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High Annexin A10 expression is correlated with poor prognosis in pancreatic ductal adenocarcinoma

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Summary. Pancreatic ductal adenocarcinoma (PDAC) is the third-leading cause of cancer-related death. Owing to its poor prognosis, new molecular biomarkers for PDAC are needed. Annexin A10 (ANXA10) is a calcium-/phospholipid-binding protein belonging to the annexin family of proteins. ANXA10 is not only associated with gastric phenotypes, but also acts an independent prognostic factor in several cancers. However, the role of ANXA10 in PDAC remains unknown. Therefore, we examined the relationship between ANXA10 and the prognosis of PDAC. We analyzed the expression of ANXA10 using data from public databases, and performed immunohistochemistry analysis for 81 PDAC cases. We then investigated the relationship between ANXA10 expression and clinicopathological features. ANXA10 was detected in 47 of 81 PDAC cases (58%). High expression of ANXA10 was significantly related to poor overall survival (OS; p=0.011). Univariate analysis of OS revealed three prognostic parameters: tumor grade (p=0.046), perineural invasion (p=0.017), and ANXA10 expression (p=0.012). Multivariate analysis indicated that ANXA10 expression (p<0.01) alone was a prognostic factor in PDAC cases. Our findings suggest that ANXA10 expression is an independent prognostic factor in PDAC cases and shows promise as a new biomarker in PDAC.

Key words: Annexin A10, Pancreatic cancer, Biomarker

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the third-leading cause of cancer-related deaths in the United States (Siegel et al., 2019) and is predicted to become the second-leading cause by 2030 (Rahib et al., 2014). A poor clinical course is often predicted for patients with PDAC. The overall 5-year survival rate is approximately 8% (Jemal et al., 2017) and that of patients with curative resection is 15-25% (Lim et al., 2003). Despite advances in this field of study, the prognosis for PDAC has not improved in the past few decades (Hidalgo et al., 2015). The high mortality rate may be attributed to the biology of pancreatic cancer and the fact that PDAC is often detected until an advanced stage when treatment options are limited.

Several studies involving next-generation sequencing have been performed to investigate the molecular landscape of PDAC (Bailey et al., 2016; Cancer Genome Atlas Research Network, 2017). KRAS, TP53, SMAD4 (DPC4), and CDKN2A have been identified as key genetic elements. Several other genetic alterations have been detected in PDAC, such as in genes involved in DNA repair (commonly BRCA2; Waddel et al., 2015), COMPASS-like complex (KMT2C and KDM6A), and the DNA-binding helicase multiprotein complex (BRG1; Bailey et al., 2016; Cancer Genome Atlas Research Network, 2017), although at a low rate. However, these studies have not led to the development of therapeutic molecular targeted drugs. Therefore, new molecular biomarkers for PDAC must be identified.

Annexin A10 (ANXA10), belonging to the annexin family of proteins, is a calcium- and phospholipid-binding protein. Annexin family proteins serve many important functions in physiological and cellular processes (Gerke et al., 2005; Lizarbe et al., 2013), which are mediated by the

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Abbreviations. ANXA10, annexin A10; PDAC, pancreatic ductal adenocarcinoma; IHC, immunohistochemistry; Pn, perineural invasion; GEO, Gene Expression Omnibus

annexin repeat (Schloer et al., 2018). Little is known about the function of ANXA10; however, we previously found that ANXA10 is associated with a gastric phenotype in gastric cancer (Ishikawa et al., 2020a). ANXA10 has been reported to be associated with prognosis in numerous gastrointestinal cancers, including esophageal (Kodaira et al., 2019), gastric (Kim et al., 2009; Ishikawa et al., 2020a,b) small intestinal (Ishikawa et al., 2021), and colorectal cancers (Bae et al., 2015). Among these, we demonstrated that ANXA10 expression is an independent poor prognostic factor in early stage gastric (Ishikawa et al., 2020b) and small intestinal cancers (Ishikawa et al., 2021).

Few studies have investigated the role of ANXA10 in the pancreas. In acute pancreatitis, ANXA10 is induced to a low extent in the cytoplasm of acinic cells (Mashima et al., 2020). ANXA10 is expressed in approximately 80% of PDAC cases (Lu et al., 2013; Zhu et al., 2017), and is observed in precancerous lesions of PDAC (Zhu et al., 2017). Moreover, ANXA10 shows the highest diagnostic performance in distinguishing between cholangiocarcinoma and PDAC (Kälsch et al., 2017). However, the relationship between ANXA10 expression and the prognosis of PDAC remains unclear.

To determine the association between ANXA10 expression and clinicopathological features in PDAC, ANXA10 expression in patients with PDAC was evaluated using immunohistochemical methods. We also investigated the correlation between ANXA10 expression and the prognosis of PDAC cases.

Materials and methods

Tissue samples

A consecutive cohort of 81 histopathologically confirmed patients with pancreatic cancer who underwent surgical resection at the Kure Medical Center and Chugoku Cancer Center (Hiroshima, Japan) between April 1, 2015 and March 31, 2020 was included in the study. Archived formalin-fixed and paraffin-embedded tumor tissues obtained from resected specimens were used in immunohistochemical analyses. One representative tumor block from each specimen was assessed via immunohistochemistry (IHC). Histological classifications and grading (G1 or G2/3/4) were determined according to the World Health Organization system. The tumor stage was determined according to the criteria defined in the Union for International Cancer Control TNM classification guide (8th edition, 2019). Informed consent was obtained from all patients. The study protocol was approved by the Ethical Committee for Human Genome Research of Kure Medical Center and Chugoku Cancer Center (2019-91), and conformed to the Helsinki Declaration of 1964 and later versions.

RNA Extraction and Real-Time PCR

The total RNA was isolated from the PDAC tissue with the ISOGEN-LS reagent (Nippon gene, Tokyo, Japan) according to the manufacturer's instruction, and total RNA was converted to cDNA using the PrimeScript™ 1st strand cDNA Synthesis Kit (Takara Bio Inc, Shiga, Japan). SYBR Green PCR Master Mix (Applied biosystems, Foster, USA) was used to detect the ANXA10 mRNA expression and β-actin was used as an internal control. The primers used for ANXA10 were Forward: 5'-TTCTGACTCAGCGCTGCAAT−3' and Reverse: 5'-ATGCTCTGGTATGCCTCTGC-3' and those for β-actin were Forward: 5'- TCACCGAGCG CGGCT−3' and Reverse: 5'- TAATGTCACGCACG ATTTCCC -3'.

Immunohistochemistry

For immunohistochemistry (IHC), 81 representative formalin-fixed and paraffin-embedded slides were cut into small sections (4 μm), deparaffinized, and rehydrated. IHC staining was performed using a Ventana Benchmark ULTRA auto-stainer (Ventana Medical Systems, Tucson, AZ, USA) according to previously described methods (Lu et al., 2013; Ishikawa et al., 2020a, 2021). The signals were visualized using 3,3'-diaminobenzidine. Antigen retrieval was performed using mild and standard cell conditioning 1 buffer. The specificity of an ANXA10 antibody was confirmed via several methods, including western blotting (Ishikawa et al., 2020a). Sections were incubated with a rabbit polyclonal anti-ANXA10 antibody (NBP1-90156; 1:500; Novus Biologicals, Littleton, CO, USA) for 32 min. ANXA10 expression was evaluated for all slides as positive or negative. The foveolar or fundic gland of the stomach in the same staining set was used as a positive control, and fibroblasts were used as the negative control. When >10% of the tumor cell nuclei were stained, the section was considered as positive for ANXA10, as described previously (Ishikawa et al., 2020a, 2021). Two surgical pathologists (A.I. and K.K.) followed this classification and independently reviewed the immunoreactivity of each specimen.

Microarray dataset analysis

The GSE dataset (GSE28735) containing data on 45 human pancreatic tumor tissue and 45 human pancreatic nontumor tissue samples was downloaded from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/) and analyzed using GEO2R.

Kaplan-Meier analysis

Kaplan-Meier analysis was performed for ANXA10 using the Kaplan-Meier Plotter software from the databases of the public Pan-cancer RNA-seq dataset (http://kmplot.com/analysis) and OncoLnc, which contains PDAC in TCGA; the data of 177 and 174 patients with PDAC were collected from these databases, respectively. To analyze the prognostic value,

the samples were assigned to two groups based on the cutoff value stipulated by the automated software program. Hazard ratios (HRs) and p values (log-rank p) were determined for each survival analysis.

Statistical analysis

ANXA10 mRNA expression level was analyzed using Mann-Whitney and Wilcoxon matched-pairs signed rank tests. Correlations between clinicopathological parameters and ANXA10 expression were analyzed via Fisher's exact test. Significant differences between survival curves were determined using the log-rank test. Univariate and multivariate Cox regressions were used to evaluate the associations between clinical covariates and overall survival (OS). The HR and 95% confidence intervals (CIs) were assessed using Cox proportional hazard models. Values of $p<0.05$ were considered to indicate significant results.

Results

ANXA10 expression in PDAC cases

To determine the localization of ANXA10 expression, we performed IHC on 81 PDAC tissue samples including non-neoplastic tissues. We detected ANXA10 expression in the area of PDAC (G1; Fig. 1A,B, G3; Fig. 1C,D). ANXA10-positive staining was observed mainly in the nuclei and, to a lower extent, in the cytoplasm of tumor cells (Fig. 1B,D). Forty-seven PDAC slides (58%) were positive for ANXA10 expression. A few PDAC cases showed ANXA10 staining heterogeneity, and heterogeneous ANXA10 expression with no trend was observed. In contrast, no ANXA10 expression was detected in either the acinar (Fig. 1E) or pancreatic duct (Fig. 1F) in non-neoplastic tissues, which is similar to the results of previous studies (Lu et al., 2013; Zhu et al., 2017). Overall, ANXA10 expression was observed in 58% of PDAC cases and was clearly distinguishable from non-neoplastic tissues.

High ANXA10 expression was detected and associated with poor prognosis in human pancreatic tumors

To analyze ANXA10 expression levels in PDAC cases, we analyzed data from the GEO database (accession no. GSE28735). ANXA10 mRNA expression was found to be significantly higher in human pancreatic tumors than in pancreatic nontumor tissues (Mann-Whitney test; Fig. 2A). To confirm this finding, we

Table 1. Patients' features with pancreatic cancer.

All	Total 81 cases (%)
Age (years)	
Mean (range)	72.9 (71-75)
Median	74
Gender	
Male	43 (53.1)
Female	38
Size (cm)	
Mean (range)	3.1 (2.8-3.5)
Median	2.8
Location	
Ph	41 (51)
Pb/Pt	40 (49)
Grade (G)	
G1	35 (43)
G2/G3/G4	46
pN	
pN0	28
pN1/2	53 (65)
Vascular invasion (V)	
V0	34
V1	47 (58)
Lymphatic invasion (Ly)	
Ly0	60
Ly1	21 (26)
Perineural invasion (Pn)	
Pn0	51
Pn1	30 (37)
ANXA10 expression	
Positive	47 (58)
Negative	34

Table 2. The relationship between ANXA10 expression and clinicopathological features in patients with pancreatic cancer.

	Annexin A10 expression		
	Positive (%)	Negative	p Value
Age (years)			0.024
<74	19 (40)	23	
≥74	28 (72)	11	
Sex			0.658
Male	26 (60)	17	
Female	21 (55)	17	
Size (cm)			0.266
<2.8	27 (64)	15	
≥2.8	20 (51)	19	
Location			0.823
Ph	23 (56)	18	
Pb/Pt	24 (60)	16	
Grade (G)			0.462
G1	22 (63)	13	
G2/G3/G4	25 (54)	21	
pN			0.482
pN0	18 (64)	10	
pN1/2	29 (55)	24	
V			0.672
V0	18 (53)	16	
V1	29 (62)	18	
Ly			0.309
Ly0	37 (62)	23	
Ly1	10 (48)	11	
Pn			0.642
Pn0	31 (61)	20	
Pn1	16 (53)	14	

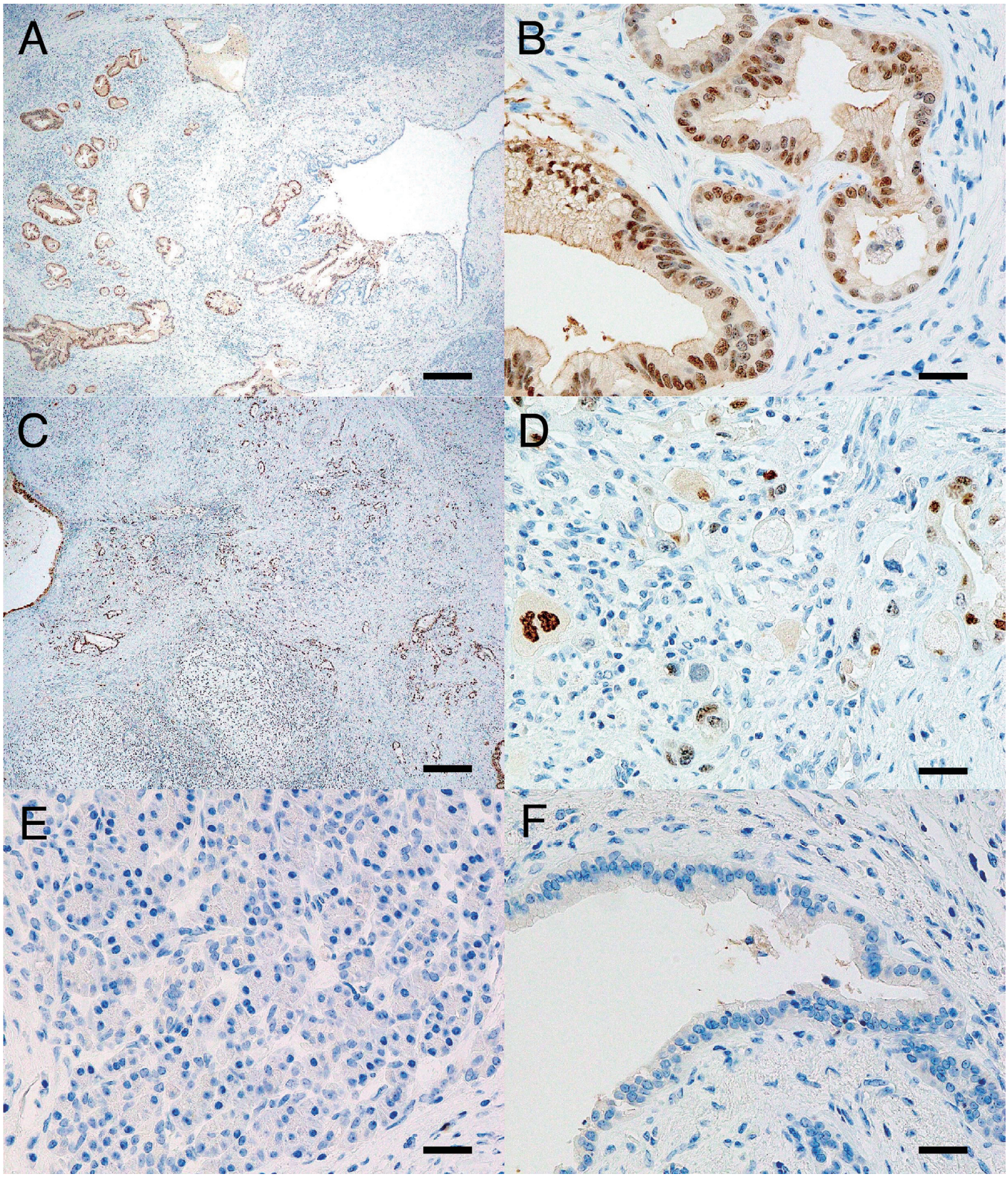

Fig. 1. Representative immunohistochemical images of annexin A10 (ANXA10). **A-D.** Immunohistochemical staining of ANXA10 in pancreatic ductal adenocarcinoma (PDAC) tissues. **A, B.** Grade 1. **C, D.** Grade 3. **E, F.** Immunohistochemical staining of ANXA10 in non-neoplastic pancreas tissue. **E.** Acinar cells. **F.** ductal epithelial cells. Scale bars: A, C, 200 μm; B, D-F, 20 μm.

performed RT-qPCR to evaluate the ANXA10 expression in 10 paired PDAC tissues collected from our hospital. The result showed that ANXA10 was upregulated in PDAC tissue (Wilcoxon matched-pairs signed rank test; Fig. 2B). TCGA data from OncoLnc showed a marginally significant difference in OS (p=0.0744; Fig. 2C). Additionally, We also investigated 177 PDAC samples from other public databases to confirm the association between ANXA10 mRNA expression and prognosis. Patients with high ANXA10 expression exhibited significantly poorer survival rates than those with low ANXA10 expression in terms of both OS (p=0.034; Fig. 2D) and recurrence-free survival (RFS; p=0.018; Fig. 2E). These results suggest that high ANXA10 expression can serve as a putative prognostic biomarker of PDAC.

Clinical and tumor characteristics

The clinicopathological characteristics of the 81 patients are summarized in Table 1. The mean and median ages were 72.9 years (range: 71-75 years) and 74 years, respectively. In total, 43 patients (53.1%) were male. The mean and median size of tumors was 3.1 cm (range: 2.8-3.5 cm) and 2.8 cm, respectively. In total, 41 cases (51%) were located in the pancreatic head and 40 cases were in the pancreatic body/pancreatic tail. Regarding pathological characteristics, 35 cases (43%) were Grade 1 (G1) and 46 cases were G2, G3, or G4. Lymph node metastasis was detected in 53 cases (65%). The numbers of cases showing vascular (V), lymphatic (Ly), and perineural (Pn) invasion were 47 (58%), 21 (26%), and 30 (37%), respectively. ANXA10 expression was detected in 47 cases (58%).

Correlation between ANXA10 expression levels and clinicopathological features in PDAC

We examined the correlation between ANXA10 expression and clinicopathological features (Table 2).

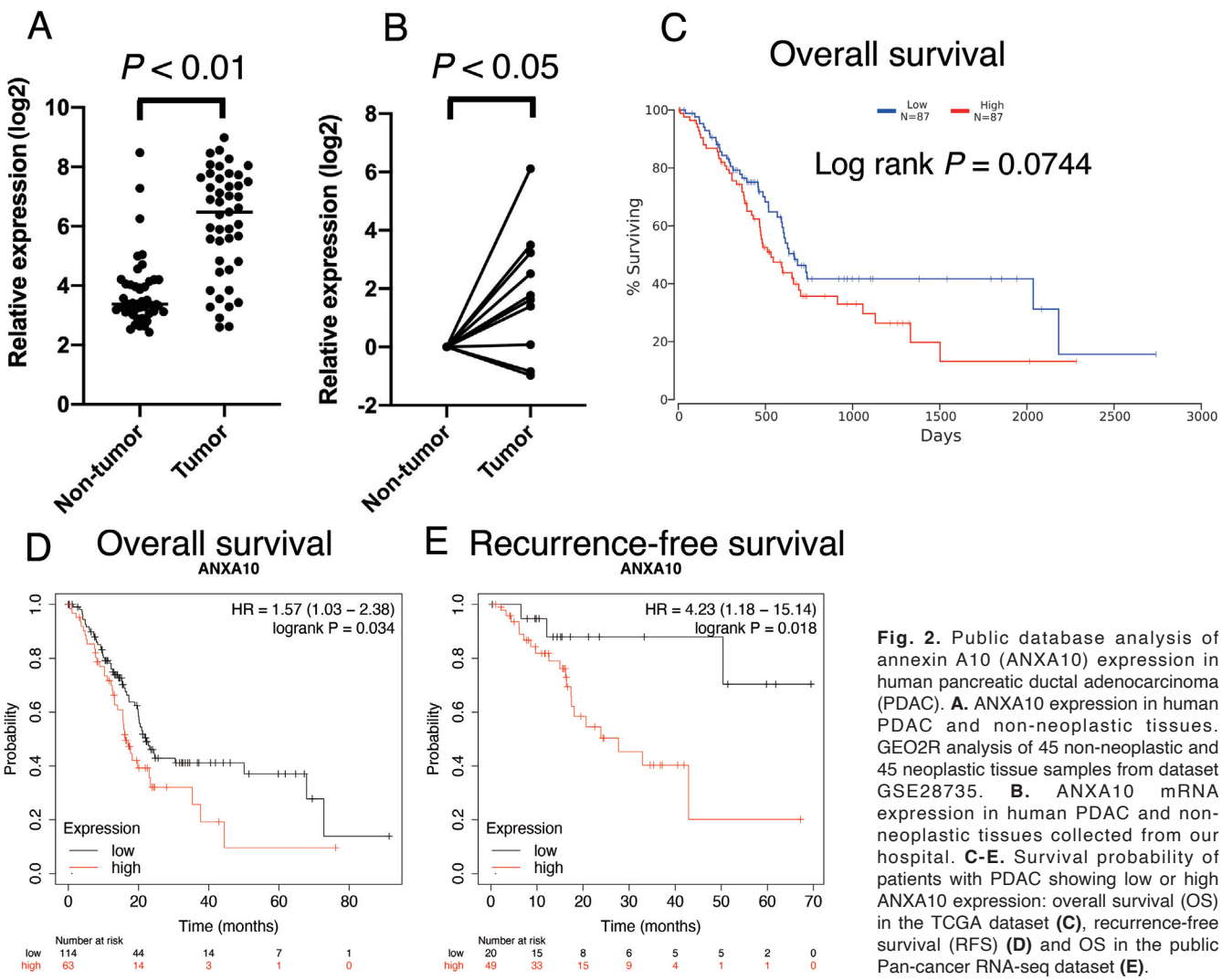

Fig. 2. Public database analysis of annexin A10 (ANXA10) expression in human pancreatic ductal adenocarcinoma (PDAC). **A.** ANXA10 expression in human PDAC and non-neoplastic tissues. GEO2R analysis of 45 non-neoplastic and 45 neoplastic tissue samples from dataset GSE28735. **B.** ANXA10 mRNA expression in human PDAC and non-neoplastic tissues collected from our hospital. **C-E.** Survival probability of patients with PDAC showing low or high ANXA10 expression: overall survival (OS) in the TCGA dataset **(C)**, recurrence-free survival (RFS) **(D)** and OS in the public Pan-cancer RNA-seq dataset **(E)**.

ANXA10 expression was positively correlated with older age (p=0.024). There were no other significant differences in the patient or pathological features, including sex (p=0.658), tumor size (p=0.0.266), location (p=0.823), grade (p=0.462), pN (p=0.482), V (p=0.672), Ly (p=0.309), or Pn (p=0.642).

Prognostic analysis of associations between ANXA10 expression and patients with PDAC

The association between ANXA10 expression levels and patient survival was assessed by Kaplan-Meier analysis with log-rank tests. ANXA10-positive PDAC cases showed significantly poorer OS probability compared with ANXA10-negative cases (p=0.011; Fig. 3A). The median OS was 26 months for ANXA10-positive cases and undefined for ANXA10-negative cases. However, RFS did not significantly differ between ANXA10-positive (16.2 months) and ANXA10-negative cases (18.5 months; p=0.150; Fig. 3B).

Finally, we performed univariate and multivariate Cox proportional hazard analyses to evaluate whether ANXA10 expression was a prognostic indicator (Table 3). Univariate analysis of OS revealed three prognostic parameters: tumor grade (HR, 2.100; 95% CI, 1.012–4.664; p=0.046), pN (HR, 2.623; 95% CI, 1.143–7.089; p=0.017), and ANXA10 expression (HR, 2.593; 95% CI, 1.223–5.886; p=0.012). Multivariate analysis revealed that only ANXA10 expression (HR, 2.849; 95% CI, 1.338–6.489; p<0.01) was an independent prognostic factor for poor outcomes in patients with PDAC. These results suggest that ANXA10 represents a prognostic biomarker in PDAC.

Discussion

ANXA10 acts as an independent prognostic factor not only in gastrointestinal cancers (Ishikawa et al., 2020b, 2021), but also in bladder cancer (Munksgaard et al., 2011), ovarian cancer (Wang et al., 2019), hepatocellular carcinoma (Liu et al., 2002), cholangiocarcinoma (Sun et al., 2019), thyroid cancer (Liu et al., 2021), and early gastric cancers (Ishikawa et

Table 3. Univariate and multivariate Cox regression analyses of ANXA10 expression and survival of pancreatic cancer patients.

Features	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p Value	HR (95%CI)	p Value
Age		0.134		
<74	1 (ref.)			
≥74	1.720 (0.844-3.527)			
Size		0.170		
<2.8 cm	1 (ref.)			
≥2.8 cm	1.670 (0.820-3.495)			
Gender		0.206		
Female	1 (ref.)			
Male	1.581 (0.778-3.305)			
Location		0.625		
Ph	1 (ref.)			
Pb/Pt	1.193 (0.586-2.444)			
Grade (G)		0.046		0.064
G1	1 (ref.)		1 (ref.)	
G2/G3/G4	2.100 (1.012-4.664)		2.029 (0.960-4.588)	
pN		0.022		0.056
pN0	1 (ref.)		1 (ref.)	
pN1/2	2.623 (1.143-7.089)		2.311 (0.981-6.362)	
V		0.1536		
V0	1 (ref.)			
V1	1.691 (0.821-3.623)			
Ly		0.501		
Ly0	1 (ref.)			
Ly1	1.313 (0.572-2.769)			
ANXA10 expression		0.012		< 0.01
Negative	1 (ref.)		1 (ref.)	
Positive	2.593 (1.223-5.886)		2.849 (1.338-6.489)	

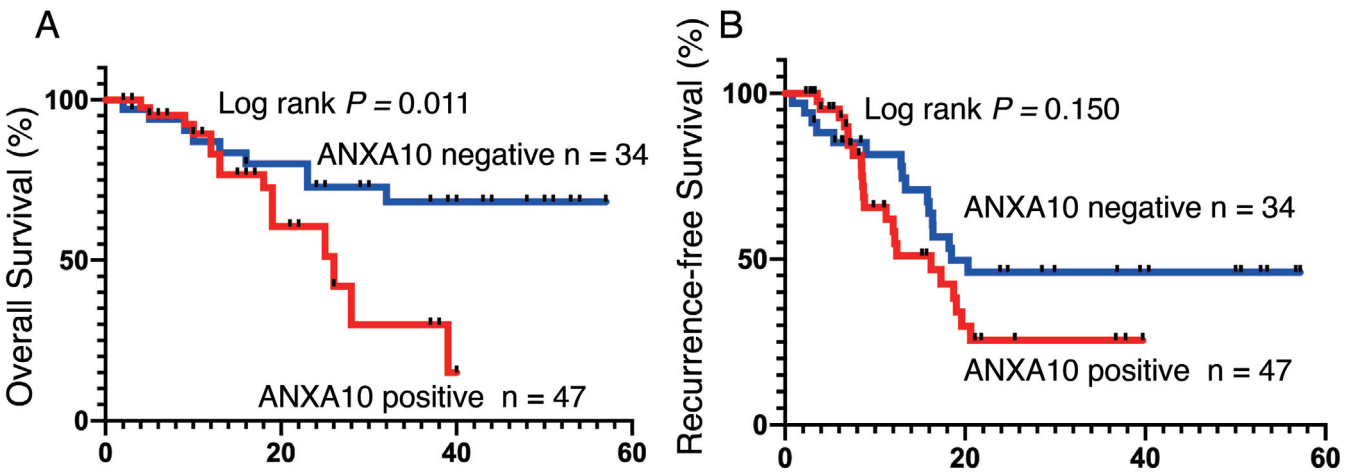

Fig. 3. Kaplan-Meier analysis of 81 pancreatic ductal adenocarcinoma (PDAC) cases. Annexin A10 (ANXA10)-positive and ANXA10-negative PDAC cases in terms of overall survival (OS) **(A)** and recurrence-free survival (RFS) **(B)**.

al., 2020b). These studies were performed using simple IHC analyses, and ANXA10 expression was found to be a useful prognostic marker for evaluating patients. To the best of our knowledge, no previous studies have described the association between ANXA10 expression and prognosis in PDAC.

In this study, using RT-qPCR and IHC, we found that ANXA10 was upregulated in PDAC, and cases showing high ANXA10 expression were associated with poor prognosis based on data in public databases. However, these were bulk tissue studies, and the localization of ANXA10 was not determined. We then analyzed ANXA10 expression in PDAC and found that ANXA10 was expressed in 58% of samples (47 of 81 cases). Previous studies reported that as ANXA10 expression changes from normal to cancerous, the positive rate changes as follows: normal pancreas is 0%, chronic pancreatitis is 20%, pancreatic intraepithelial neoplasia (PanIN)-1 is 65%, PanIN-3 is 80%, and PDAC is 75% (Zhu et al., 2017). As ANXA10 is expressed in low levels in the cytoplasm in acute pancreatitis (Mashima et al., 2020), the role of ANXA10 in the nucleus may differ from that in the cytoplasm. In this study, ANXA10 expression in the nucleus was regarded as positive. In other studies, ANXA10 expression is also detected in the cytoplasm; however, the difference was not clear (Ishikawa et al., 2020b, 2021). Detection of high expression of ANXA10 by next-generation sequencing may require further evaluation to determine its localization and significance.

We then examined the expression and clinicopathological importance of ANXA10 in PDAC; however, no correlation was found between ANXA10 expression levels and other clinicopathological factors except for age. ANXA10 has been reported to be associated with various factors (e.g., tumor stage, metastasis, tumor location, and gender) in several cancers (Liu et al., 2002; Kim et al., 2014; Tsai et al., 2015; Ishikawa et al., 2020a). The relationship between aging and the expression of the annexin family of proteins has not been reported (Lizarbe et al., 2013; Grewal et al., 2021); however, these proteins may be associated with aging related to PDAC. ANXA10 expression was found to be correlated with OS and served as an independent prognostic marker of PDAC cases. However, there was no significant difference in RFS. Previous studies have reported that the expression and secretion of annexin A3 are related to cisplatin resistance (Yan et al., 2010; Yin et al., 2012). Therefore, ANXA10 may be associated with anticancer drug resistance.

A limitation of the present study was the use of a single analytical method for IHC, and the subjective assessment of IHC staining. We performed and evaluated IHC staining according to previous methods (Lu et al., 2013; Ishikawa et al., 2020a). Image analysis software may be used to decrease subjectivity. However, because of the difficulty in selecting representative sections and identifying the tumor area, the judgment of pathologists, who are well-versed in morphology, may be affected. Additionally, ANXA10 expression is detected in both the nucleus and cytoplasm, making it difficult to automate the distinction between them.

In summary, we demonstrated that ANXA10 expression is associated with poor prognosis and represents an independent prognostic factor in PDAC. In clinical practice, simple immunostaining of ANXA10 may provide a new prognostic biomarker for PDAC cases.

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Conflicts of interest. The authors declare that there are no conflicts of interest.

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