Contributions of ADAM12 via HB-EGF/EGFR signaling cascades to EMT and cancer progression in pancreas

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Abstract. Pancreatic cancer (PC) is among the most aggressive malignancies, with a five-year survival rate of <7% in China. The substantial stromal component and activation of epithelial-mesenchymal transition (EMT) in PC contribute to drug resistance and poor outcomes. Between January 2017 and December 2020, 62 pancreatic specimens were obtained via surgical resection from two hospitals. In alignment with the GEPIA database, the expression levels of a disintegrin and metalloproteinase 12 (ADAM12) and heparin-binding epidermal growth factor (HB-EGF) were significantly elevated in 43 PC tissues compared with 19 benign pancreatic masses. Furthermore, elevated expression of ADAM12 and HB-EGF was significantly associated with lymph node metastasis, advanced TNM stage, and reduced survival rates. Additionally, high ADAM12 expression was correlated with the upregulation of EGFR and EMT markers. Collectively, the present findings suggested that ADAM12 is involved in PC progression and may facilitate the shedding of HB-EGF, thereby inducing EMT through the EGFR pathway. These results suggest that targeting the ADAM12/HB-EGF/EGFR signaling pathway could represent a potential therapeutic strategy, warranting further *in vivo* and *in vitro* investigations to elucidate the underlying mechanisms.

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Introduction

According to GLOBOCAN 2022, pancreatic cancer (PC) ranks as the sixth leading cause of cancer-related mortality among both sexes globally. The 5-year relative survival rate remains critically low at 5.9%, although this represents a slight improvement from previous figures. The global age-standardized incidence rate for PC is 4.7 per 100,000 individuals, with a corresponding mortality rate of 4.2 per 100,000 (1). As illustrated in Fig. 1, the age-standardized incidence rate of PC in China was 4.4 per 100,000, and the mortality rate was 3.9 per 100,000, as of 2022. In China, PC ranks as the 13th most prevalent cancer and the eighth leading cause of cancer-related death among both sexes.

The stroma constitutes a significant component of the prostate, accounting for over 70% of its mass. This substantial presence contributes to the insidious onset, challenges in early detection, and the development of drug resistance (2). Cancer-associated fibroblasts (CAFs) are critical elements within the tumor stroma and play an essential role in promoting malignancy. Pancreatic stellate cells (PSCs), which serve as the primary source of CAFs in PC, stimulate tumor growth and enhance cell survival and metastasis (3). Cytokines (4), including transforming growth factor β, platelet-derived growth factor and angiotensin II, among others, secreted by PC cells can promote activation of CAFs (Fig. 2). Through paracrine or autocrine signaling mechanisms, activated CAFs target EGFR and the downstream PI3K-AKT-mTOR pathway, leading to both enhanced tumor proliferation and reduced tumor suppression (5).

Activation of PSCs leads to an increased expression of ADAM12 (6). ADAM12 is a type I transmembrane multidomain protein that is overexpressed in various cancers, including glioblastoma, breast cancer, bladder cancer, prostate cancer, lung cancer, liver cancer and PC (7-13). As a protease, ADAM12 plays a significant role in tumorigenesis and metastasis by proteolyzing downstream substrates. Notable

substrates include HB-EGF, Delta-like 1, Ephrin-A1, among others (14,15). The overexpression of HB-EGF has been documented in numerous tumors, including PC, hepatocellular carcinoma, colorectal carcinoma and bladder cancers (16,17). Its upregulation correlates with PC cell proliferation, metastasis, chemoresistance and poor outcomes. Furthermore, the interaction between HB-EGF and EGFR in PC cells promotes tumor development, proliferation, differentiation and migration (Fig. 3) (18,19). Additionally, the activation of the EGFR signaling pathway plays a critical role in EMT with PC (20). EMT has been recognized as a pivotal step in the progression and development of drug resistance in various tumors, including PC (21,22). The specific contribution of ADAM12 to regulating EMT has been observed across diverse human cancer cell types (23,24).

Clinically, remarkably poor chemotherapeutic efficacy was observed in PC, which is primarily attributed to the abundant presence of stromal cells within tumor tissues. Furthermore, extensive studies have highlighted the pivotal role of EMT in pancreatic carcinogenesis. Motivated by these findings, it was hypothesized that stromal components within pancreatic tumors may drive its pathogenesis and progression, and it was aimed to elucidate their functional mechanisms while identifying potential therapeutic targets. According to the report, circulating levels of ADAM12 may serve as a prognostic indicator for patients with PC. As previously mentioned, ADAM12 is likely to promote EMT through the HB-EGF/EGFR signaling pathway, contributing to poor outcomes and chemoresistance in PC. The present study systematically examined the expression levels of ADAM12, HB-EGF, EGFR and EMT markers in PC using immunohistochemical (IHC) analysis, followed by an assessment of survival outcomes in patients with PC. The primary objective is to elucidate how ADAM12 influences the progression of EMT in PC by modulating the HB-EGF/EGFR signaling pathway.

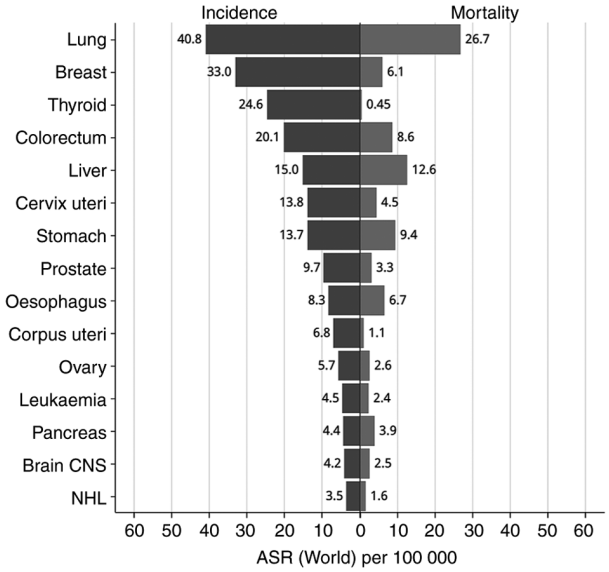

Figure 1. Age-standardized incidence and mortality rates of PC in China. There are age-standardized incidence and mortality rates for PC in both sexes. Data source: GLOBOCAN 2022. Graph production: IARC (http://gco.iarc.fr/today.), World Health Organization. PC, pancreatic cancer.

Materials and methods

Patients and specimens. The present study was approved by the academic committee at Lihuili Hospital of Ningbo Medical Center (approval no. KYSB2021SL023-01; Ningbo, China). All experiments were conducted in accordance with relevant guidelines and regulations. Informed consent was obtained from each patient, and the research was conducted in accordance with the Declaration of Helsinki (2013). From January 2017 to December 2020, a total of 62 patients with pancreatic masses were recruited from Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University (Guangzhou, China), and Lihuili Hospital of Ningbo Medical Center (Ningbo, China). Initially, it was aimed to collect pancreatic tissue via endoscopic ultrasound-guided fine-needle aspiration; however, it became evident that the specimen volume was insufficient for multiple IHC staining procedures. Consequently, all pancreatic tissue specimens were ultimately acquired through surgical resections. There were 43 PC tissues.

Furthermore, the remaining 19 benign pancreatic tissues were all derived from patients with surgically resected chronic pancreatitis, benign pancreatic mucinous tumors, autoimmune pancreatitis, and other conditions. Patients diagnosed with PC were offered follow-up for at least 2 years and subjected to the following inclusion conditions: i) complete follow-up data, ii) histologically confirmed PC cases, iii) no history of another malignant tumor, iv) no history of any antitumor treatment and v) no death within 30 days of surgery caused by postoperative complications. Relevant data on ADAM12 and HB-EGF were retrieved from the GEPIA database (http://gepia.cancer-pku.cn/) as supplementary controls.

IHC. Paraffin-embedded samples were sectioned at a thickness of 4 μm. Specimens were incubated with antibodies specific for ADAM12 (1:100; rabbit anti-human; Abcam), HB-EGF (1:100; rabbit anti-human; Abcam), EGFR (1:100; rabbit anti-human; Abcam), vimentin (1:100; rabbit anti-human; Abcam), or E-cadherin (1:100; mouse anti-human; Abcam) overnight at 4˚C according to the manufacturer's instructions. Two experienced pathologists independently evaluated 63 samples. The scores were recorded, each value corresponding to a range of the positive percentage: The score of 0 is negative, the score of 1 is 1-25%, the score of 2 is 26-50%, the score of 3 is 51-75%, and the score of 4 is ≥76%. Lower expression was considered as a score ≤2, while higher expression was considered as a score of 4.

Statistical analysis. SPSS version 19.0 (IBM Corp.) was used for statistical analyses. The Mann-Whitney U test was applied for the analysis of group differences, and Pearson's chi-square test and Spearman's rank correlation were used to evaluate the results of IHC. Survival curves were plotted by the Kaplan-Meier method and evaluated by the log-rank test. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological features. Of the 62 participants involved in the present study, 69.4% (n=43) were diagnosed with PC,

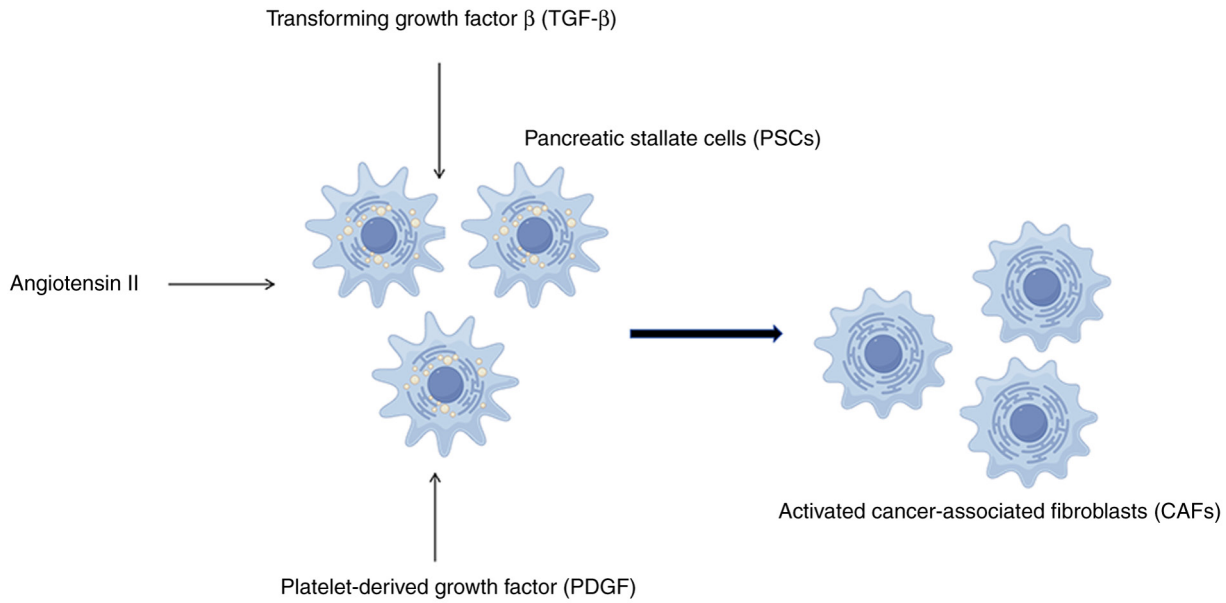

Figure 2. Activation of pancreatic stellate cells. Transforming growth factor β, platelet-derived growth factor and angiotensin II, secreted by pancreatic cancer, can promote activation of cancer-associated fibroblasts.

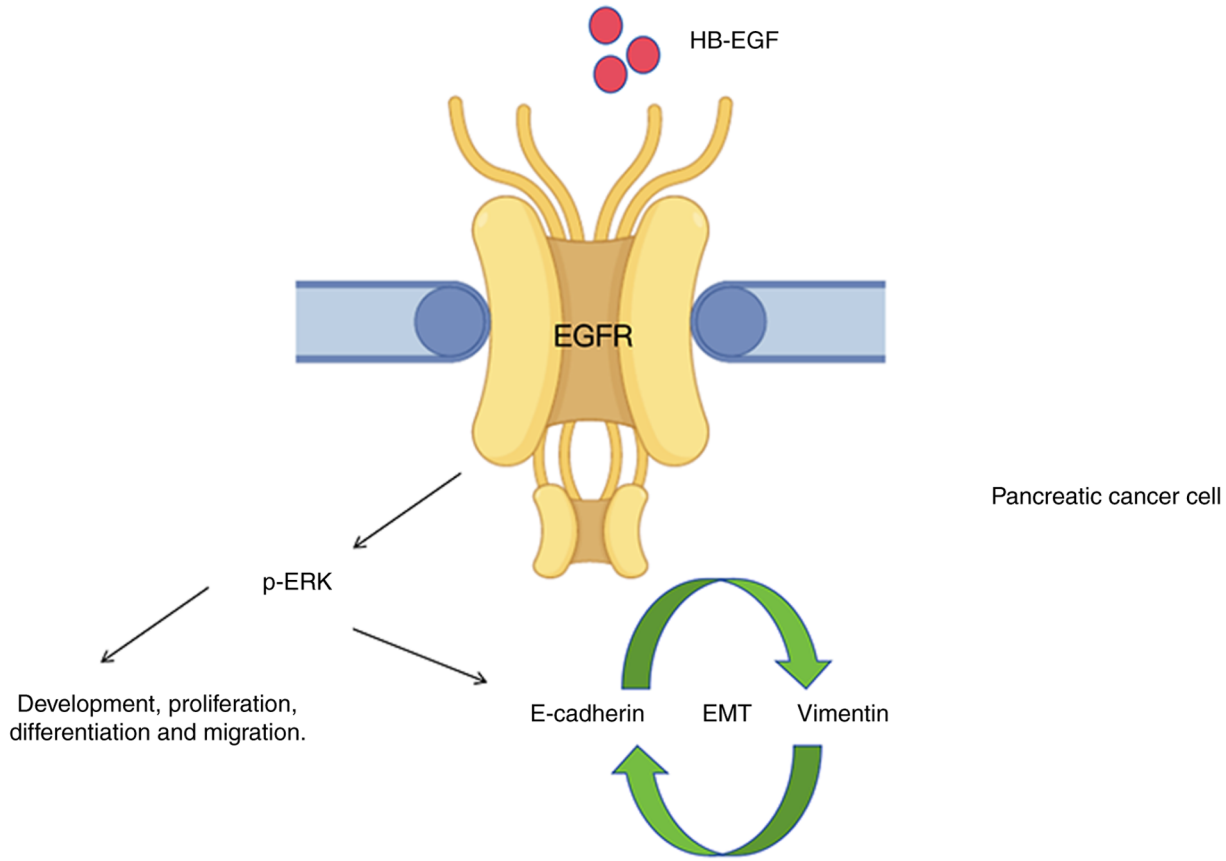

Figure 3. Diagram depicts HB-EGF/EGFR mediated development and migration in PC cells. The binding of HB-EGF to EGFR promotes the activation of the EGFR signaling pathway, which plays a critical role in PC cell proliferation, metastasis, chemoresistance, poor prognosis and EMT through p-ERK. However, the specific mechanisms remain unclear. HB-EGF, heparin-binding epidermal growth factor; EGFR, EGF receptor; PC, pancreatic cancer; EMT, epithelial-mesenchymal transition; p-ERK, phosphorylated extracellular signal-regulated kinase.

and their clinical characteristics and outcomes are detailed in Table I. The median age of the entire cohort was 69 years (range 42-83), with a predominance of male patients, comprising 27 individuals (62.8%). Consistent with previous literature (25), tumors were predominantly located in the pancreatic head, accounting for 29 cases (67.4%), while those situated in the

Table I. Clinicopathological characteristics and outcomes of patients with PC.

Characteristics	Total number (percentage of all PC cases)
Sex	
Male	27 (62.8%)
Female	16 (37.2%)
Tumor site	
Head	29 (67.4%)
Body/Tail	14 (32.6%)
Tumor size, cm	
≤3.0	13 (30.2%)
>3.0	30 (69.8%)
Histopathologic grade	
G1	4 (9.3%)
G2	32 (74.4%)
G3	7 (16.3%)
Lymph node status	
Positive	17 (39.5%)
Negative	26 (60.5%)
Metastases	
Positive	2 (4.7%)
Negative	41 (95.3%)
TNM staging	
I	15 (34.9%)
II	16 (37.2%)
III	10 (23.3%)
IV	2 (4.7%)
Chemotherapy	
Yes	21 (51.2%)
No	22 (48.8%)
Outcomes	
Death	24 (55.8%)
Survive	19 (44.2%)

PC, pancreatic cancer.

body/tail comprised 14 cases (32.6%). At diagnosis, a significant proportion of patients presented with larger tumor sizes (>3.0 cm) at a rate of 69.8%, and histologic grade II was observed in 74.4% of cases. Given that most participants in our cohort had resectable or borderline resectable PC, 31 patients were categorized (72.0%) as early stage (I/II) and the remaining 12 patients (28.0%) as advanced stage (III/IV). Furthermore, the incidence of positive lymph nodes was relatively low at 39.5% and only two patients (4.7%) exhibited distant metastases. Among 43 patients with PC, treatment modalities included chemotherapy for 21 individuals (51.2%), while there was a total of 24 deaths recorded with this population; specifically, these fatalities included 15 male and 9 female patients.

Expression of ADAM12, HB-EGF, EGFR and EMT markers in PC. The IHC examination revealed that the expression levels of ADAM12, as well as HB-EGF, EGFR and vimentin were significantly upregulated in 43 PC tissues compared with to 19 benign pancreatic mass (P<0.0001, Fig. 4). Conversely, E-cadherin was found to be significantly downregulated in PC tissues (P<0.0001, Fig. 4). Furthermore, a significant correlation was observed between high ADAM12 expression and lymph node metastasis (P<0.0001) and T stage (P=0.024), along with E-cadherin (P=0.035, P=0.010) and vimentin (P=0.021, P=0.005). The elevated expression levels of HB-EGF and EGFR were positively correlated with lymph node metastasis (P=0.004 and P=0.032), but not with T stage (P=0.097 and P=0.243). Additionally, high ADAM12 expression was associated with increased levels of HB-EGF (P=0.025), EGFR (P=0.012), and vimentin (P=0.001), while it correlated negatively with E-cadherin levels (P=0.012). Consistently, results from the GEPIA database indicated that both ADAM12 and HB-EGF are upregulated in PC tissues (Fig. 5A and B). In the current study cohort, there were 17 cases of lymph node metastasis vs. 26 cases without metastasis; higher expression levels of ADAM12 (P<0.0001), HB-EGF (P=0.020), EGFR (P=0.024) and vimentin (P=0.029) were significantly associated with advanced TNM stage (III and IV stage). It is noteworthy that most PCs collected for the present study were classified as stage II, with only a small proportion categorized into other stages. Thus, the sample size for correlation analysis is insufficient. That was the reason for conducting differential analyses solely between the I/II stage group and the III/IV stage group.

Association between ADAM12 and HB-EGF protein expression with survival. The median overall survival (OS) for the 43 patients with PC was 17 months. These patients were categorized into two groups based on their IHC scores: A high-expression group (IHC ≥ score 3) and a low-expression group (IHC ≤ score 2). Specifically, the median OS was found to be 36 months in the ADAM12 low-expression group compared with just 6 months in the high-expression group. Similarly, for HB-EGF, the median OS was 36 months in the low-expression group and 11 months in the high-expression group. Kaplan-Meier survival analysis was conducted to assess the relationship between protein levels and outcomes. Analysis of data from 198 patients with PC revealed a significant correlation with outcomes, which our findings corroborated (Fig. 6B and D). Conversely, while high expression of ADAM12 demonstrated a significant association with poor OS among this cohort (Fig. 6A), it did not reach statistical significance within the GEPIA database (Fig. 6C). This discrepancy may stem from differing criteria used for grouping: Patients were classified based on IHC score levels (high vs. low), whereas stratification in the GEPIA database utilized median IHC scores.

Discussion

Based on the GLOBOCAN 2022 estimates, PC was the eighth most diagnosed cancer type in China. There were 124,994 new cases of PC and 121,853 deaths attributed to this disease. The observed 5-year survival rate was a mere 6.6%. The incidence rates were reported as 6.3 per 100,000 men (age-standardized for China) and 4.2 per 100,000 women; mortality rates stood at 6.0 per 100,000 men and 4.2 per 100,000 women. In the

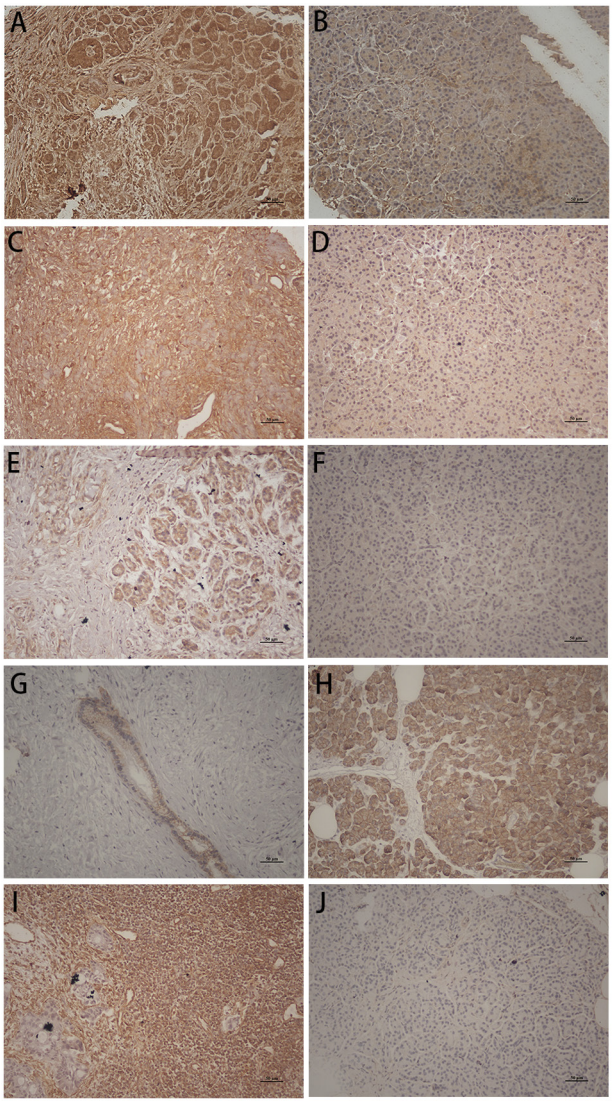

Figure 4. Distinction between PC tissue and benign pancreatic mass. (A) A disintegrin and metalloproteinase 12, (C) heparin-binding EGF, (E) EGF receptor and (I) vimentin show strong staining of the PC tissue, while benign pancreatic mass is weak (B, D, F and J); by contrast, (G) E-cadherin shows weak staining of the PC tissue, while benign pancreatic mass is strong (H). H&E stain, x200 magnification, all images. PC, pancreatic cancer; EGF, epidermal growth factor.

present study, data from 43 patients with PC were analyzed, comprising 27 males and 16 females. Among these patients, there were a total of 24 deaths (15 males and nine females), indicating that men exhibit a higher risk and poorer outcomes for PC compared with women. Consistent with findings from other studies, it was observed that most tumors (67.4%) were located in the head of the pancreas. Due to the insidious onset of PC, it is frequently diagnosed at an advanced stage; indeed, in the present study cohort, it was found that tumor sizes exceeded 3 cm in 30 cases (69.8%). However, few patients included in our analysis presented with lymph node or distant metastasis. This phenomenon can be attributed to our tissue samples being obtained from surgical resections, where most operable patients with PC do not exhibit lymphatic or distant spread. In alignment with previous research findings, it was identified that ADAM12 was highly expressed in PC tissues but not present in benign pancreatic tissues.

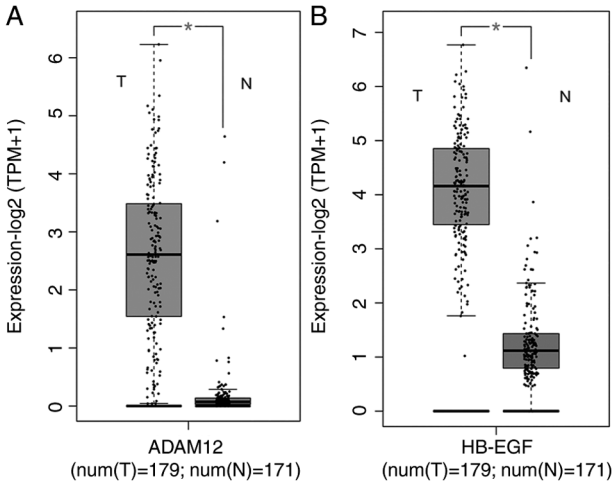

Figure 5. (A) ADAM12 and (B) HB-EGF are upregulated in pancreatic cancer. Images were obtained from the GEPIA online database (http://gepia.cancer-pku.cn). *P<0.01. ADAM12, a disintegrin and metalloproteinase 12; HB-EGF, heparin-binding epidermal growth factor; T, tumor; N, normal.

ADAM12 has been identified as essential for myotube formation, playing significant roles in proteolysis, cell adhesion, fusion, apoptosis and signal transduction. Its diagnostic and prognostic value has been established across various diseases, including Alzheimer's disease, arthritis, cardiac hypertrophy and various cancers (26). The ADAM12 gene, located on chromosome 10q26, encodes two distinct isoforms: A long transmembrane isoform (ADAM12L) and a short, secreted variant (ADAM12S). Both isoforms can activate or inhibit pathways involved in cell proliferation and invasion by proteolytically processing substrates. In PC, an upregulation of ADAM12 has been observed; however, its functional contributions remain unexplored (13). Consistent with this finding, the present study demonstrated a marked upregulation of ADAM12 in PC tissues compared with benign pancreatic tissues. This finding suggests that ADAM12 may play a critical role in the progression of PC. ADAM12 interacts with numerous substrates, including insulin-like growth factor binding proteins 3 and 5 (IGFBP-3 and -5), HB-EGF and others (27). The shedding of HE-EGF, mediated by ADAM12, promotes cell proliferation and contributes to cardiac hypertrophy through its interaction with EGFR (28). In breast cancer studies, it was shown that the extracellular domain of HB-EGF released by ADAM12 enhances cellular migration and invasion capabilities (29).

Furthermore, research on pituitary adenoma revealed that the shedding of HB-EGF by ADAM12 plays a pivotal role in facilitating cell migration and invadopodia formation through EGFR activation (23). In the current investigation, significantly elevated levels of both HB-EGF and EGFR expression were observed in PC tissues. Collectively, these findings suggested that ADAM12 may be implicated in the activation of the HB-EGF/EGFR signaling pathway during tumorigenesis and progression. However, the underlying mechanism remains to be elucidated.

According to previous studies on various tumors, it has been demonstrated that ADAM12 can promote tumor progression and metastasis by modulating EMT (30), a relationship

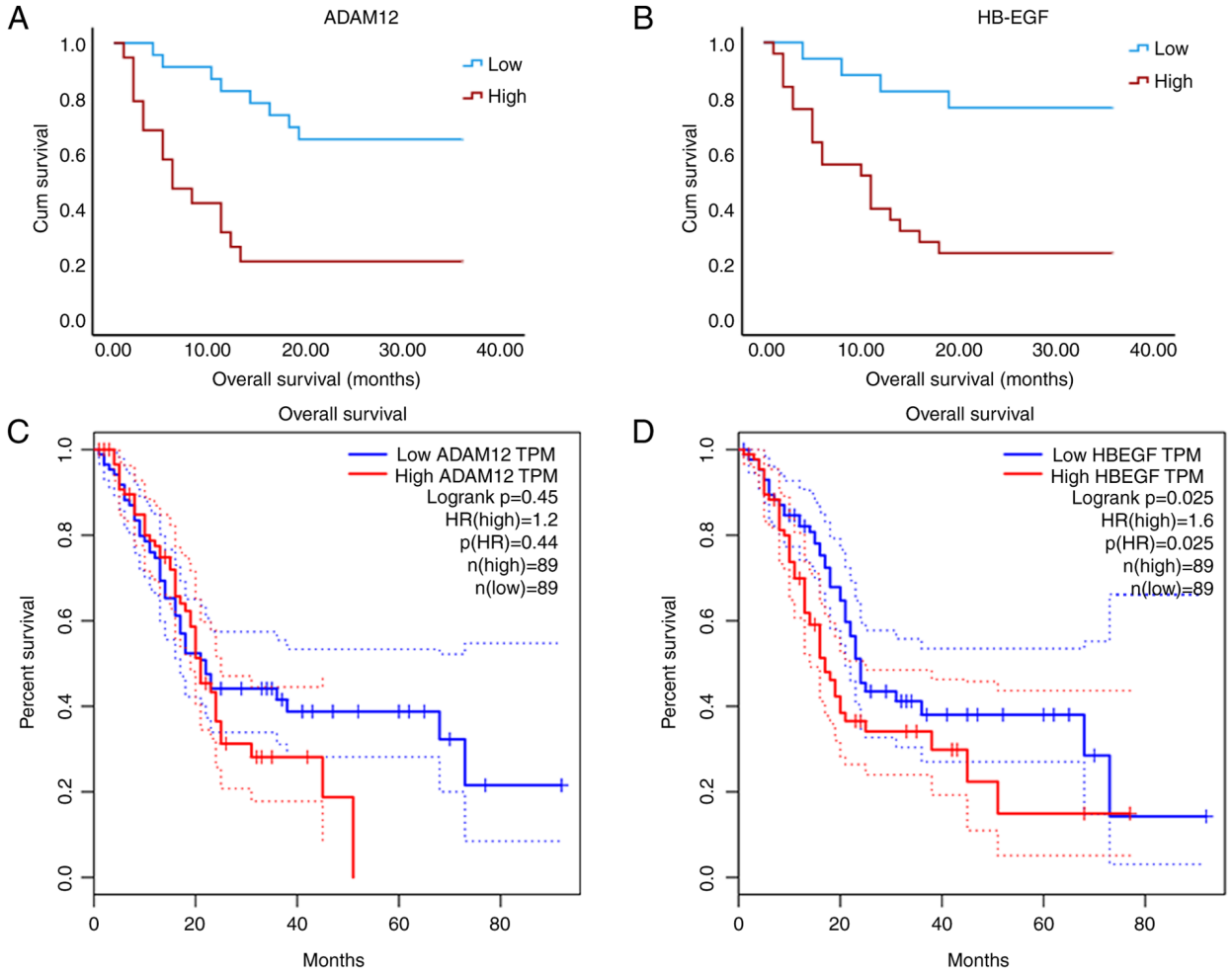

Figure 6. Kaplan-Meier survival analysis of ADAM12 and HB-EGF and PC survival. (A) Patients with ADAM12 lower expression showed a superior OS to patients with higher expression of ADAM12 (P<0.0001). (B) Patients with HB-EGF lower expression showed a superior OS to patients with higher expression of HB-EGF (P=0.001). In GEPIA database, (D) HB-EGF was significantly predicting the prognosis of patients with PC (n=198) by Kaplan-Meier analysis (P<0.05), while (C) ADAM12 was not. ADAM12, a disintegrin and metalloproteinase 12; HB-EGF, heparin-binding epidermal growth factor; OS, overall survival.

that remains unclear in PC. EMT involves the transition from an epithelial phenotype to a mesenchymal-like phenotype and plays a crucial role in the initiation of tumor invasion and metastasis (31). Major hallmarks of EMT include the increased expression of vimentin and decreased expression of E-cadherin. It is well established that EMT is induced in PC, facilitating cell migration and metastasis. Consistent with prior research, the present study observed upregulation of vimentin and downregulation of E-cadherin expression in PC tissues.

In the present study, 62 pancreatic specimens were collected through surgical resection from two hospitals. Among these specimens, 19 served as controls and were derived from patients with surgically resected chronic pancreatitis, benign pancreatic mucinous tumors, autoimmune pancreatitis, and other related conditions. It is acknowledged that some may question the appropriateness of our control group sample. This concern arises because most of the pancreas that can be surgically removed exhibits inflammation; thus, it is impossible to completely excise normal pancreatic tissue. Therefore, it is contended that this represents the most suitable non-cancerous pancreatic tissue for use as a normal control in our research.

Furthermore, positive correlations were found between lymph node metastasis, TNM staging, and the expression levels of ADAM12, HB-EGF, EGFR and vimentin. Taken together, the authors propose that ADAM12 may activate EGFR through the shedding of HB-EGF, thereby promoting tumor progression and metastasis in PC. These hypotheses warrant future studies.

Patients with PC and elevated expression levels of ADAM12 exhibited poorer survival outcomes in both the present study and the GEPIA database. According to the GEPIA database, a trend toward worse survival was noted in patients with PC with higher ADAM12 expression; however, no statistically significant difference was observed between the two groups (Fig. 6C). A recent investigation indicated that increased circulating levels of ADAM12 were predictive of worse survival for patients with PC following surgical resection or treatment with nab-paclitaxel. In contrast to ADAM12, the expression of HB-EGF demonstrated a significant association with patient survival in both our study and the GEPIA database.

In summary, the present study demonstrated that ADAM12 is highly expressed in PC, and the upregulation of ADAM12 may serve as a potential marker for poor outcomes in PC.

However, the expression level of ADAM12 does not show a significant association with the survival of patients with PC based on the GEPIA database. This discrepancy may be attributed to varying cutoff points, as elaborated in the results section. The impact of ADAM12 on outcomes remains controversial, necessitating larger sample sizes for future research. Furthermore, it was found that ADAM12 expression is significantly associated with the HB-EGF/EGFR pathway and EMT in PC. Therefore, it was hypothesized that activation of ADAM12 in PC may lead to EGFR-mediated EMT through shedding of HB-EGF, which could contribute to metastasis and poor outcomes among patients with PC. As a malignant tumor characterized by an abundant stroma, PC exhibits a deleterious propensity for drug resistance (32,33). It is now widely accepted that modulation of EMT represents a promising strategy for enhancing treatment efficacy in patients with PC (34). In the present study, correlations between ADAM12 and EMT markers were observed, as well as disease progression in PC, potentially mediated through the HB-EGF/EGFR signaling pathway. Collectively, these findings suggested that ADAM12 may emerge as a novel therapeutic for treating PC. Moving forward, we cell experiments in conjunction with *in vitro* analysis will be conducted in the future to elucidate further the role of this pathway in both the onset and progression of PC.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

QZ, FX, ZG, XD, YM, HL and KH contributed to the study conception and design. KH and ZG collected specimens and data. XD performed data analysis. QZ wrote the first draft of the manuscript. FX, YM and HL reviewed and edited the manuscript. QZ and ZG confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. KYSB2021SL023-01) by the academic committee at Lihuili Hospital of Ningbo Medical Center (Ningbo, China). All experiments were performed in accordance with relevant guidelines and regulations. Informed consent was obtained from each patient. The research was performed in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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