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Dynamic evaluation of postoperative survival in pancreatic ductal adenocarcinoma

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Abstract

The pancreatic ductal adenocarcinoma has a high degree of malignancy, and traditional prognostic assessment methods have limited evaluative capacity. This study is based on the Kallikrein-related peptidase 7 (KLK7) expression and uses conditional survival algorithms to perform dynamic survival assessments of patients. The Cox proportional hazards model was employed for identifying and adjusting for potential confounders. The Kaplan–Meier technique was utilized to estimate the overall survival rate. The computation of the likelihood of patients surviving an additional year after X years of survival was achieved using the equation CS1 = OS(X + 1)/OS(X). A subgroup analysis based on CS1 was conducted for each individual risk factor. A total of 243 eligible patients were included in the study. Conditioned survival (CS) refers to the years a patient has already survived and the predicted years they are likely to survive in the future, while conducting a time-varying analysis of the factors influencing prognosis. The survival probability assessed by CS1 increased year by year, with the 1-, 2-, and 3-year survival rates rising from 50.4% to 91.2%. In contrast, the actuarial overall survival (OS) decreased from 81.9% at 1 year to 38.6% at 3 years post-surgery. The results of the conditional analysis indicate that patients who survive longer within a certain timeframe have better survival expectations in the future. Adverse factors, including KLK7, have a decreasing impact on survival over time. Conditional survival analysis based on KLK7 can provide more accurate survival predictions for patients who has identified KLK7.

Abbreviations: CS = conditioned survival, KLK7 = Kallikrein-related peptidase 7, OS = overall survival, PDAC = pancreatic ductal adenocarcinoma.

Keywords: conditional survival, KLK7, pancreatic ductal adenocarcinoma, prognosis

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is highly malignant with a poor prognosis,[1] being the 4th leading cause of cancer-related deaths.[2] Surgery is one of the effective treatments for PDAC.[3] However, the prognosis after surgery remains poor, with a 5-year survival rate of only 15%–20%.[4] One of the key concerns for patients is their expected survival after surgery. A low survival expectation often leads to pessimism regarding treatment, indirectly affecting patients' adherence to therapy. Although many studies have explored methods for predicting survival, few have been able to conduct dynamic survival analyses. Based on the years patients have already survived, combined with the prognostic marker Kallikrein-related peptidase 7 (KLK7), dynamically predicting future survival is particularly important in clinical practice.[5,6]

The impact of adverse prognostic factors changes over time; thus, assessing a patient's prognosis should be dynamic.[7] Currently, overall survival (OS) is commonly used to evaluate patient prognosis. However, OS only reflects a constant hazard probability and survival probability calculated from initial follow-up, which can lead to pessimistic attitudes among patients and does not accurately assess prognosis dynamically.[8] Conditional survival analysis is essential, as it considers the changes in survival rates over time, assessing the probability of future long-term survival based on the time already survived, and provides a stratified analysis of the effects of prognostic factors.[9,10]

The expression levels of KLK7 can reflect the migratory and invasive abilities of PDAC cells.[11] It has been confirmed that KLK7 is significantly overexpressed in PDAC tissues, and reducing KLK7 expression can significantly decrease the proliferation, metastasis, and invasion of PDAC cells.[12] Several studies have shown that KLK7 overexpression can serve as an important prognostic marker for various malignancies.[5,12] Therefore,

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

This research approved by the Ethics Committee of the First Clinical Medical College of Three Gorges University. This study is a retrospective study, and therefore, individual patient informed consent was waived (IRB: 2021-086-01).

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combining KLK7 with conditional survival can effectively and dynamically assess patient prognosis.

In this study, based on KLK7 and the risk factors affecting prognosis, we calculated the conditional survival time for patients with PDAC and conducted further analysis on CS1, aiming to dynamically evaluate the prognosis of patients with PDAC.

2. Materials and methods

2.1. Patient and data collection

This research approved by the Ethics Committee of the First Clinical Medical College of Three Gorges University. This study is a retrospective study, and therefore, individual patient informed consent was waived (IRB: 2021-086-01). Tumor specimens consisted of 243 pancreatic cancer tissues obtained from patients with PDAC who went through radical resection from 2009 to 2016 in the First Clinical Medical College of Three Gorges University, China. The clinical pathology and essential characteristics including age, gender, tumor size, tumor differentiation, tumor stage, perineural infiltration state, vascular invasion, lymph node metastasis, etc. There were 163 males and 80 females who were aged from 31 to 80 years old and the median age is 59 years old. All specimens were confirmed to be PDAC by pathology after surgery.

2.2. Follow-up

According to standard follow-up procedures, the patients were followed up every 3 months for the first 2 years, and then every 3–6 months. During follow-up, routine monitoring included medical record collection, blood test, and imaging. The time between the date of surgery and death for any reason or the last follow-up was defined as OS.

2.3. Immunohistochemistry

The formalin-fixed paraffin block of the clinical sample was sectioned (4 μm), and perform immunohistochemical staining in a 2-step method. The quick steps are as follows: After the tissue sections baking at 65 °C, they deparaffinized with xylene and alcohol gradients. Peroxidase inactivated by 3% hydrogen peroxide at room temperature for 15 minutes. Sodium citrate was used for antigen retrieval and rinsing. After blocking with 3% fetal bovine serum protein for 30 minutes and kept it at 4 °C Incubate overnight, after rinse for 3 times, incubate at 37 °C for 2 hours in the dark, we add the KLK7 goat antihuman primary antibody (1:800) and rabbit anti-goat secondary antibody (1:1000) as well as color reagent, stop staining when light yellow appears but hematoxylin will regain dye to set up positive and negative controls.

2.4. Statistical analysis

In this study, we utilized the Kaplan–Meier estimator to assess overall survival (OS) predictions for the entire cohort, tracking time from the date of surgery until the most recent follow-up or the occurrence of death. To compare survival rates among different groups, we applied the log-rank test. The Cox proportional hazards model was employed to examine the relationship between clinicopathological factors and OS.

We calculated the conditional survival probabilities for an additional year (CS1) using the formula: $CS1 = S(X + 1)/S(X)$, where S represents the years of survival following surgery. To evaluate differences in CS1 across various subgroups, we computed standardized differences, known as d-values, using the formula: $(P2 - P1)/\sqrt{[P(1 - P)]}$, where P indicates the weighted average of P1 and P2. A d-value of |0.1| or below was interpreted as a negligible difference, while d-values between |0.1| and |0.3| suggested minor differences. d-Values ranging from |0.3| to |0.5| indicated moderate differences, and those of |0.5| or greater were considered significant differences. All statistical analyses were performed using R software, version 4.4.0 (http://www.r-project.org).

3. Results

3.1. Baseline characteristics of patients

A total of 243 patients were included in the study and completed follow-up, as shown in Table 1, which presents the basic information of the patients. The median age of the patients was 59.00 years; in terms of gender distribution, there were 80 females, accounting for 32.92%, and 163 males, accounting for 67.08%; in the distribution of tumor stages, there were 12 patients with stage IA, accounting for 4.94%, 14 patients with stage IB, accounting for 5.76%, 24 patients with stage IIA, accounting for 9.88%, 93 patients with stage IIB, accounting for 38.27%, 100 patients with stage III, accounting for 41.15%; in the distribution of T stages, there were 13 patients with T1, accounting for 5.35%, 23 patients with T2, accounting for 9.47%, 109 patients with T3, accounting for 44.86%, and 98 patients with T4, accounting for 40.33%; in the distribution of M stages, all patients (243) had M0, accounting for 100.00%; in the distribution of N stages, there were 70 patients with N0, accounting for 28.81%, 172 patients with N1, accounting for 70.78%, and 1 patient with N2, accounting for 0.41%;

Table 1

Baseline characteristics of patients.

Variables	Total (n = 243)
Age, M (Q_1, Q_3)	59.00 (53.00, 65.00)
Gender, n(%)	
Female	80 (32.92)
Male	163 (67.08)
T, n (%)	
T1	13 (5.35)
T2	23 (9.47)
T3	109 (44.86)
T4	98 (40.33)
N, n (%)	
N0	70 (28.81)
N1	172 (70.78)
N2	1 (0.41)
M, n (%)	
M0	243 (100.00)
Stage, n (%)	
Stage IA	12 (4.94)
Stage IB	14 (5.76)
Stage IIA	24 (9.88)
Stage IIB	93 (38.27)
Stage III	100 (41.15)
KLK7, n (%)	
Low	122 (50.21)
High	121 (49.79)
Perineural infiltration, n (%)	
No	82 (33.74)
Yes	161 (66.26)
Vascular invasion, n (%)	
No	91 (37.45)
Yes	152 (62.55)
Tumor differentiation, n (%)	
High and intermediate	68 (27.98)
Low	175 (72.02)
Time, M (Q_1, Q_3)	15.98 (11.31, 23.15)

M = median, Q_1 = 1st quartile, Q_3 = 3st quartile, KLK7 = Kallikrein-7.

Table 2

Cox regression of patients of CS1.

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Male	0.89 (0.62–1.30)	.553		
Age	1.00 (0.98–1.01)	.657		
T2	5.67 (1.27–25.40)	.023	3.06 (0.67–14.05)	.15
T3	6.58 (1.60–27.03)	.009	1.99 (0.45–8.86)	.366
T4	9.11 (2.21–37.49)	.002	2.60 (0.58–11.66)	.213
N1	1.31 (0.88–1.94)	.186		
N2	3.32 (0.45–24.43)	.239		
High KLK7	1.79 (1.26–2.55)	.001	1.60 (1.12–2.30)	.011
Perineural infiltration	0.98 (0.68–1.42)	.908		
Vascular invasion	2.49 (1.69–3.69)	<.001	1.85 (1.22–2.81)	.004
Low tumor differentiation	3.53 (2.23–5.60)	<.001	2.54 (1.52–4.27)	<.001

HR = hazard ratio, CI = confidence interval, KLK7 = Kallikrein-7.

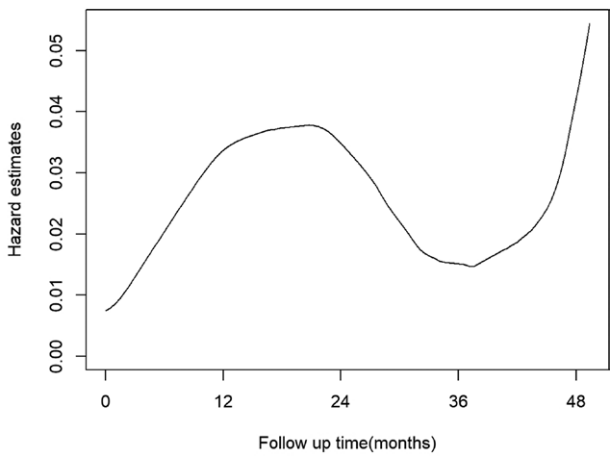

Figure 1. Hazard estimates of death among for all patients.

in the distribution of KLK7 expression, there were 122 patients with low expression, accounting for 50.21%, and 121 patients with high expression, accounting for 49.79%; 82 patients had no perineural infiltration, accounting for 33.74%; 91 patients had no vascular invasion, accounting for 37.45%; in the distribution of tumor differentiation, there were 68 patients with high and intermediate differentiation, accounting for 27.98%, and 175 patients with low differentiation, accounting for 72.02%.

3.2. Cox regression of patients of CS1

Univariate Cox regression analysis showed that T stage, KLK7 expression status, and vascular invasion were factors affecting prognosis. Multivariate Cox regression analysis indicated that KLK7 expression status (HR = 1.60 [1.12–2.30]), vascular invasion (HR = 1.85 [1.22–2.81]), and vascular invasion again (HR = 2.54 [1.52–4.27]) were independent risk factors affecting prognosis (Table 2).

3.3. OS and CS estimates

All enrolled patients completed follow-up with a median follow-up time of 15.98 months. Kaplan–Meier analysis was performed to determine the 1-year, 3-year, and 5-year survival rates, which were 81.9%, 38.6%, and 26.7%, respectively. The risk curve indicates that the 24 months postoperatively is a critical period for analyzing prognosis. After 24 months, the risk of death significantly decreased, suggesting that the patients may experience a significant improvement in long-term survival after 24 months (Figs. 1 and 2).

Table 3

Probability of postoperative conditional survival.

Total survival time (yr)	If the patient has survived to (%)			
	1 year	2 years	3 years	4 years
1 year				
2 years	50.4			
3 years	47.1	93.5		
4 years	43	85.2	91.2	
5 years	32.6	64.6	69.1	75.8

Subsequently, we calculated the conditional survival rates, and the results showed that the probability of surviving another year for patients who survived for 1 year postoperatively was 50.4%, for those who survived for 2 years postoperatively was 93.5%, and for those who survived for 3 years postoperatively was 91.2%. The calculated conditional survival time was significantly higher than the time calculated using simply OS, which means that within the time frame, the longer patients survive, the higher their probability of long-term survival will be (Table 3).

To further analyze the impact of prognostic risk factors on conditional survival, we calculated the conditional survival probabilities for patients who had survived for 2 years within each risk factor subgroup (Fig. 3). The results showed that the impact of all risk factors on survival decreased over time. Taking tumor differentiation as an example, after 2 years of survival, the future survival probability of patients with moderate-high tumor differentiation was basically no different from that of patients with low tumor differentiation. Further subgroup analysis showed that within all subgroups stratified by independent risk factors, the calculated conditional survival rates were all higher than the actuarial OS (Table 4).

3.4. KLK7 overexpressed in pancreatic cancer tissues

The immunohistochemistry was adopted to detect the expression of KLK7 in 243 patients with radically resected pancreatic cancer tissue samples. KLK7 expression in normal pancreatic tissue adjacent to cancer is lower than that in pancreatic cancer tissue (Fig. 4).

4. Discussion

PDAC is a highly malignant disease with a poor prognosis, with a 5-year survival rate after surgery ranging from only 15%

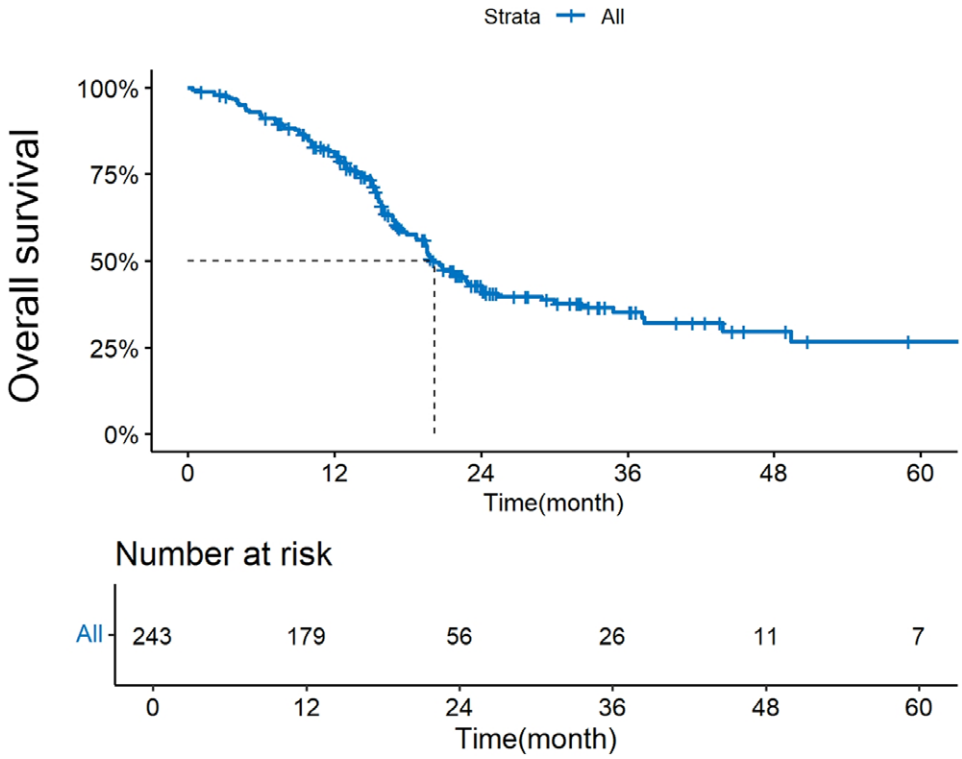

Figure 2. OS (overall survival) of all patients.

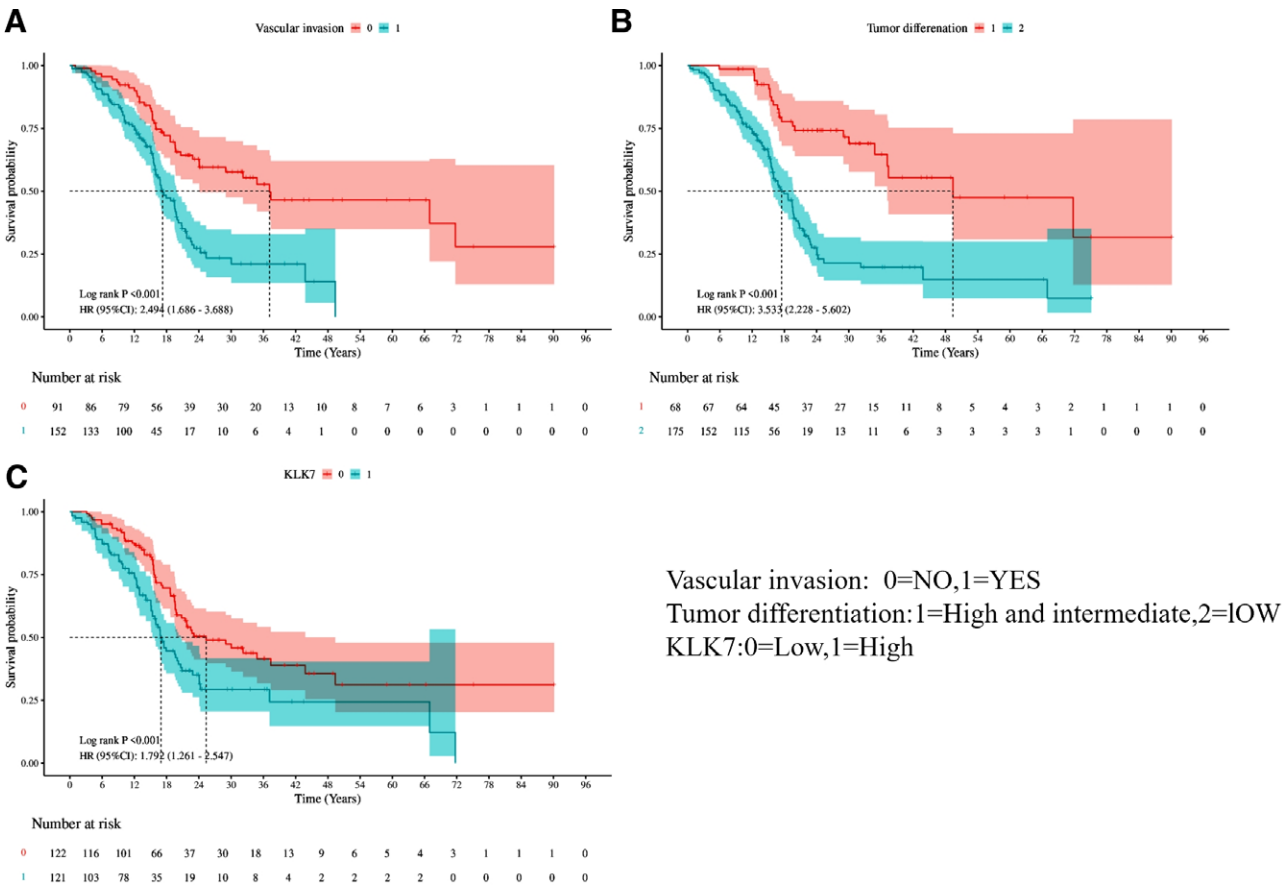

Figure 3. Overall survival stratified by tumor vascular invasion (A), tumor differentiation (B) and KLK7 (C). KLK7 = Kallikrein-related peptidase 7.

to 20%, significantly lower than that of other diseases.[13,14] Previous studies have analyzed various factors contributing to the poor prognosis of PDAC, such as tumor size and lymph node involvement. However, they often overlook the temporal changes in patient prognosis; factors influencing prognosis may diminish over time.[15] Therefore, utilizing conditional survival rates for survival analysis is more appropriate.

In recent years, there has been a growing interest in conditional survival analysis.[16] According to the principles of conditional analysis, patients who survive longer within a defined period are expected to have better future survival outcomes. Thus, predictions for potential future survival can be made based on the time a patient has already survived. In our study, we identified independent prognostic factors affecting survival, including the expression of KLK7 (HR = 1.60 [1.12–2.30]), vascular invasion (HR = 1.85 [1.22–2.81]), and perineural invasion (HR = 2.54 [1.52–4.27]). Further analysis indicated that the prognostic impact of these factors diminishes over time, consistent with previous findings.[17,18] We also evaluated the time-dependent effects of KLK7 expression on prognosis and calculated specific probabilities, revealing that patients with high KLK7 expression who survive beyond 2 years experience an increased likelihood of future survival.

Table 4

Multivariate analysis of the 1-year conditional survival.

		If the patients has survival to (%)		
Variables	**Categories**		**1 year**	**2 years**
KLK7		Low	82.3	61.9
		High	77.9	39
	d		0.28	0.97
Vascular invasion		No	78.2	62.5
		Yes	77.6	51.5
	d		0.03	0.45
Tumor differentiation		High and intermediate	80.1	64.1
		Low	80	60.2
	d		0.01	0.16

KLK7 = Kallikrein-7, d = Cohen d value.

Public databases and immunohistochemical studies show that KLK7 is highly expressed in pancreatic cancer tissues but has low expression in adjacent noncancerous tissues.[19] Patients with high KLK7 expression tend to have poorer long-term survival outcomes.[20,21] These findings suggest that KLK7 can serve as an independent predictor for assessing the long-term prognosis of pancreatic cancer patients.[22] Traditional prognostic factors, such as tumor size and differentiation, reflect past outcomes rather than integrating the process of pancreatic cancer development.[23] In contrast, KLK7 expression can offer more accurate prognostic predictions and could also serve as a new therapeutic target.

Historically, KLK7 has been used solely in conventional survival analyses, which do not dynamically reflect its impact on survival, thereby limiting its utility. By incorporating KLK7 into conditional survival analysis, we provide a dynamic reference for patients with KLK7 indicators, enhancing the accuracy of prognostic assessments.

However, our study has certain limitations. Firstly, the sample size is relatively small, and the dimensions influencing prognosis are limited. Expanding the sample size could strengthen the validity of our dynamic analysis. Secondly, being a single-center study may introduce selection bias. Consequently, we plan to conduct a multicenter joint analysis in the future to broaden the application of KLK7 as a biomarker.

5. Conclusion

Conditional survival analysis can dynamically predict the survival of patients with PDAC. Based on KLK7, this approach provides a valuable reference for assessing survival outcomes.

Author contributions

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Funding acquisition: Ru-Cheng Yao.
Investigation: Xin-Yu Yang.
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Writing – review & editing: Jun Zheng.

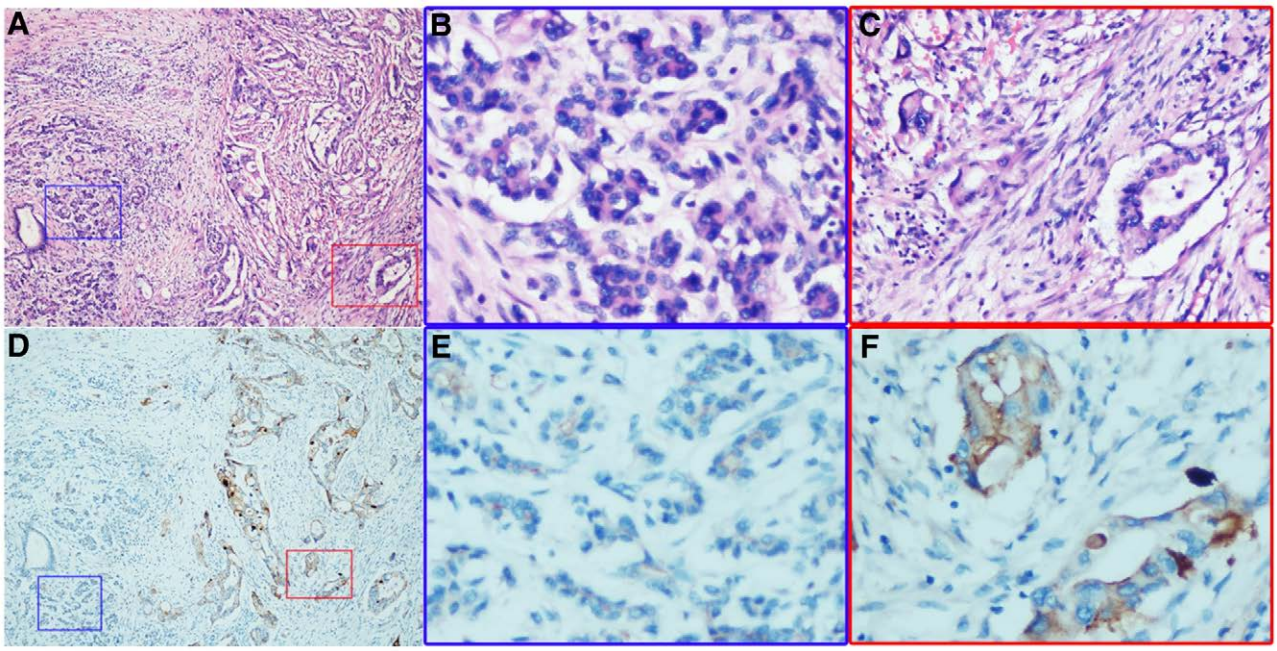

Figure 4. The expression of KLK7 in pancreatic cancer tissues and adjacent tissues. KLK7 = Kallikrein-related peptidase 7.

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