


Upregulated Expression of Actin-Like 6A is a Risk Factor Affecting the Prognosis of Pancreatic Cancer

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Purpose: Actin-like 6A (ACTL6A), a regulatory subunit of the ATP-dependent chromatin-remodeling complex SWI/SNF, acts as an oncogenic factor. This study is aimed at evaluating the correlation between ACTL6A expression and clinicopathological parameters in pancreatic cancer (PC) patients.

Methods: The differences of *Actl6a* mRNA expression between PC tissues and normal pancreatic tissues were analyzed in public databases, and ACTL6A expression was then determined and confirmed in 60 paired tissue specimens using immunohistochemistry staining. The association analysis between ACTL6A expression and the clinicopathological characteristics was analyzed, as well as Kaplan–Meier survival analysis. Univariate and multivariate Cox analyses were performed to identify the prognostic factors in the overall survival (OS) of patients with PC.

Results: The mRNA expression of *Actl6a* showed significantly higher in PC compared to normal controls ($p < 0.05$) from public databases. The score of immunohistochemistry staining further confirmed that ACTL6A expression was significantly upregulated in PC tissues ($p < 0.001$) through immunohistochemistry staining. High ACTL6A expression was associated with lymphovascular space invasion of PC. Kaplan–Meier analysis revealed that the high expression of ACTL6A was markedly associated with poor OS. Moreover, univariate and multivariate analysis demonstrated that ACTL6A acted as an independent risk factor for PC prognosis.

Conclusion: ACTL6A is upregulated in PC and acts as a risk factor for poor prognosis in patients with PC, and therefore clinicians could around it design preventive measures and individualized treatment to improve mortality in patients with PC.

Keywords: pancreatic cancer, risk factors, actin-like 6A, prognosis, biomarkers

Introduction

Pancreatic cancer (PC) with high aggressiveness and malignancy has become an enormously common cancer of the digestive system during 10 years. Globally, the 5-year overall survival (OS) rate of patients with PC is less than 9%, and the mortality rate is predicted to peak by 2030.¹ Due to insidious symptoms, only less than 10% of PC is initially diagnosed with a local stage, and the prognosis of PC is extremely poor.² Therefore, further investigation into novel cancer-related genes is required and meaningful for the improvement of prognosis.

SWI/SNF complexes are evolutionarily conserved multi-subunit molecular machines that mediate transcriptional regulation³ and are linked to a poor prognosis across several cancer types.^{4–6} Among them, Actin-like 6A (ACTL6A), encoded by *Actl6a*, acts as a chromatin-remodeling factor and regulates the function of

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progenitor and stem cell transcriptionally.^{7,8} In addition, ACTL6A expression is associated with prognosis in many types of cancer, such as hepatocellular carcinoma,⁹ colon cancer,¹⁰ and esophageal squamous cell carcinoma.¹¹ Recently, research revealed that epithelial-to-mesenchymal transition (EMT) was also regulated by ACTL6A.^{9,12} In addition, the study showed that ACTL6A overexpression could lead to increased repair of cisplatin-DNA adducts and cisplatin resistance.¹³ However, the role of ACTL6A in tumorigenicity and clinical prognosis of PC remains unclear so far.

In this connection, we analyzed the differences of ACTL6A expression in PC tissues and normal tissues, and we investigated the prognostic effect of ACTL6A on PC based on cases in public databases and confirmed it in our center.

Materials and Methods

Analysis of Database

Differential expression of Actl6a mRNA between pancreatic tumor and normal tissues was analyzed using the Gene Expression Profiling Interactive Analysis website (GEPIA; <http://gepia.cancer-pku.cn/>). Data for 179 patients with PC and 171 normal tissue samples analyzed on the GEPIA website were obtained from TCGA and normal tissue samples from Genotype-Tissue Expression (GTEx).^{14–16} The gene expression, determined as transcripts per million (TPM), was calculated by $\log_2(\text{TPM} + 1)$ for comparison. Based on the expression levels of Actl6a mRNA, the overall survival (OS) of patients was also analyzed.

Patients and Tissue Specimens

A total of 60 patients with PC confirmed by histopathology from January 2013 to June 2020 at Zhongda Hospital, Medical School of Southeast University were selected for the study. Sixty paired pancreatic tumor and normal tissues from patients who did not receive chemotherapy or radiotherapy were obtained to detect ACTL6A expression. Any patients with incomplete epidemiological and clinical information or lack of follow-up information were excluded. The results of serum tumor markers were collected from 60 healthy individuals who were admitted to the hospital for physical examination at the same time. All patients provided informed consent. Patients were followed up by telephone or at office visits every 3 months from the end date of surgery. The latest follow-up ended in July 2021. According to the eighth edition of the American

Joint Committee on Cancer (AJCC) Cancer Staging Manual, pathological stages were validated. The study was conducted with approval from the ethics committee of Zhongda Hospital, Southeast University. The study protocol protected the private information of enrolled patients in accordance with the provisions of the Helsinki Declaration.

Immunohistochemistry Staining

The paraffin-embedded pathological specimens were cut into 4- μm -thick sections. After being dewaxed in xylene and rehydrated in grade alcohol, the paraffin sections were submerged in a pH 6.0 citric acid solution and heated at 95°C for approximately 15 minutes for antigen retrieval. Next, the sections were incubated with rabbit ACTL6A antibody (Abcam Corp, USA, diluted 1:200) overnight at 4°C and washed 3 times with phosphate buffer saline (PBS). The sections were then incubated with horseradish peroxidase-conjugated secondary antibody for 30 minutes at room temperature in the dark. After stained with freshly prepared 3,3'-diaminobenzidine (DAB), they were counterstained with hematoxylin and differentiated with 1% hydrochloric acid. PBS was used to substitute the primary antibody as negative control. Finally, the sections were dehydrated with alcohol and sealed with neutral gum, and pictures were taken by microscope for positive cell calculation. Immunohistochemical staining analysis was performed independently by two pathologists according to the staining intensity and the percentage of positive cells. The staining intensities were 0 (negative), 1 (positive 1+), 2 (positive 2+), and 3 (positive 3+), respectively. The percentages of cells were 0 (negative), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%), respectively.^{17,18} Total scores were calculated by multiplying the scores of staining intensity and percentage.

Statistical Analysis

Statistical analyses and mapping were performed using SPSS software (version 18.0, IBM Corporation, Armonk, NY, USA), GraphPad Prism (Version 8.4.3, GraphPad Software, La Jolla, CA, USA), and R (version 3.4.1, <http://www.r-project.org/>) in the present study. Wilcoxon test was used to evaluate significant differences between pancreatic cancer and normal tissues, and the χ^2 test and continuity correction were used to explore the relationship between ACTL6A expression and clinicopathological features. The diagnostic efficiency of ACTL6A expression was analyzed through receiver operating characteristic (ROC) curves for PC. The

sensitivity and specificity were evaluated at an optimal cutoff. The expression of ACTL6A was classified as high expression and low expression according to the cutoff. Survival analysis was analyzed using Kaplan–Meier curve, and difference among groups was assessed using Log rank test. Both univariable and multivariable analyses were used in survival analysis, respectively. The clinicopathological factors with significant associations ($p < 0.1$) in the aforementioned univariable analysis were subjected to multivariate analysis. $p < 0.05$ was considered to be statistically significant.

Results

ACTL6A Expression in PC and Normal Tissues

To explore the potential role of ACTL6A in PC, the expression of Actl6a mRNA was analyzed with the publicly available

GEPIA database. In clinical PC specimens ($n = 178$) and normal tissues ($n = 171$), Actl6a mRNA had significant differential expression between the two groups. What is more, Actl6a mRNA was upregulated in PC than normal tissues ($p < 0.05$, Figure 1A). Then, the protein expression of ACTL6A was validated and compared in PC samples ($n = 60$) and normal tissues ($n = 60$) with immunohistochemistry staining in our center. The typical immunohistochemical results of normal tissues and PC tissues are shown in Figure 1B, which demonstrated that ACTL6A was mainly observed in the nucleus of cells. By multiplying the staining intensity and percentage, the protein expression of ACTL6A was also over-expressed in pancreatic cancer ($p < 0.001$, Figure 1C). Table 1 shows the number of patients with different scores based on immunohistochemistry staining. The results above indicated that ACTL6A was upregulated in PC.

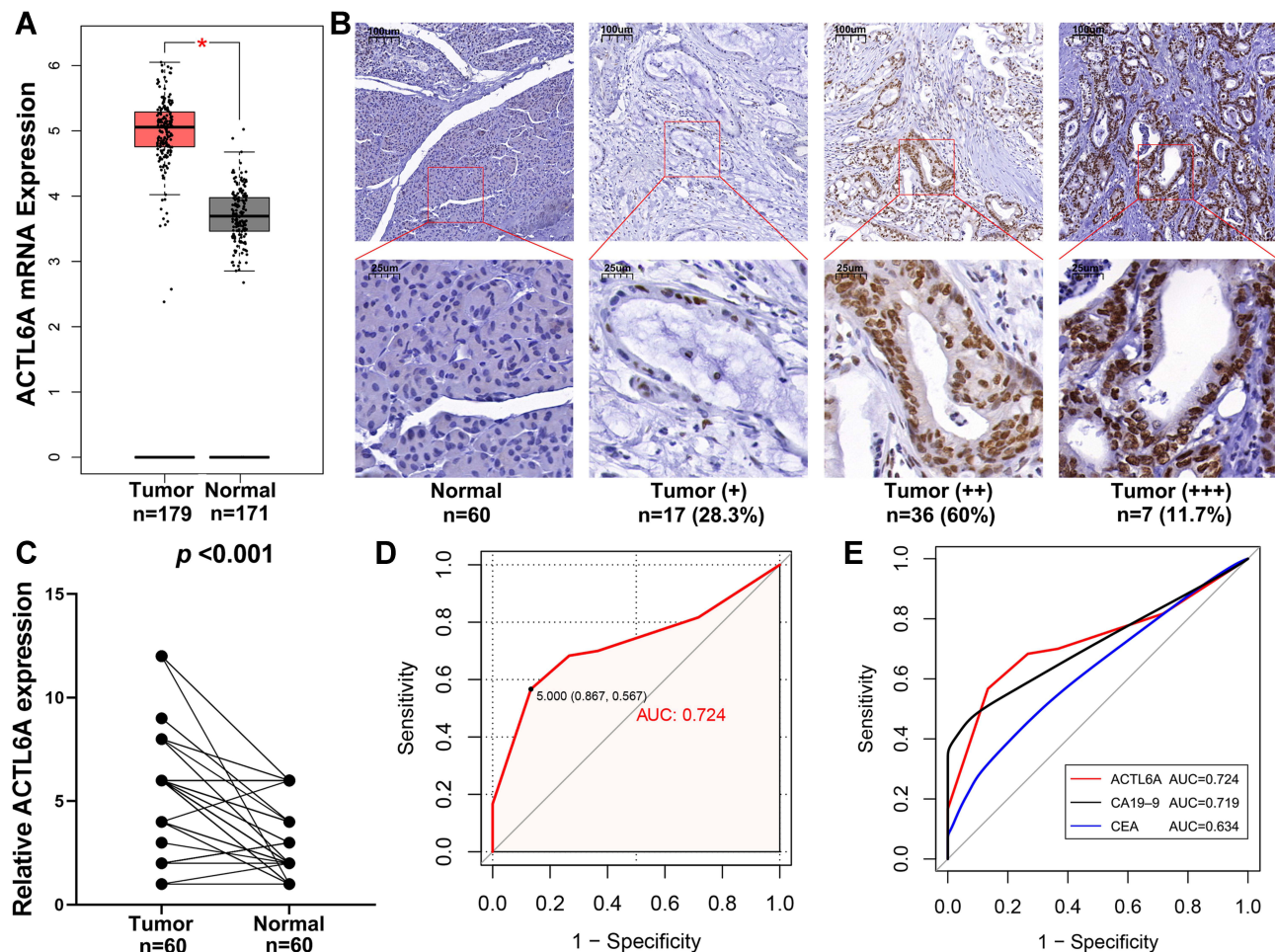


Figure 1 Expression of ACTL6A in PC and normal tissues. **(A)** Differential expression of *Actl6a* mRNA between pancreatic tumor and normal tissues. **(B)** Immunohistochemical results of typical normal tissues and PC tissues with different staining intensities. **(C)** Differential expression of ACTL6A between pancreatic tumor and normal tissues. **(D)** ACTL6A represented a moderate diagnostic value. The ROC of pancreatic cancer samples and normal tissues. **(E)** ROC for the diagnostic efficiency of ACTL6A, serum CEA, and serum CA19-9. * $p < 0.05$.

Abbreviations: ACTL6A, actin like 6A; PC, pancreatic cancer; ROC, receiver operating characteristic curves; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

Table 1 The Number of Patients in Different Scores Based on Immunohistochemistry Staining

Scores	No. of Patients (%)	
	Tumor	Normal
1	11 (18.3)	17 (28.3)
2	7 (11.7)	21 (35.0)
3	1 (1.7)	6 (10.0)
4	7 (11.7)	8 (13.3)
6	24 (40.0)	8 (13.3)
8	5 (8.3)	0 (0.0)
9	2 (3.3)	0 (0.0)
12	3 (5.0)	0 (0.0)

Diagnostic Value of ACTL6A Expression for PC

To investigate the diagnostic value of ACTL6A expression for PC, we performed ROC analysis on total scores of pancreatic cancer and normal pancreatic tissue, as shown in [Figure 1D](#) and [E](#), and the AUC value was 0.724, which was higher than that of carbohydrate antigen 19–9 (CA19–9) and carcinoembryonic antigen (CEA). These results represented a moderate diagnostic value for PC. The specificity and sensitivity of ACTL6A expression for PC diagnosis were 0.867 and 0.567, respectively. The cut-off value established for ACTL6A expression for the diagnosis of PC was 5.

Relationships Between ACTL6A Expression and Clinicopathological Variables

To further understand the role of ACTL6A in PC, we analyzed the relationship between ACTL6A expression and the clinicopathological characteristics. Patients with PC were divided into ACTL6A low-expression group (score 0–5; $n = 34$) and ACTL6A high-expression group (score 6–12; $n = 26$) with the cut-off value of score 5. The relationship between ACTL6A expression and clinicopathological factors of pancreatic cancer is summarized in [Table 2](#). Lymphovascular space invasion (LVSI) of PC was significantly associated with ACTL6A expression, which was more likely to occur in the ACTL6A high group. LVSI was present in 55.9% (19/34) of patients in the ACTL6A high group and 26.9% (7/26) in ACTL6A low group.

Relationships Between ACTL6A Expression and Overall Survival in PC

The survival data of 178 PC patients was obtained from TCGA dataset. Patients are split into two groups according

Table 2 Relationships Between the Expression Level of ACTL6A and the Clinicopathological Characteristics of PC Patients

Characteristics	No. of Patients	Expression of ACTL6A		p value
		High	Low	
Age(years)				0.151
<65	26	12	14	
≥65	34	22	12	
Sex				0.889
Male	34	15	19	
Female	26	11	15	
Tumor site				0.651
Head	32	19	13	
Other ^a	28	15	13	
Grade				0.713
Well/moderately	40	22	18	
Poorly/undifferentiated	20	12	8	
T stage				0.505
T1+T2	26	16	10	
T3+T4	34	18	16	
N stage				0.930
N0	25	14	11	
N1+N2	35	20	15	
M stage				0.339
M0	57	31	26	
M1	3	3	0	
TNM stage				0.702
I	13	7	6	
II–IV	47	27	20	
LVSI				0.025
Yes	26	19	7	
No	34	15	19	

Note: ^aPancreatic body and tail.

Abbreviations: ACTL6A, actin-Like 6A; PC, pancreatic cancer; LVSI, lymphovascular space invasion.

to the median value of Actl6a mRNA expression. One-half (89 patients) was defined as high *Actl6a* mRNA expression, and the other was defined as low *Actl6a* mRNA expression. Obviously, high *Actl6a* mRNA was associated with poor overall survival in patients with PC ($p < 0.001$, [Figure 2A](#)). Furthermore, based on data from our center, the Kaplan–Meier method was used to investigate the relationship between the expression of ACTL6A protein and OS of patients. The median OS in PC patients for the high and low expression of ACTL6A was 8.0 ± 0.4 months and 13.0 ± 1.6 months, respectively. Obviously, patients with low ACTL6A expression had significantly longer survival time than those with high ACTL6A expression ($p < 0.001$, [Figure 2B](#)).

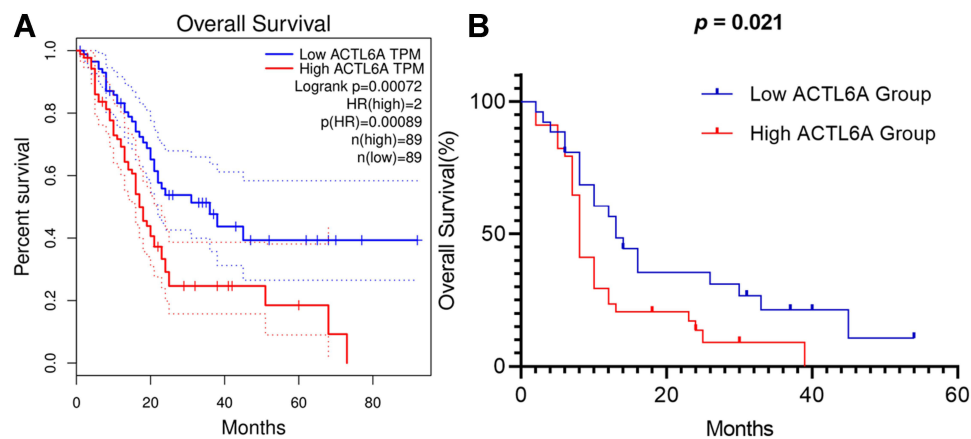


Figure 2 (A) Kaplan–Meier curves of overall survival in PC patients with high and low *Actl6a* mRNA expression. **(B)** Kaplan–Meier curves of overall survival in PC patients with high and low ACTL6A expression.

Abbreviations: ACTL6A, actin like 6A; PC, pancreatic cancer.

ACTL6A Overexpression as an Independent Risk Factor in Patients with PC

Univariate and multivariate Cox analyses were performed to identify the prognostic factors on OS of patients with PC. The results demonstrated that ACTL6A overexpression ($p = 0.032$) and grade ($p = 0.008$) were risk factors for survival in patients with PC through univariate Cox analysis. Further multivariate Cox analysis showed that ACTL6A expression ($p = 0.046$) was an independent risk factor for poor prognosis of PC (Table 3). As shown in Figure 3A and B, the forest plot visualizes the specific HR of risk factors.

Discussion

Worldwide, PC has become a malignancy with a dismal prognosis and high mortality, which has a 5-year survival rate of less than 10%.¹⁹ There are two clinical features that are involved with the poor prognosis of PC. First, initial symptoms of PC are insidious, which leads to many challenges for early diagnosis. Second, PC has a significant potential for invasion and metastasis.²⁰ In detail, the distant spread may occur in the early stages of PC, and more than 50% of patients with PC have no possibility to be treated with surgical resection.²¹ Scientific problems covering early diagnosis, the mechanisms of metastasis, and the risk factors of prognosis are necessary to be solved to improve survival of PC. In this study, we clarified that ACTL6A is highly expressed in PC, and it is a reliable marker for predicting the prognosis of PC patients.

ACTL6A is involved in a variety of cellular processes, including vesicle transport, spindle orientation, nuclear

migration, and chromatin remodeling.^{7,22} Increasing evidence has suggested its involvement with tumorigenesis and development of cancer.⁷ ACTL6A has been reported to be overexpressed in a variety of malignancies, including hepatocellular carcinoma,⁹ ovarian cancer,¹⁸ cervical cancer,²³ and esophageal squamous cell carcinoma,¹¹ which is correlated with the prognosis of patients with malignancies. This evidence suggests that ACTL6A is a potential oncogene, and it is observed that ACTL6A expression is also upregulated in PC in our study, which is consistent with previous studies. Researchers have been constantly exploring diagnostic markers for PC. Jelski et al reported that the activity of alcohol dehydrogenase (ADH) class III isoenzyme in pancreatic cancer was significantly higher than that in normal tissues.²⁴ And the total activity of ADH and class III isoenzyme was increased in the serum of patients with PC, which can be due to the release of this isoenzyme from PC cells.²⁵ Nevertheless, it was not observed that other types of ADH isoenzymes (I, II, IV) had a significant change in either pancreatic tissue or serum. Further exploration revealed that ADH III had the diagnostic value for PC.²⁶ Also, our evidence demonstrated a potential role for ACTL6A as a marker of PC.

ACTL6A plays a vital role in the invasion and metastasis of tumors by promoting EMT, leading to poor prognosis. ACTL6A expression is higher in fibroblasts and progenitor cells and inhibits the epithelial properties of epidermal tissues.^{27,28} Moreover, the functions of ACTL6A are similar to features of stem cells, including the inhibition of cell differentiation and the ability of self-renewal, which is closely related to the biological functions of EMT.²⁸ In hepatocellular carcinoma, ACTL6A activated Notch1 signaling via

Table 3 Univariate and Multivariate Analysis of Clinicopathological Characteristics Affecting Prognosis of Patients with PC

Characteristics	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
ACTL6A						
Low		Ref			Ref	
High	1.899	1.056–3.415	0.032	1.810	1.010–3.243	0.046
Age(years)						
<65		Ref				
≥65	1.053	0.600–1.848	0.857			
Sex						
Male		Ref				
Female	0.646	0.365–1.141	0.132			
Tumor site						
Head		Ref				
Other ^a	0.736	0.422–1.284	0.281			
Grade						
Well/moderately		Ref			Ref	
Poorly/undifferentiated	2.198	1.231–3.924	0.008	2.021	1.127–3.624	0.018
T stage						
T1+T2		Ref			Ref	
T3+T4	1.737	0.973–3.103	0.062	1.575	0.880–2.819	0.126
N stage						
N0		Ref				
N1+N2	1.442	0.816–2.550	0.208			
M stage						
M0		Ref				
M1	2.205	0.673–7.221	0.191			
TNM stage						
I		Ref				
II–IV	1.759	0.853–3.626	0.126			
LVSI						
No		Ref				
Yes	1.434	0.822–2.501	0.204			

Note: ^aPancreatic body and tail.

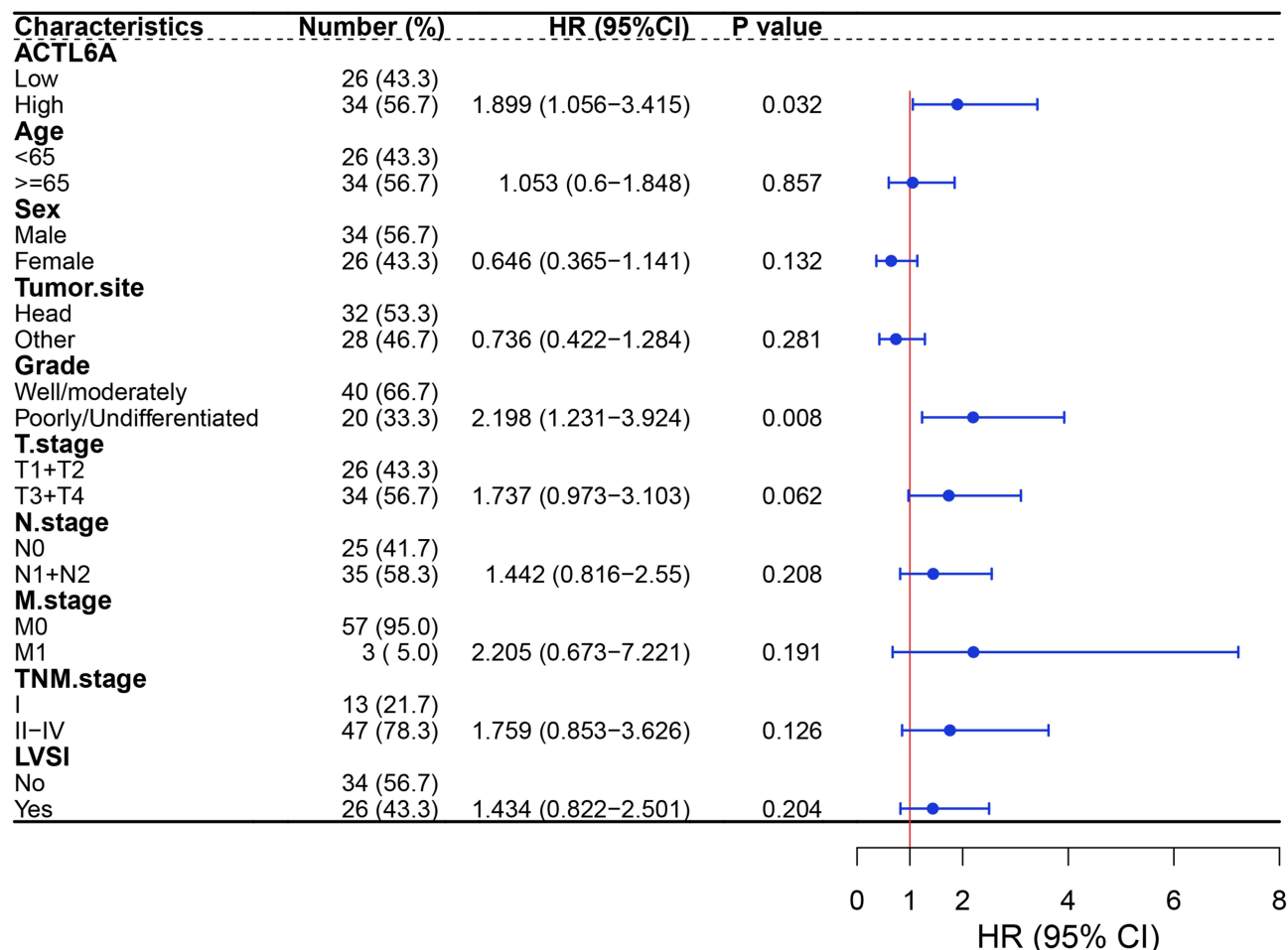
Abbreviations: ACTL6A, actin-Like 6A; PC, pancreatic cancer; LVSI, lymphovascular space invasion.

SOX2, which regulated EMT to affect the biological function and clinical prognosis of hepatocellular carcinoma. Other studies also revealed ACTL6A as an EMT activator to promote metastasis in osteosarcoma²⁹ and colon cancer,¹⁰ respectively. Some studies mentioned the potential role of ACTL6A involvement with tumors. Zhang et al found that ACTL6A was a glycolytic regulator by phosphoglycerate kinase 1 (PGK1) in ovarian cancer and participated in FSH-induced tumorigenesis of ovarian cancer.¹⁸ And in triple negative breast cancer, ACTL6A promoted tumor cell proliferation by enhancing the stability of MYC oncogene.³⁰ Additional evidence suggested that ACTL6A promoted the progression of cervical cancer and laryngeal squamous cell carcinoma through activation of yes-associated protein (YAP) signaling.^{23,31} Besides, ACTL6A could stabilize transcriptional regulators YAP and transcriptional coactivator

with PDZ-binding motif (TAZ) to regulate the proliferation, migration, and invasion of glioma.³² Further studies revealed that the knockdown of ACTL6A gene resulted in the inhibition of protein kinase B (AKT) signaling pathway to suppress cell migration and increased sensitivity of glioma cells to temozolomide.³³ Moreover, in vivo and in vitro, Shrestha et al revealed that p21^{Cip1}, a tumor suppressor, was suppressed by ACTL6A in epidermal squamous cell carcinoma, leading to epidermal squamous cell carcinoma progression.³⁴ More importantly, overexpressed ACTL6A was related to cisplatin-induced DNA damage and led to resistance to cisplatin.¹³ These studies have further confirmed the contribution of ACTL6A in the invasion, metastasis, and clinical prognosis of tumors.

In this research, we reveal a correlation between the expression of ACTL6A and the invasion and prognosis of

A Forest plot of univariate cox regression



B Forest plot of multivariate cox regression

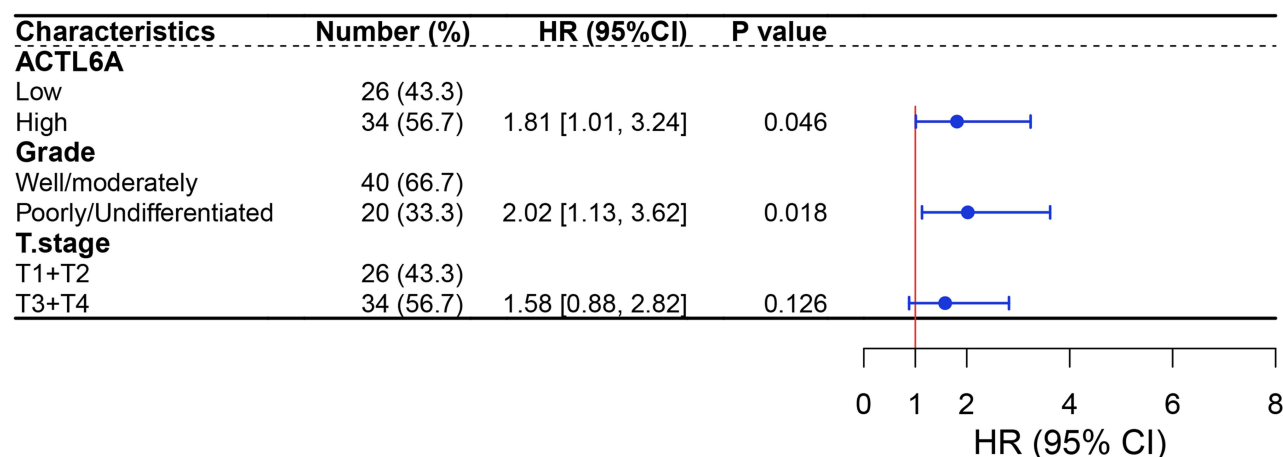


Figure 3 Forest plot of univariate (A) and multivariate (B) cox regression.

Abbreviations: ACTL6A, actin like 6A; PC, pancreatic cancer; LVSI, lymphovascular space invasion.

PC. It was found that LVSI was more likely to occur in PC patients with high ACTL6A expression, which might be related to the high aggressiveness caused by ACTL6A.

Univariate and multivariate Cox analysis suggested that ACTL6A expression and grade were independent risk factors for poor prognosis of PC. This study also

confirmed ACTL6A as a valid prognostic biomarker and potential therapeutic target in PC. Given a follow-up and survival analysis of survival data of PC patients, patients with high ACTL6A expression had significantly poorer prognosis. It was suggested that ACTL6A expression in PC was a risk factor, which was consistent with the existing studies. And ACTL6A overexpression was associated with tumor progression. However, whether ACTL6A could induce PC cell proliferation, invasion, and metastasis in vitro, as well as the specific regulatory mechanisms, deserved further investigation.

Conclusion

In conclusion, it was found that levels of ACTL6A expression were elevated in PC tissues, which was associated with LVSI. Moreover, it was demonstrated that ACTL6A was an independent risk prognostic indicator for PC. ACTL6A could be used as a valuable biomarker to predict the prognosis of PC, assisting clinicians to develop preventative measures and better treatment strategies to improve mortality in patients with PC.

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Disclosure

The authors report no conflicts of interest in this work.

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