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Cadherin 11 Expression Correlates with Pancreatic Carcinogenesis and Clinical Stage in Patients with Pancreatic Cancer

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Abstract

Objective: The main purpose was to investigate expression of CDH11 in pancreatic tissues and analyze its relations with clinical characteristics of patients with pancreatic cancer (PC). **Methods:** Expression of CDH11 in cancerous tissues and cancer adjacent tissues were detected by immunohistochemistry staining, and their associations with clinical characteristics were analyzed. The text mining methods were used to assist the study of the effect of CDH11 on prognosis. **Results:** A total of 79 patients with PC were enrolled in the study, including 51 (64.6%) men and 28 (35.4%) women with a median age of 62 (41 - 84). The CDH11 expression in cancerous tissues was higher than that in adjacent tissues and the expression of CDH11 in both tissues was positively correlated ($P < 0.001$). CDH11 of stage II was significantly higher than that of stage I ($P < 0.001$), while the CDH11 expression in stages III & IV was not different from that in stage I and II (stage I vs III & IV, $P > 0.999$; stage II vs III & IV, $P = 0.308$). A higher level of CDH11 expression correlated with worse overall survival (OS) time ($P = 0.015$). **Conclusion:** CDH11 may be involved in the development of early PC and lead to poor prognosis and could be a new target molecule for early diagnosis and treatment of PC.

Keywords

Cadherin 11, Pancreatic Cancer, Prognosis

1. Introduction

Pancreatic cancer (PC) is a rapidly progressing digestive tract tumor. However,

the clinical manifestations of PC are usually hidden, and timely diagnosis is impossible in most patients [1]. Even with advances in PC diagnostic and treatment methods in recent years [2] [3], the long-term survival rate of PC is unsatisfactory, and it is still the most threatening disease in the world [4]. Surgical resection is the only way to cure PC [5]. However, 90% of patients may still experience recurrence or death without adjuvant therapy [6], and the postoperative survival rate is only 50% [7]. Although molecular targeted drugs [8] [9] [10] [11] [12] have been found to be effective for PC, the related toxicity of these drugs cannot be ignored [13]. Therefore, more effective molecular targets for PC and clarification of the mechanism of PC targets are of great clinical significance.

Cadherin 11 (CDH 11) was originally screened by Okazaki M *et al.* from the cDNA library of a mouse osteoblast line [14]. The coding gene CDH11 is located in the region adjacent to the interface between 16q21 and 16q22 [15]. CDH is a large family [16] in which CDH11 is mainly present in mesenchymal cells during embryogenesis [17] but cannot be detected in epithelial tissue; thus, it can be used as an important biomarker of mesenchymal cell phenotype [18]. As a group of transmembrane glycoproteins, CDH can mediate calcium-dependent adhesion between endothelial cells [19] [20] and plays an important role in cell proliferation, differentiation, apoptosis, cell polarity and other cellular behaviors [21] [22]. CDH is mainly involved in mediating cell-to-cell recognition, cytoskeletal tissue formation and signal transduction [23] [24].

Most previous studies have studied the role of CDH11 in various cancer species from the molecular level, but few have explored the relationship between CDH11 and clinical characteristics. The potential clinical value still needed to be further elucidated. This study enrolled PC patients and investigated the relationship between pancreatic CDH11 expression and clinical characteristics from a real-world point of view to discuss the possible roles of CDH11 in the development of PC.

2. Materials and Methods

Ethics approval

The study was approved by the Medical Ethics Committee of Shandong Provincial Qianfoshan Hospital (approval No. 2021S890). The need to obtain informed consent was waived due to the retrospective nature of the study.

Patient information and specimens

Seventy-nine patients with a postsurgical pathological diagnosis of PC, including 51 males and 28 females, were enrolled for this study. The clinical information of the patients was reviewed. Inclusion criteria: 1) pancreatic cancer was confirmed by pathology and imaging; 2) the pathological tissues were well preserved and available for detection; 3) baseline data were available. Exclusion criteria: 1) combined with tumors other than pancreatic cancer; 2) baseline clinical data were missing. Patients were clinically staged according to the AJCC

staging system. For pathological study, tissues were collected after surgical resection and then made into a tissue microarray by Shandong Jiekai Biotechnology Company (Jinan, Shandong Province, China). The tissue chip contains 79 cancerous and 69 cancer adjacent tissues. Cancer adjacent tissues were obtained 2 cm from the edge of the cancer lesion. All procedures were carried out with the adequate understanding and written consent of each subject.

Immunohistochemical staining and analyses

Briefly, the tissue chip was baked in an oven at 72˚C for 2 hours, dewaxed and hydrated with anhydrous ethanol and 95% and 85% ethanol in turn, and then rinsed thoroughly with water for 3 minutes followed by tissue repair. Tissue repair adopted high temperature and high pressure method: added about 1000ml of 0.01 M antigen retrieval solution with pH 6.0 to the pressure cooker. The repair time was 2 minutes. A total of 60 μl primary antibody (1:50, CDH11 rabbit polyclonal antibody, A8110, ABclonal, Wuhan, China) was incubated overnight at 4˚C and then incubated with 70 μl of secondary antibody (1:200, horseradish peroxidase-conjugated goat anti-rabbit IgG, GB23303, Servicebio, Beijing, China) at 37˚C for 40 minutes. The chips were stained with DAB chromogenic agent to develop color. Differentiate in 1% hydrochloric acid alcohol solution for 3 seconds, rinse with running water, blue for 10 seconds, rinse with running water. Afterwards, slices were dehydrated in 85% ethanol, 95% ethanol for 1 minute each, and absolute ethanol I and II for 2 minutes each. Finally, neutral glue was used to mount the slides.

For evaluation, dark brown tissue staining was recognized as strong positive, brown as moderate positive, light yellow as weak positive and blue as negative. The percentage of positive tissues was calculated, and the histochemical score (H-score) was used as a staining index for quantitative statistical analyses. The tissue chip was scanned by a scanner (Pannoramic 250/MIDI, 3D Histech, Hungry) and then viewed with Pannoramic viewer software. All samples and files were evaluated blindly by the same pathologist.

Public database analyses

Survival analysis was performed according to GEPIA, an interactive web application (http://gepia.cancer-pku.cn) based on gene expression analysis of samples from TCGA and GTEx databases [25].

Statistical analyses

The data were analyzed by SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). The continuous variables of non-normal distribution were expressed as median (quartile spacing) and compared by nonparametric test. The Mann-Whitney's U test was used to compare the two groups, and the Kruskal-Wallis H test followed by multiple-comparison post-hoc test was performed for comparison of three or more subgroups. For correlation analysis between variables, the Spearman correlation coefficient method was used. Survival data were used to construct Kaplan-Meier curves and analyzed by the Log-rank test. The threshold P value was accepted as 0.05 for statistical significance.

3. Results

CDH11 expression in cancer and adjacent tissues

According to the results of our current study, the expression of CDH11 in cancerous tissues [121.6 (113.6 - 126.9)] was significantly higher than that in adjacent tissues [107.0 (99.3 - 116.8)] ($P < 0.001$) (Figure 1). Further analyses suggested a positive correlation between CDH11 expression in cancer tissues and adjacent tissues ($r = 0.440$, $P < 0.001$). As Figure 2 shows, when CDH11 expression increases in cancer tissues, its expression in adjacent tissues increases accordingly.

CDH11 expression in patients with different clinical stages

There were significant differences in the expression of CDH11 in different clinical stages ($P < 0.001$). The expression of CDH11 in stage II patients [125.7 (119.7 - 129.3)] was significantly higher than that in stage I patients [115.7 (103.1 - 122.6) ($P < 0.001$), while the CDH11 expression in stage III & IV [117.4 (109.4 - 127.2)] was not different from that in stage I and II patients (stage I vs III & IV, $P > 0.999$; stage II vs III & IV, $P = 0.308$) (Figure 3(A), Figure 3(B)).

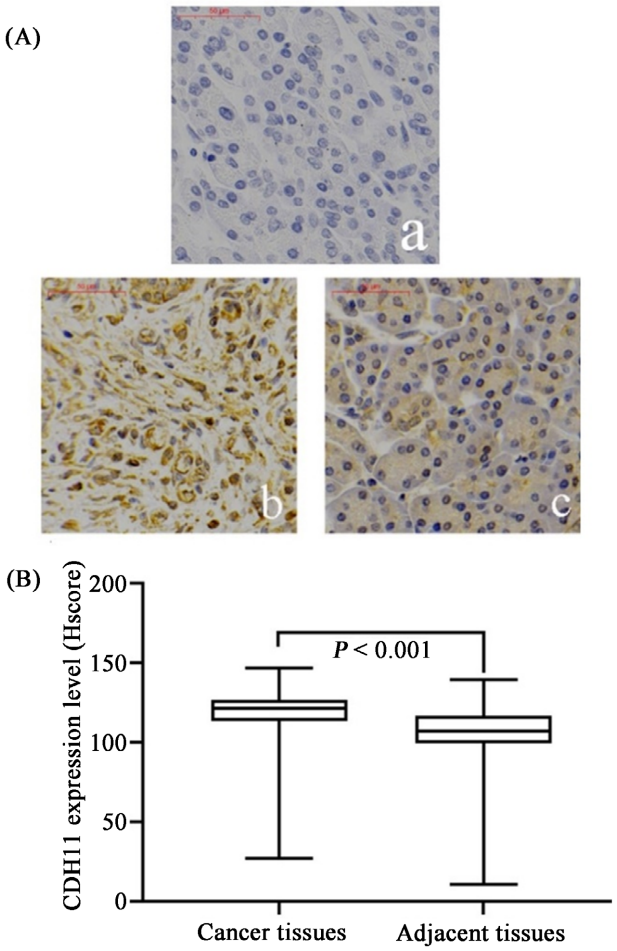

Figure 1. Expression of CDH11 in cancerous and adjacent tissues by immunohistochemistry. (A) Immunohistochemistry staining (scale bar, 50 μm) shows the expression of CDH11 in cancerous and adjacent tissues: a, negative control 400×; b. cancerous tissue 400×; c. adjacent tissue 400×. (B) Statistical analysis of CDH11 expression ($P < 0.001$).

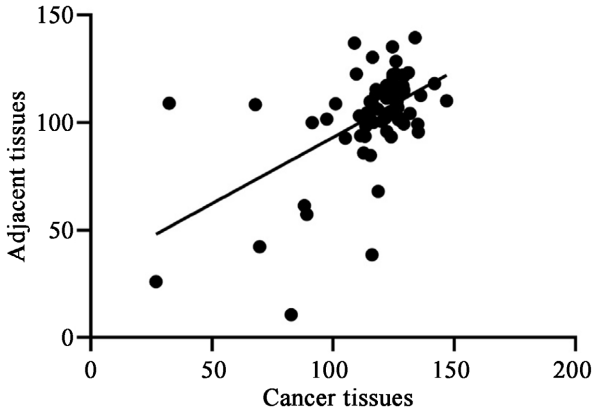

Figure 2. CDH11 expression in cancer tissues and adjacent tissues. The figure shows a positive correlation between cancer tissues and adjacent tissues expression of CDH11 (r = 0.440, P < 0.001).

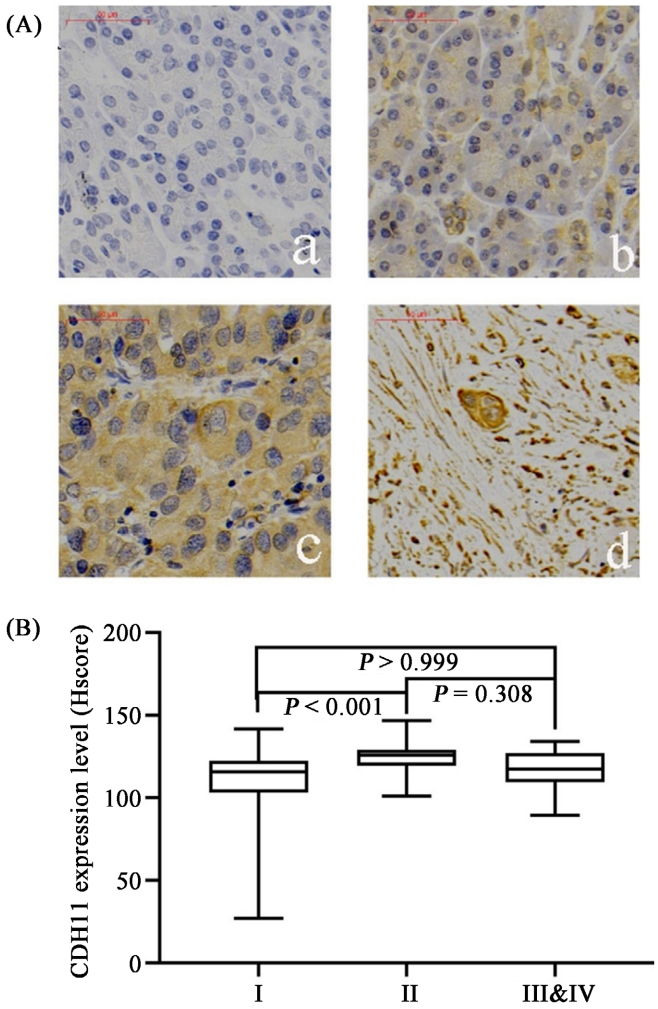

Figure 3. Expression of CDH11 in different stages by immunohistochemistry. (A) Immunohistochemistry staining (scale bar, 50 μm) shows the expression of CDH11 in different clinical stages: a. negative control, 400×; b. clinical stage I, 400×; c. clinical stage II, 400×; d. clinical stage III & IV, 400×; (B) Statistical analysis of CDH11 expression in different clinical stages.

Relationship between CDH11 expression and other clinical characteristics

A total of 79 patients with pancreatic cancer were enrolled in the study, including 51 men and 28 women with a median age of 62 (41 - 84). The pathological type of 69 patients was pancreatic ductal adenocarcinoma, while 10 patients were pancreatic adenosquamous carcinoma. PC patients were divided into different subgroups according to clinical characteristics, including age, sex, tumor location, tumor size, histology, and distant metastasis. No differences in CDH11 expression were found in the different subgroups ($P > 0.05$, respectively) (Table 1).

Relationship between CDH11 expression and prognosis of PC patients

The relationship between CDH11 expression and prognosis was also analyzed according to public databases. As a result, for PC patients, a higher level of CDH11 expression correlated with worse overall survival (OS) time ($P = 0.015$) (Figure 4(A)). Nevertheless, CDH11 expression was not related to disease-free survival (DFS) time ($P = 0.240$) (Figure 4(B)).

4. Discussion

According to our study, CDH11 may be involved in pancreatic carcinogenesis

Table 1. CDH11 expression and clinical characteristics of patients with PC.

Clinical characteristics	Case number (n, %)	CDH11 [median (25% - 75%)]	Z Value	P Value
Age				
<60	31 (39.2%)	122.0 (112.7 - 126.9)	−0.221	0.825
≥60	48 (60.8%)	119.7 (113.6 - 128.0)		
Sex				
Male	51 (64.6%)	119.2 (113.1 - 126.3)	−0.758	0.448
Female	28 (35.4%)	122.9 (113.6 - 128.9)		
Tumor location				
Head	54 (68.4%)	122.1 (111.3 - 128.4)	−0.232	0.817
Body or/and tail	25 (31.6%)	119.2 (114.5 - 126.3)		
Tumor size				
<5 cm	58 (73.4%)	119.3 (111.3 - 126.1)	−1.654	0.098
≥5 cm	21 (26.6%)	123.7 (116.5 - 129.0)		
Histology				
Pancreatic ductal adenocarcinoma	69 (87.3%)	121.6 (112.9 - 127.6)	−0.206	0.836
Pancreatic adenosquamous carcinoma	10 (12.7%)	121.0 (115.4 - 126.9)		
Distant metastasis				
No	71 (89.9%)	122.0 (113.6 - 126.9)	−0.390	0.697
Yes	8 (10.1%)	117.5 (109.4 - 127.2)		

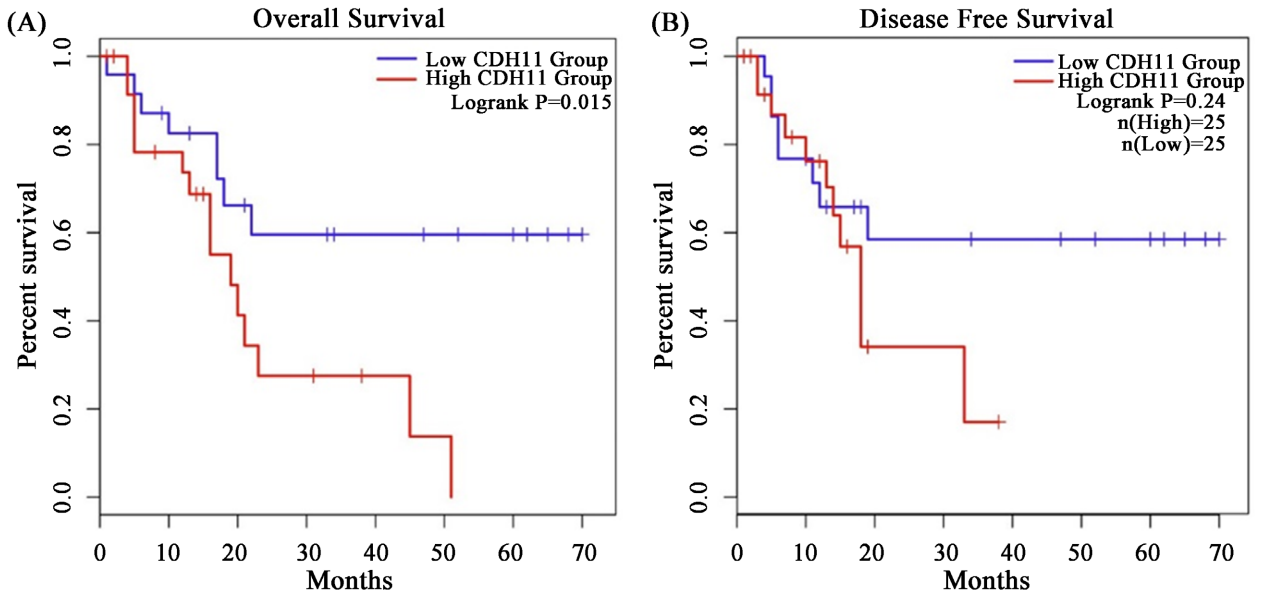

Figure 4. The prognostic value of CDH11 in PC patients. The overall survival time (A) and disease-free survival time (B) of the low-expressing CDH11 group are better than those of the high-expressing CDH11 group, but this difference is only meaningful in the comparison of overall survival time (P = 0.015).

and its expression level varies with clinical stage. Firstly, by detecting the expression of CHD11 in cancer tissue and adjacent tissue, the results showed that CDH11 could be expressed in both tissues, but the expression level in cancer tissues was significantly higher than that in adjacent tissues. CDH11 acts through a variety of biological mechanisms in cancer tissue, including a previous study showing that it could contribute to the activation of pancreatic stellate cells (PSCs) [26]. Not only that, Birtolo C *et al.* [27] also found that the expression of CDH11 was significantly increased in PSCs. Activated PSCs promote tumor interstitial hyperplasia and induce invasive tumor growth, distant metastasis, and resistance to drug therapy [28] [29] [30] [31], and PSCs can also interact with cancer cells to regulate the histological characteristics of PC within the tumor microenvironment [32]. Additionally, previous studies have shown that PSCs can enhance the expression of nerve growth factor and matrix metalloproteinase 9 and further promote tumor invasion and metastasis [33] [34] [35]. In a recent mice study, CDH11 has also been shown to promote immunosuppression and extracellular matrix deposition, contributing to the growth of pancreatic cancer [36].

Taken together, we speculate that CDH11, as a physiological adhesion molecule, may be expressed in pancreatic tissues "normally" but upregulated when carcinogenesis occurs under certain circumstances and then promotes tumor development via PSCs activation. In addition, we also found that CDH11 expression in adjacent tissues increased together with its expression in cancer tissues. This may indicate that a high level of CDH11 in tumor tissues may gradually induce carcinogenesis in surrounding normal tissues, resulting in tumor invasion, continuous progression, and metastasis. Therefore, it also reflects that

CDH11 does play an important role in the development and progression of pancreatic cancer.

In order to evaluate the clinical value of CDH11 more accurately and objectively, we analyzed its correlation with different clinical characteristics and found that it was closely related to clinical stages. The CDH11 level in cancer tissues of stage II patients was significantly higher than that of stage I patients; however, the CDH11 level of stage III and IV patients was not significantly different when compared with stage I or stage II patients. We speculate that CDH11 may be related to local cell proliferation and invasion and would be expressed rapidly to a peak level after carcinogenesis is initiated in pancreatic tissues. Although patient's tumor may develop to an advanced stage, CDH11 expression does not continue to increase accordingly. The results suggest that the tumor in a patient with a higher level of CDH11 may progress rapidly. In addition, no relationships were found between CDH11 expression and tumor size or distant metastasis in our study, suggesting that the high expression of CDH11 may be related to local proliferation and invasion of PC rather than distant metastasis.

Meanwhile, the GEPIA database (http://gepia.cancer-pku.cn) was used for survival analysis and the Kaplan-Meier plotter website data showed that high expression of CDH11 also led to poor OS in pancreatic cancer, but did not affect DFS in patients with pancreatic cancer. In the future, further patient survival data will be collected to validate the results of this database. Therefore, it can be speculated that CDH11 may be a poor prognostic factor and diagnostic index of early PC, or suggest that PC with high expression of CDH11 progress rapidly. Whether CDH11 could be a diagnostic or prognostic marker for pancreatic cancer and changes in serum soluble CDH11 levels in PC patients should be further investigated through clinical and experimental studies.

Although we have tried our best to perfect the study, there were still some shortcomings. First, this study focused on the association between CDH11 and clinical characteristics, and the potential mechanism research still needed to be further explored. Second, patients enrolled in this study were limited, more experimental and clinical studies were required to further clarify the significance of CDH11 and discuss whether it could be a new target molecule for the early diagnosis and treatment of PC. In conclusion, CDH11 may be involved in the development of early PC and lead to poor prognosis and could be a new target molecule for early diagnosis and treatment of PC.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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