.008*
	T3–T4	62	3.57±2.62		
LN	No	50	3.95±2.72	1.017	0.312
	Yes	28	3.31±2.57		
M	No	95	4.25±3.14	1.241	0.240
	Yes	9	3.24±2.24		
Pathologic stage	I	172	4.71±2.91	F=2.770[a]	0.042*
	II	22	4.62±2.98		
	III	52	4.04±2.61		
	IV	15	2.71±2.17		

SD – standard deviation; KIRP – kidney chromophobe; T – tumor; LN – lymph node; M –metastasis. [a] Analysis of variance (ANOVA) was used. * p<0.05 was considered statistically significant.

significantly higher (p<0.05; Figure 1A), consistent with the results of our analysis using the TCGA database. In addition, the protein expression of CDH4 was analyzed using an immunochemistry staining assay. To our surprise, we did not observe a significant dysregulation of CDH4 between KIRC and samples of adjacent normal kidney tissue (Figure 1B, 1C). However, the location of CDH4 was remarkably altered, with higher expression in the cell membrane of KIRC, but mainly located in membrane and cytoplasm in adjacent normal kidney tissues. We speculated that this was due to the pathological changes in KIRC. Lipid and glycogen are rich in the cytoplasm of KIRC cells, thus affecting the location of cytoplasmic molecules.

The diagnostic value of CDH4 mRNA levels in RCC

The ROC curve was used to evaluate the diagnostic efficacy of CDH4 expression in KIRC, KICH, and KIRP (Figure 2A–2C); based on the RNA sequencing data in the TCGA database, the AUCs were 0.795 (p<0.001), 0.833 (p<0.001), and 0.644 (p=0.008), respectively. The diagnostic efficacy was relatively low in KIRP, in contrast with KIRC and KICH. We also performed ROC analysis based on our RT-PCR data shown in Figure 1A. The AUC was 0.799 (p=0.013), which is close to the result based on the TCGA database. These indicate that the mRNA expression level of CDH4 is as a potential diagnostic biomarker of KIRC and KICH (Figure 2D).

The prognostic value of CDH4 mRNA levels in RCC

The relationship between CDH4 mRNA levels and clinicopathological parameters in patients with RCC was analyzed. The expression of CDH4 differed remarkably according to lymphatic metastasis, distant metastasis, and pathological stages. Although the transcription of CDH4 was higher in RCC tissues than in normal kidneys, it gradually decreased with the malignant progression of tumors (Table 1). In KIRC, the lower mRNA level of CDH4 was remarkably different in distant metastatic stage and later pathological stages (Table 2). We found no significant difference between the clinical characteristics and the expression of CDH4 in KICH patients (Table 3). Among KIRP patients, the relative expression of CDH4 was higher in patients <60 years than those ages ≥60 years. The lower transcription of CDH4 was also remarkably correlated with higher T stage and pathological stages (Table 4). These results suggest that the downregulation of CDH4 mRNA is correlated with the progression of KIRC and KIRP.

In addition, we used the TCGA database to assess the overall survival (OS), primarily to investigate the value of CDH4 mRNA expression in the prognosis of patients with RCC. We found that KIRC (median=6.78, p<0.001) and KICH (median=0.93, p=0.022) patients with lower expression of CDH4 had poorer survival (Figure 3A, 3B). However, no statistically significant

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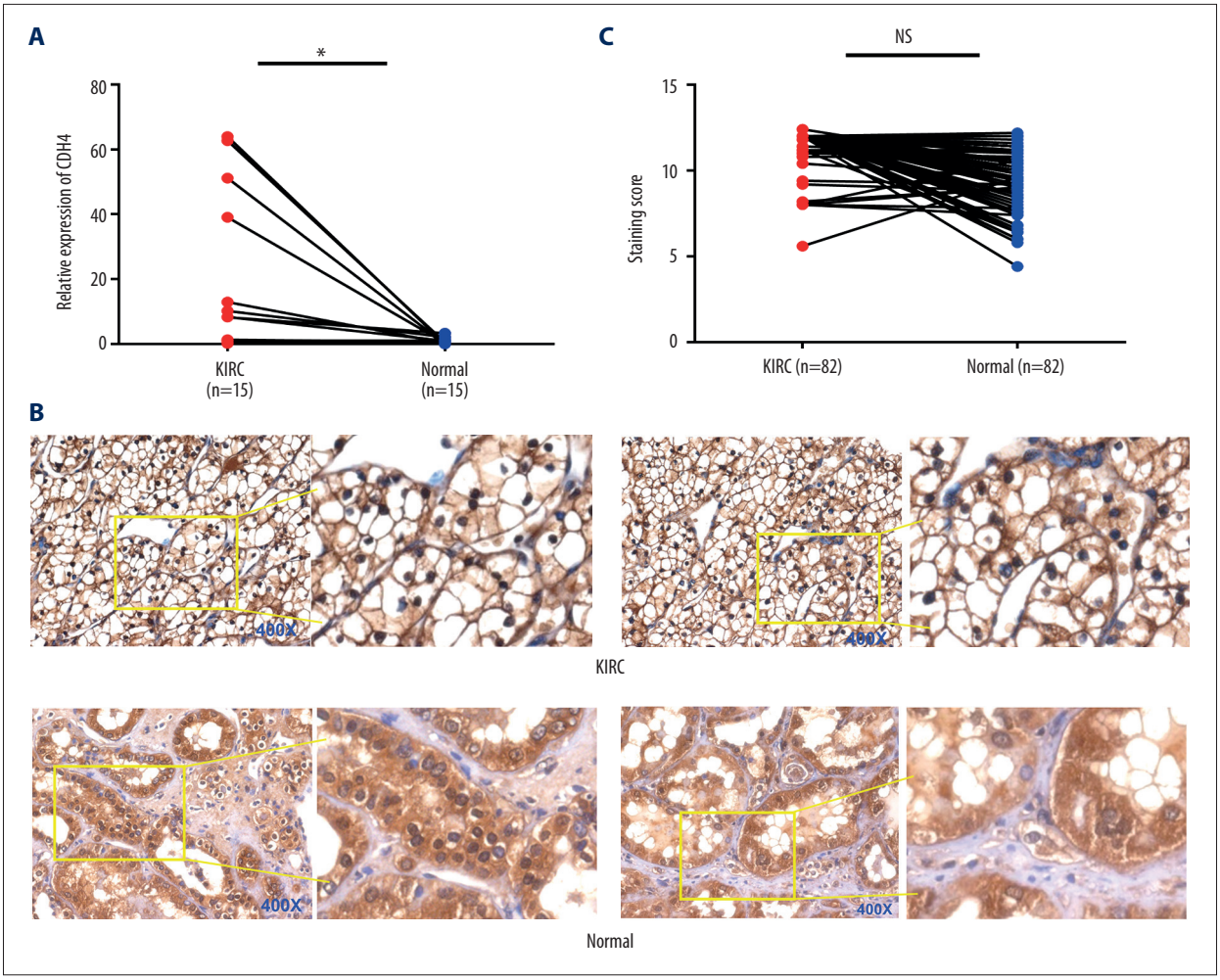

Figure 1. Dysregulation of CDH4 in clear cell renal cell carcinoma (KIRC). (**A**) The transcription level of CDH4 in 15 pairs of KIRC tissue matched to their adjacent renal samples were verified by real-time quantitative RT-PCR. (**B**) Representative slides of KIRC tissues and matched control tissues, stained by anti-CDH4 antibody. (**C**) The expression level of CDH4 protein in KIRC and matched normal control samples (n=82). * p<0.05; NS – no significance.

difference was observed in KIRP patients (Figure 3C). Therefore, the mRNA level of CDH4 could be a prognostic biomarker for KIRC and KICH.

Discussion

To the best of our knowledge, this is the first study to describe the characteristics of CDH4 transcription and protein expression in RCC in contrast with normal kidney tissue. By using the TCGA database, we found an upregulation of CDH4 in RCC, which differs among different subtypes of RCC, including KIRC, KIRP, and KICH. CDH4 was elevated in KIRC and KIRP but decreased in KICH, suggesting that the expression of CDH4 varies in different pathological types of RCC, with various pathogenic mechanisms. Nevertheless, with the increasing pathological stages, the mRNA level of CDH4 decreased remarkably in RCC. Notably, RCC patients with lower expression of CDH4 tended to have worse outcomes. Our data indicate that CDH4 acts as a tumor suppressor during the progression of RCC.

It appears that the expression and biological function of CDH4 differs in different types of tumors. For instance, CDH4 is downregulated due to its promoter hypermethylation in nasopharyngeal carcinoma, where ectopic expression of CDH4 inhibits cell migration [31]. In hepatocellular carcinoma, the CDH4-RAC1 pathway is targeted by long non-coding RNA linc-cdh4-2, which results in inhibition of migration and invasion [32]. Co-expression of E-cadherin and R-cadherin remarkably suppresses the malignant progression of salivary adenoid cystic carcinoma [33]. Here, we reported that lower expression of CDH4 is significantly associated with RCC patients with lymph node and distant organ metastasis, suggesting that the expression of CDH4 mainly affects the motility

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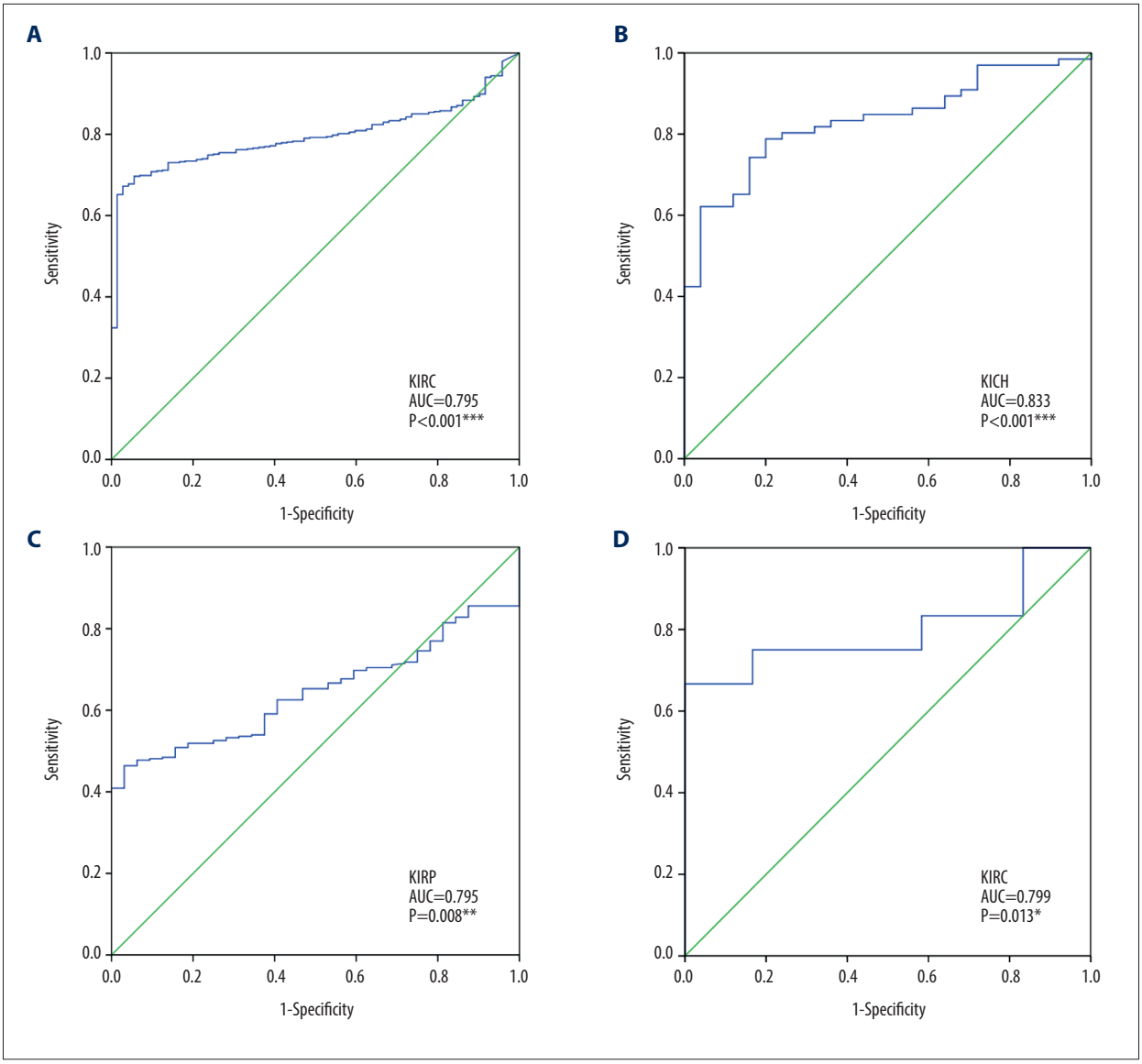

Figure 2. Based on the TCGA database, an ROC curve was used to assess the diagnostic efficacy of CDH4 mRNA in 534 cases of KIRC *vs.* 72 cases of non-malignant renal tissues (**A**), 66 cases of KICH *vs.* 25 cases of control renal tissues (**B**), and 291 cases of KIRP *vs.* 32 cases of non-malignant renal tissues (**C**). The relative expression level of CDH4 examined by qPCR was used to perform the ROC curve for evaluating its diagnostic efficacy in KIRC cDNA microarray, containing 15 pairs of KIRC and matched normal samples (**D**). * p<0.05; ** p<0.01; *** p<0.001.

of RCC cells. In addition, the mRNA expression of CDH4 is decreased in lung cancer, and is positively associated with lower histotype and grade [34], indicating that CDH4 contributes to the differentiation of cancer cells. In addition, the single-nucleotide polymorphisms of CDH4 result in its lower expression in pancreatic cancer, which is associated with weaker response to gemcitabine treatment [35].

However, several studies identified a positive effect of CDH4 on tumor progression. The amplification of CDH4 in human osteosarcoma apparently facilitates the progression of osteosarcoma by inducing the JNK pathway, which in turn activates the AP1 downstream targets, including MMP1 and Nestin oncogenes [27]. Overexpression of CDH4 transformed normal myoblasts by inhibiting cell cycle exit, and inactivation of CDH4 in rhabdomyosarcoma retarded tumor growth *in vivo* [28]. Ectopic expression of CDH4 in BT-20 breast tumor cells induced lamellipodia formation and motility via Rho GTPase activation [36]. A recent study demonstrated that inactivating CDH4 impaired the *in vivo* tumorigenic potential of glioblastoma cells [29]. CDH4 competes with CDH1 for p120 protein and results in endocytosis of cellular surface CDH1,

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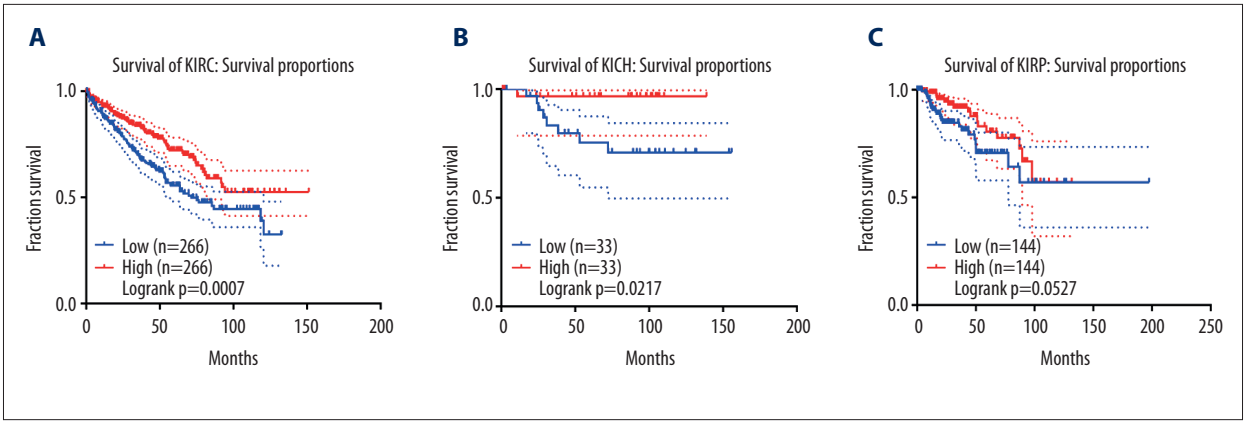

Figure 3. Prognostic value of CDH4 mRNA in RCC. Overall survival curves of patients with high or low expression levels of CDH4 in KIRC (**A**), KICH (**B**), and KIRP (**C**) were estimated with the Kaplan-Meier method by log-rank test.

thereby facilitating cell motility [37]. These studies suggest an oncogenic effect of CDH4. Such discordance in CDH4-mediated influences on oncogenic transformation processes may depend on different functions in different types of tissue.

Other cadherins have been identified widely in RCC. CDH1 is of the most analyzed one. Positive expression of CDH1 was associated with a better prognosis of RCC patients [38]. Using bioinformatics analysis assay, CDH1 was defined as one of the hub genes and may be a therapeutic target and diagnostic biomarker of ccRCC [39]. As an important marker for epithelium, CDH1 is commonly used in the verification of epithelial-mesenchymal transition (EMT). Those oncogenic or tumor-suppressive genes involved in regulating the EMT process in RCC have shown the alteration of CDH1, which favors enhanced cell invasion and migration [40,41]. CDH2 encodes N-cadherin, normally expressed in neuronal tissue. In type I and II papillary RCC, the total expression of CDH2 did not significantly change. Interestingly, the location of CDH2 in membrane and cytoplasm differs, acting as an immunohistochemical marker between different types of papillary RCC [42]. Aberrant expression of CDH6 is correlated with poor survival of RCC patients, especially in patients without CDH1 [43,44]. In addition, mRNA of CDH6 can be detected in peripheral blood from RCC patients with distant metastasis. Therefore, it is a potential marker for circulating tumor cells in RCC [45]. CDH8 could be detected only in the early stage of RCC, indicating its possible function in the tumorigenesis of RCC [46]. These finding suggest that many members of the cadherin family have significant roles in RCC, and their expression pattern and locations need further comprehensive investigation.

Evidence shows the existence of cadherin heterodimers formed by CDH2 and CDH4 [47], but their dynamic alteration and potential function in tumorigenesis and tumor progression remain unclear. We found that the transcriptional level of CDH2 was remarkably elevated in RCC, and patients with distant metastasis had higher expression of CDH2 in tumor tissues (data not shown). In line with CDH2, CDH4 mRNA is upregulated in RCC compared with normal kidney samples. Intriguingly, unlike CDH2, CDH4 only increases in the early stages and subsequently decreases at later stages of RCC, and is negatively correlated with patients with metastasis. It may be that CDH4 has a dual function in RCC tumorigenesis and progression. Further experiments are needed to explore its dual roles and underlying regulatory mechanisms.

Conclusions

We described the transcriptional pattern of CDH4 in 3 main types of RCC. Our data suggest that the mRNA level of CDH4 is a potential diagnostic and prognostic biomarker for KIRC.

Conflicts of interest

None.

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