OncoTargets and Therapy

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ORIGINAL RESEARCH

ITGA3 serves as a diagnostic and prognostic biomarker for pancreatic cancer

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Background and objective: ITGA3 is a cell surface adhesion protein that interacts with extracellular matrix proteins which function in cancer metastasis. We examined the relationship of pancreatic *ITGA3* expression with the clinical and pathological characteristics of patients with pancreatic cancer.

Methods: Data mining was used to analyze pancreatic cancer data from The Cancer Genome Atlas database. A Chi squared test was used to evaluate correlations of *ITGA3* expression with clinical and pathological parameters. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of *ITGA3* expression. Survival analysis and Cox regression analysis were used to examine the prognostic value of *ITGA3* expression. Gene Set Enrichment Analysis (GSEA) was used to identify signaling pathways related to *ITGA3* expression.

Results: Pancreatic expression of *ITGA3* was greater in patients with pancreatic cancer than those without cancer, and was also associated with histological type, histological grade, stage, T classification, vital status, and relapse. ROC analysis indicated that *ITGA3* had significant diagnostic value, in that high expression correlated with poor overall survival and relapse-free survival, especially in patients with early-stage cancer. Cox analysis indicated that high *ITGA3* expression was an independent prognostic factor for pancreatic cancer. GSEA analysis identified 9 signaling pathways that were enriched in the presence of high *ITGA3* expression.

Conclusion: Expression of *ITGA3* can be used as a diagnostic and prognostic biomarker in pancreatic cancer.

Keywords: pancreatic cancer, diagnosis, prognosis, *ITGA3*, TCGA

Introduction

Pancreatic cancer is associated with a high mortality rate and poor prognosis, especially in patients with advanced-stage cancer. Although there have been improvements in the treatments for this cancer, such as surgery and neoadjuvant therapies, the overall survival rate has not improved. Many patients diagnosed with advanced-stage disease experience relapse and metastasis. Thus, the identification of new biomarkers for pancreatic cancer that provide detection of early-stage disease may allow earlier initiation of treatment and help to improve patient prognosis.

The *ITGA3* gene encodes integrin alpha-3, a member of the integrin family of proteins. ITGA3 is located on the cell membrane and functions as a cell surface adhesion molecule. A previous study reported that ITGA3 interacts with extracellular matrix proteins, including members of the laminin family, and that its

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http://doi.org/10.2147/OTT.S201675

expression correlates with cancer metastasis.[1] In addition, many omics studies have identified *ITGA3* as a key molecular marker in several cancers,[2,3] although its value in clinical settings is uncertain. In particular, little is known about the correlation of *ITGA3* expression with the clinical and pathological parameters of pancreatic cancer.

The present study of pancreatic cancer patients measured the association of *ITGA3* expression with clinical characteristics of patients, determined its diagnostic performance using survival curve analysis, and performed Cox regression analysis to evaluate its ability to predict overall survival and relapse-free survival.

Materials and methods

Data source

The expression of *ITGA3* (from RNA-seq data) and the clinical data of patients with pancreatic cancer were extracted at The Cancer Genome Atlas-Pancreatic Adenocarcinoma (TCGA-PAAD) cohort (https://cancergenome.nih.gov/). Data processing and analyses were performed using R (version 3.5.1).[4]

Statistical analysis

Expression of *ITGA3* mRNA is presented as box-plots using ggplot2 software.[5] The Wilcoxon rank-sum test was used to determine the significance of differences. The chi-square test and Fisher's exact test were used to evaluate the significance of the correlations of IGTA3 expression with clinical and pathological parameters. The diagnostic performance of *ITGA3* was evaluated using receiver operating characteristic (ROC) analysis and calculation of the area under the curve (AUC) using the pROC package for R.[6] In this analysis, patients were divided into two groups (high *ITGA3* expression and low *ITGA3* expression), and ROC curves were used to determine the best cutoff value based on survival.

Survival analysis was also used to examine the use of *ITGA3* expression in prediction of overall survival and relapse-free survival using Survival package in R.[7,8] Univariate and multivariate Cox analysis was used to determine the prognostic value of *ITGA3* expression.

Gene set enrichment analysis (GSEA)

GSEA determines whether an a priori defined set of genes has statistically significant differences in expression under two different biological conditions.[9,10] This analysis,

Table 1 Patient characteristics of TCGA-PAAD cohort

Characteristics	Numbers of cases (%)
Age	
<55	34(18.99)
≥55	145(81.01)
Gender	
Female	80(44.69)
Male	99(55.31)
Alcohol history	
No	65(36.31)
Yes	102(56.98)
NA	12(6.7)
Anatomic subdivision	
Body of pancreas	14(7.82)
Head of pancreas	139(77.65)
Other (please specify)	11(6.15)
Tail of pancreas	15(8.38)
Histological type	
Adenocarcinoma other subtype	26(14.53)
Adenocarcinoma ductal type	147(82.12)
Colloid carcinoma	4(2.23)
Undifferentiated carcinoma	1(0.56)
NA	1(0.56)
Histologic grade	
G1	31(17.32)
G2	96(53.63)
G3	48(26.82)
G4	2(1.12)
GX	2(1.12)
Stage	
I	21(11.73)
II	147(82.12)
III	4(2.23)
IV	5(2.79)
NA	2(1.12)
T classification	
T1	7(3.91)
T2	24(13.41)
T3	143(79.89)
T4	3(1.68)
TX	1(0.56)
NA	1(0.56)
N classification	
N0	50(27.93)
N1	124(69.27)
NX	4(2.23)
NA	1(0.56)
M classification	

(*Continued*)

Table 1 (Continued).

Characteristics	Numbers of cases (%)
M0	80(44.69)
M1	5(2.79)
MX	94(52.51)
Residual tumor	
R0	107(59.78)
R1	53(29.61)
R2	5(2.79)
RX	4(2.23)
NA	10(5.59)
Vital status	
Deceased	93(51.96)
Living	86(48.04)
Relapse	
Yes	98(62.82)
No	58(37.18)
ITGA3	
High	123(68.72)
Low	56(31.28)

Abbreviation: TCGA-PAAD, The Cancer Genome Atlas-Pancreatic Adenocarcinoma.

performed using GSEA software 3.0 from the Broad Institute, was used for analysis of RNAseq data from TCGA-PAAD. The gene set of "h.all.v6.2.symbols.gmt", which summarizes and represents specific, well-defined biological states or processes, was downloaded from the Molecular Signatures Database (http://software.broadinstitute.org/gsea/msigdb/index.jsp). The normalized enrichment score (NES) was determined by analysis of 1000 permutations. A gene set was considered significantly enriched when the *p*-value was less than 0.05 and the false discovery rate (FDR) was less than 0.25.

Results

Patient characteristics

We used data mining to analyze pancreatic expression of *ITGA3* from the TCGA-PAAD cohort. Table 1 shows the clinical data of the patients, including age, sex, cancer stage, TNM classification, vital status, relapse, histologic grade, and histological type.

High expression of ITGA3 in pancreatic cancer

Analysis of pancreatic *ITGA3* expression indicated greater levels in patients with pancreatic cancer than in those without this cancer (Figure 1). In addition, *ITGA3* expression was greater in tumors with more advanced histologic grade and in deceased patients than living patients.

Diagnostic performance of ITGA3 expression

Comparison of cancerous and non-cancerous pancreatic tissues using ROC analysis indicated the AUC of *ITGA3* expression was 0.803, indicating moderate diagnostic performance (Figure 2). In addition, subgroup analysis which compared non-cancerous tissues and tissues with different stages of cancer indicated that the AUC was 0.643 for stage I cancer, 0.835 for stage II cancer, 0.688 for stage III cancer, and 0.850 for stage IV cancer.

Correlation of ITGA3 expression with clinical and pathological parameters

We first divided patients into two groups (high and low expression of *ITGA3*), and then calculated ROC curves to identify the optimal cutoff value for pancreatic cancer (Table 2). The results indicated that high *ITGA3* expression was positively associated with histological type (p=0.025), advanced histological grade (p<0.001), advanced stage (p=0.005), high T classification (p=0.005), mortality (p<0.001), and relapse (p=0.004).

Prognostic performance of ITGA3 expression

Survival analysis showed that patients with high *ITGA3* expression had poorer overall survival (p=0.00026, Figure 3). In addition, expression of *ITGA3* was significantly different in grade 1 (G1) and grade 2 (G2) tumors (p=0.00018), in patients with stage I/II and stage III/IV cancer (p=0.00051), in T2 (p=0.019) and T3 (p=0.031) tumors relative to T1 tumors, and in patients with M0 cancer (p=0.013). Further analysis indicated that high *ITGA3* expression was associated with poor relapse-free survival (p=0.00074), especially in those with G1/G2 tumors (p=0.00012), stage I/II cancer (p=0.0013), stage T1 cancer (p=0.036), and stage N0 cancer (p=0.00024) (Figure 4).

We also performed univariate and multivariate Cox regression analysis to identify variables associated with survival (Tables 3 and 4). The multivariate analysis indicated that *ITGA3* expression was a significant and independent prognostic factor for overall survival (HR =1.97, p=0.015) and relapse-free survival (HR =2.14, p=0.042).

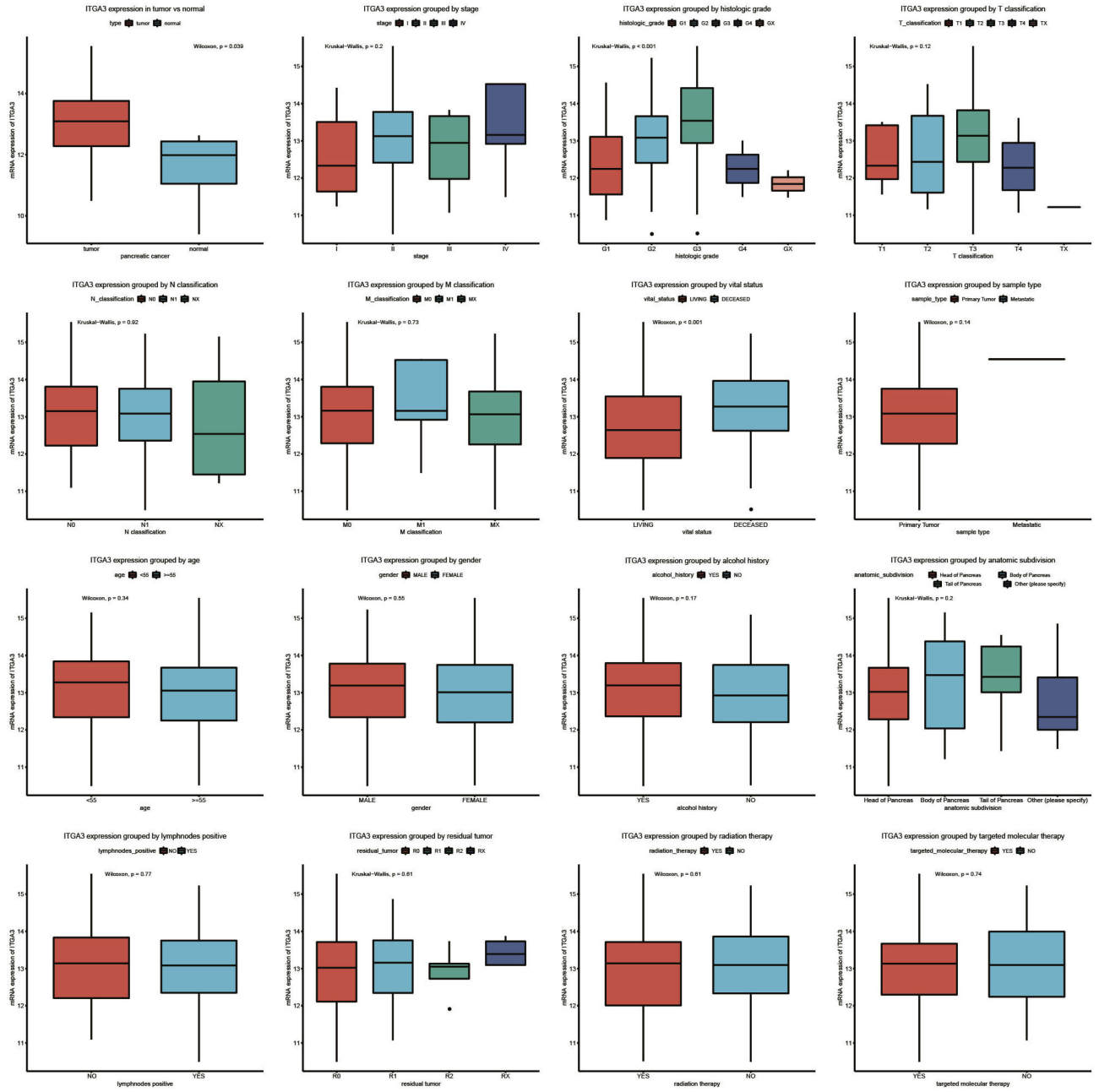

Figure 1 Pancreatic expression of *ITGA3* according to cancer histological type, stage, T classification, N classification, M classification, histologic grade, residual tumor, and vital status. Box plots show medians, first and third quartiles, and maxima and minima.

GSEA identifies ITGA3-related signaling pathway

We compared the data sets for low and high *ITGA3* expression using GSEA to identify signaling pathways activated during pancreatic cancer. The results indicated significant differences (FDR <0.25, NOM *p*-value <0.05) in the enrichment of the MSigDB collection (h.all.v6.2.symbols.gmt; Table 5). We selected the most significantly enriched signaling pathways, based on normalized enrichment score (NES) (Figure 5, Table 5). The results indicated the data set with high *ITGA3* expression was enriched for glycolysis, notch signaling, P53 signaling, TGF-β signaling, the mitotic spindle, interferon alpha response, G2M checkpoint, estrogen response, and mTOR signaling.

Discussion

Pancreatic cancer is one of the most deadly malignancies. The prognosis is poor because most patients are diagnosed

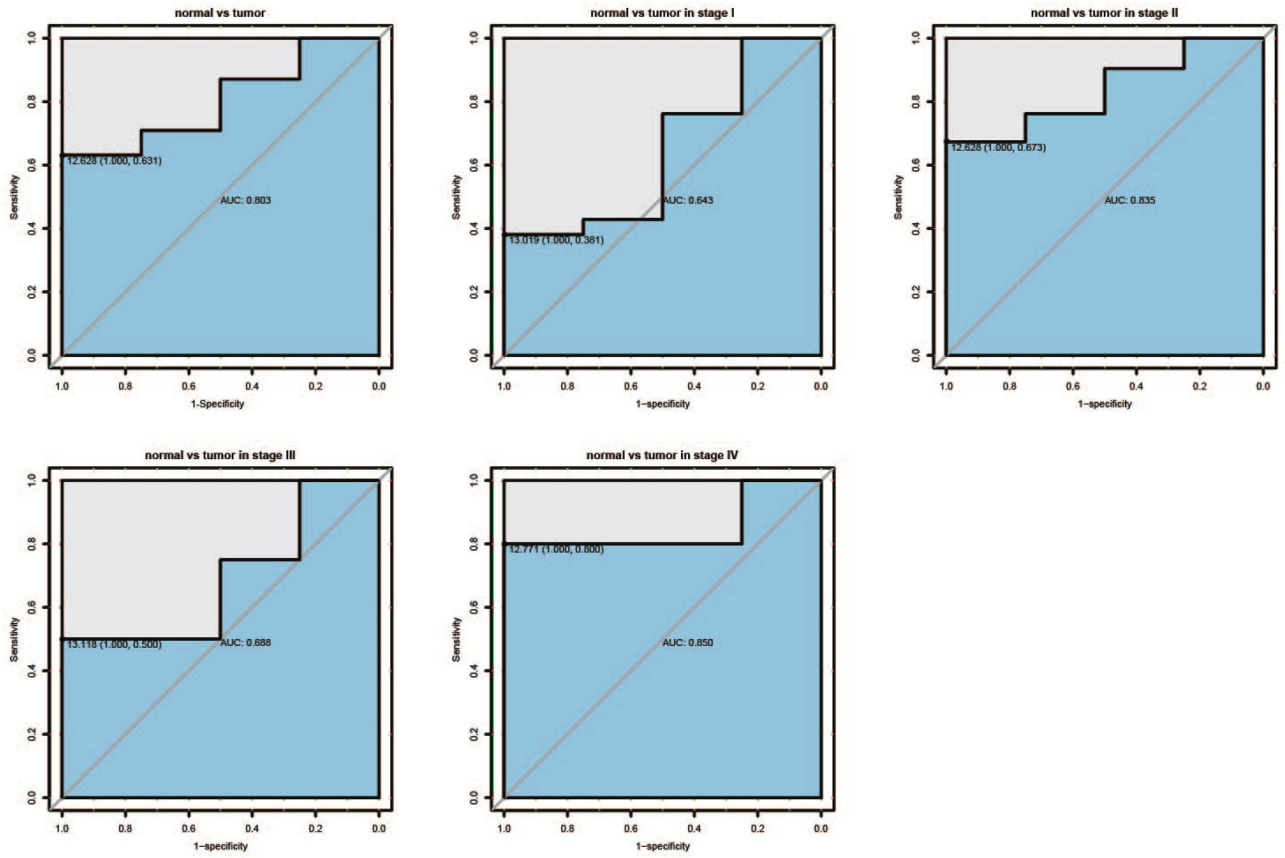

Figure 2 ROC curves of pancreatic *ITGA3* expression in the PAAD cohort. Comparison of non-tumor sample vs tumor sample; comparison of non-tumor sample vs tumor samples of stage I, II, III, and IV.

with late-stage disease, when available treatments are less effective. Therefore, identification of novel prognostic and diagnostic biomarkers that can help to diagnose early-stage cancers may help to improve the outcomes of patients with pancreatic cancer. Our team previously identified diagnostic and prognostic biomarkers for several other cancers.[11–13] In the present study, we found that high pancreatic expression of *ITGA3* correlated with histological type, histological grade, cancer stage, T classification, vital status, and relapse. We also found that high *ITGA3* expression was an independent prognostic factor for poor overall survival and relapse-free survival. Thus, *ITGA3* expression appears to be a useful diagnostic and prognostic biomarker for pancreatic cancer.

Previous studies reported elevated expression of *ITGA3* in many cancers, including gastric cancer,[14] esophageal adenocarcinoma,[15] non-small cell lung cancer,[16] prostate cancer,[17] thyroid carcinoma,[18] head and neck cancer,[19] tongue cancer,[20] colorectal cancer,[21] and bladder cancer.[22] However, there is only limited evidence for increased expression of *ITGA3* in pancreatic cancer.[23] Our data mining analysis indicated elevated expression of *ITGA3* in pancreatic cancer, suggesting that *ITGA3* may be a potential biomarker or therapeutic target for pancreatic cancer. Although there was a previous report that *ITGA3* has a role in pancreatic duct adenocarcinoma,[23] we examined this issue in more detail by performing subgroup analysis. An interesting finding of our subgroup analysis is that *ITGA3* expression gradually increased from histological G1 to G3, but was lower in G4. Therefore, ITGA3 might contribute to cancer onset and initial progression, so its measurement might help to detect patients with early-stage or rapidly progressing pancreatic cancer. Moreover, the higher expression of *ITGA3* in deceased than living patients suggests it may also be useful as a prognostic indicator for pancreatic cancer.

A previous study found that ITGA3 may facilitate cancer development by activating the PI3K-Akt signaling pathway, which increases proliferation, migration, and invasion in many cancers.[20] Our results also indicated that high pancreatic expression of *ITGA3* was associated with the histological type, histological grade, stage, T classification, vital status, and relapse. ITGA3-activation of the PI3K-Akt signaling

Table 2 Correlation between the clinicopathologic variables and ITGA3 mRNA expression in pancreatic cancer.

Parameter	Variable	N	ITGA3 mRNA expression				$\chi 2$	*p*value
			High	%	Low	%		
Age	<55	34	24	19.51	10	17.86	0.003	0.955
	≥55	145	99	80.49	46	82.14		
Gender	Female	80	54	43.90	26	46.43	0.023	0.878
	Male	99	69	56.10	30	53.57		
Alcohol history	No	65	42	36.21	23	45.10	0.834	0.361
	Yes	102	74	63.79	28	54.90		
Anatomic subdivision	Body of Pancreas	14	10	8.13	4	7.14	3.713	0.309*
	Head of Pancreas	139	96	78.05	43	76.79		
	Other	11	5	4.07	6	10.71		
	Tail of Pancreas	15	12	9.76	3	5.36		
Histological type	Adenocarcinoma-Other Subtype	26	13	10.66	13	23.21	9.351	**0.025***
	Adenocarcinoma Ductal Type	147	107	87.70	40	71.43		
	Colloid Carcinoma	4	1	0.82	3	5.36		
	Undifferentiated Carcinoma	1	1	0.82	0	0.00		
Histologic grade	G1	31	12	9.76	19	33.93	24.376	**0.000***
	G2	96	69	56.10	27	48.21		
	G3	48	41	33.33	7	12.50		
	G4	2	1	0.81	1	1.79		
	GX	2	0	0.00	2	3.57		
Stage	I	21	8	6.50	13	24.07	12.246	**0.005***
	II	147	109	88.62	38	70.37		
	III	4	2	1.63	2	3.70		
	IV	5	4	3.25	1	1.85		
T classification	T1	7	3	2.44	4	7.27	12.587	**0.005***
	T2	24	12	9.76	12	21.82		
	T3	143	107	86.99	36	65.45		
	T4	3	1	0.81	2	3.64		
	TX	1	0	0.00	1	1.82		

(*Continued*)

Table 2 (Continued).

Parameter	Variable	N	ITGA3 mRNA expression				χ2	*p*value
			High	%	Low	%		
N classification	N0 N1 NX	50 124 4	31 90 2	25.20 73.17 1.63	19 34 2	34.55 61.82 3.64	2.568	0.220*
M classification	M0 M1 MX	80 5 94	55 4 64	44.72 3.25 52.03	25 1 30	44.64 1.79 53.57	0.314	0.855*
Residual tumor	R0 R1 R2 RX	107 53 5 4	66 39 4 4	58.41 34.51 3.54 3.54	41 14 1 0	73.21 25.00 1.79 0.00	4.749	0.215*
Vital status	Deceased Living	93 86	77 46	62.60 37.40	16 40	28.57 71.43	16.515	**0.000**
Relapse	No Yes	98 58	58 48	54.72 45.28	40 10	80.00 20.00	8.247	**0.004**

Notes: Bold represents $p<0.05$; *represents Fisher's exact test.

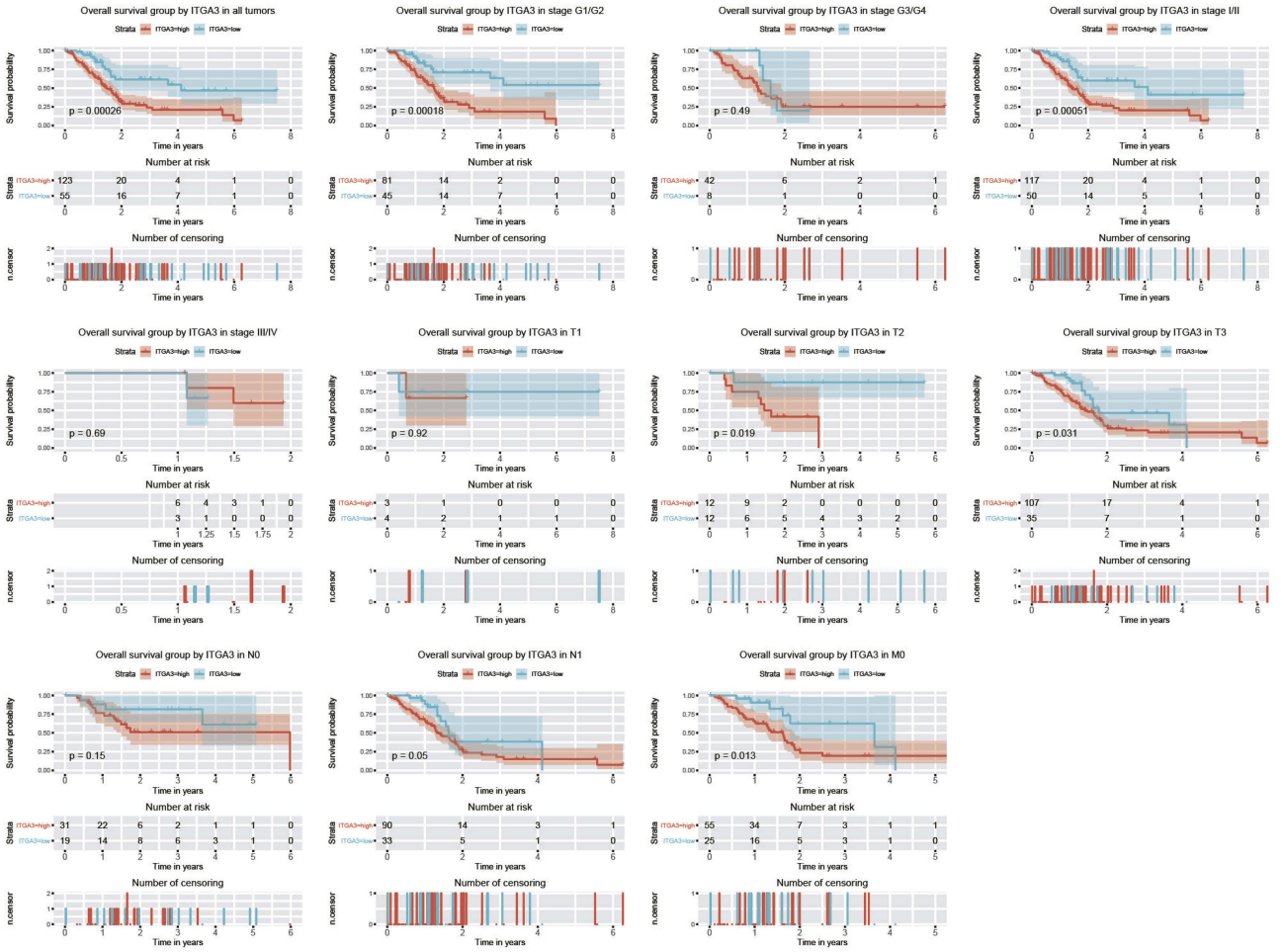

Figure 3 Relationship of pancreatic expression of *ITGA3* with overall survival. Kaplan– Meier curves show overall survival following subgrouping according to clinical stage (I/II and III/IV), histological grade (G1/G2 and G3/G4), T classification (T1, T2, and T3), N classification (N0 and N1), and M classification (M0).

pathway may be the mechanism underlying these clinical correlations. We also used GSEA to analyze the potential ITGA3-related signaling pathways. The results indicated that ITGA3 influences glycolysis, notch signaling, P53 signaling, TGF-β signaling, the mitotic spindle, interferon alpha response, G2M checkpoint, estrogen response, and mTOR signaling. These findings require verification by future studies with different data sets.

Because of the important role of *ITGA3* in multiple cancers, recent research has examined its potential as a prognostic marker. These studies found that *ITGA3* was a useful prognostic marker for endometrioid endometrial cancer,[24] head and neck cancer,[19,25] tongue cancer,[20] and bladder cancer.[22] We found that *ITGA3* expression was also a useful prognostic marker for overall survival and relapse-free survival in patients with pancreatic cancer, in accordance with previous work.[23] Furthermore, our subgroup analysis indicated that *ITGA3* expression was useful for distinguishing cancer G1 and G2 and stage I and II, suggesting its use as a prognostic indicator might be most effective for patients with mild or early pancreatic cancer.

Relapse and metastasis are the most serious problems in pancreatic and other cancers. The biology that underlies relapse and metastasis includes the epithelial-mesenchymal transition (EMT), cell migration, and invasion, and there is evidence that ITGA3 promotes these three processes in many cancers.[1,26] In addition, previous studies verified the prognostic value of *ITGA3* expression on relapse and metastasis in colorectal cancer,[3,27] oral squamous cell carcinoma,[28] lung cancer,[2] breast cancer,[2] prostate cancer[17,26] and gastric cancer.[29] We verified the prognostic potential of *ITGA3* for relapse-free survival, especially in G1/G2 and stage I/II cancer, and that *ITGA3* may be an independent prognostic biomarker for relapse and metastasis of early-stage pancreatic cancer.

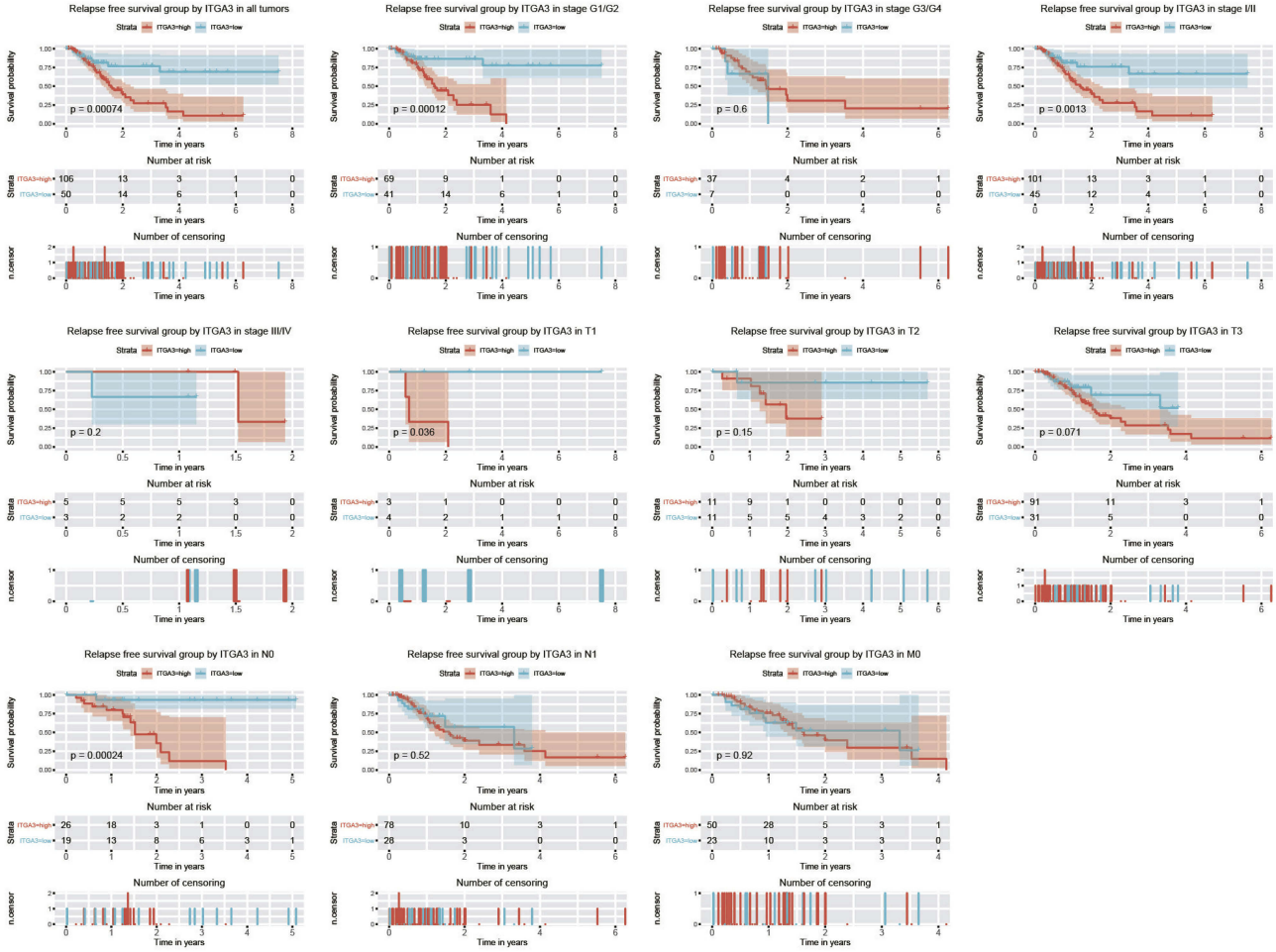

Figure 4 Relationship of pancreatic *ITGA3* expression with relapse-free survival. Kaplan– Meier curves show relapse-free survival following subgrouping for clinical stage (I/II and III/IV), histological grade (G1/G2 and G3/G4), T classification (T1, T2, and T3), N classification (N0 and N1), and M classification (M0).

Table 3 Univariate and multivariate analysis of overall survival in patients with pancreatic cancer

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age (≥55/<55)	1.22	0.73-2.05	0.446			
Gender (male/female)	0.81	0.54-1.22	0.320			
alcohol history (yes/no)	1.09	0.79-1.5	0.604			
histological type (Undifferentiated/ Colloid/ Ductal Type/ Other Subtype)	2.07	1.36-3.16	0.001	1.75	1.09-2.81	**0.021**
Histologic grade (G4/G3/G2/G1)	1.33	1.04-1.7	0.021	1.18	0.89-1.56	0.245
Stage (IV/III/II/I)	1.33	0.96-1.84	0.089			
T classification (T4/T3/T2/T1/NX)	1.64	1.08-2.49	0.021	1.17	0.72-1.89	0.535
N classification (N1/N0/NX)	1.93	1.23-3.03	0.005	1.36	0.85-2.2	0.203
M classification (M1/M0/MX)	1.13	0.79-1.64	0.500			
Residual tumor (RX/R2/R1/R0)	1.36	1.06-1.76	0.018	1.37	1.07-1.77	**0.014**
ITGA3 (high/low)	2.65	1.54-4.56	0.000	1.97	1.14-3.4	**0.015**

Note: Bold represents $p<0.05$.

Table 4 Univariate and multivariate analysis of relapse-free survival in patients with pancreatic cancer

Parameters	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age (≥55/<55)	0.93	0.51-1.71	0.827			
Gender (male/female)	1.12	0.67-1.89	0.667			
Alcohol history (yes/no)	1.22	0.79-1.87	0.364			
Histological type	1.09	0.65-1.84	0.733			
(Undifferentiated/ Colloid/ Ductal Type/ Other Subtype)						
Histologic grade (G4/G3/G2/G1)	1.56	1.13-2.17	0.007	1.39	0.96-2.01	0.083
Stage (IV/III/II/I)	1.41	0.98-2.04	0.064			
T classification (T4/T3/T2/T1/NX)	1.51	0.94-2.41	0.088			
N classification (N1/N0/NX)	2.03	1.17-3.52	0.012	1.53	0.87-2.7	0.143
M classification (M1/M0/MX)	1.42	0.92-2.21	0.116			
Residual tumor (RX/R2/R1/R0)	1.73	1.23-2.42	0.002	1.66	1.2-2.29	**0.002**
ITGA3 (high/low)	3.12	1.56-6.24	0.001	2.14	1.03-4.43	**0.042**

Note: Bold represents $p<0.05$.

Table 5 Gene sets enriched in phenotype high.

NAME	ES	NES	NOM p-val	FDR q-val
HALLMARK_GLYCOLYSIS	0.52	1.96	0.00	0.08
HALLMARK_NOTCH_SIGNALING	0.63	1.86	0.00	0.10
HALLMARK_MITOTIC_SPINDLE	0.53	1.83	0.01	0.09
HALLMARK_MTORC1_SIGNALING	0.44	1.77	0.03	0.09
HALLMARK_P53_PATHWAY	0.46	1.77	0.01	0.08
HALLMARK_TGF_BETA_SIGNALING	0.54	1.77	0.01	0.06
HALLMARK_G2M_CHECKPOINT	0.67	1.74	0.02	0.07
HALLMARK_INTERFERON_ALPHA_RESPONSE	0.67	1.70	0.01	0.08
HALLMARK_ESTROGEN_RESPONSE_LATE	0.47	1.58	0.02	0.15
HALLMARK_ESTROGEN_RESPONSE_EARLY	0.45	1.52	0.03	0.19

Notes: Gene sets with NOM $p<0.05$ and FDR $q<0.25$ are considered significance.
Abbreviations: ES, enrichment score; NES, normalized enrichment score; NOM, nominal; FDR, false discovery rate.

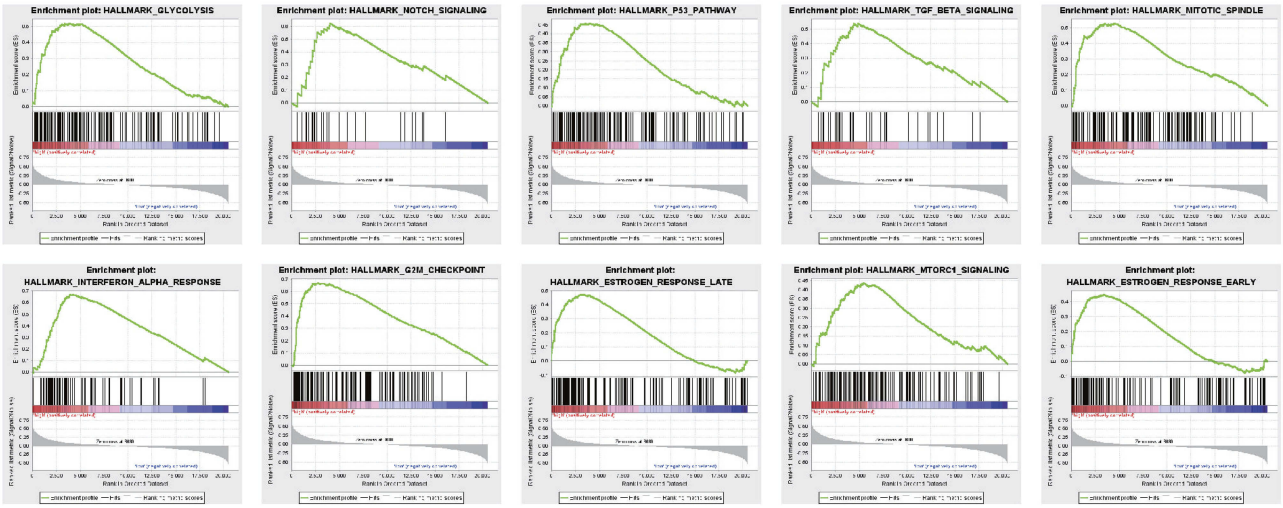

Figure 5 Gene set enrichment analysis (GSEA) of signaling pathways activated during pancreatic cancer. Comparison of data sets with low and high expression of *ITGA3* indicated the high expression phenotype had enrichment of glycolysis, notch signaling, P53 signaling, TGF-β signaling, the mitotic spindle, interferon alpha response, G2M checkpoint, estrogen response, and mTOR signaling.

We used data mining to examine the relationship of *ITGA3* expression with pancreatic cancer. Together with previous research, the present study contributed to the identification of novel diagnostic and prognostic biomarkers for pancreatic cancer. However, the rather small sample size of our study is a limitation that must be considered. Thus, we plan to extend the current study by using a larger sample size and a different data set to assess the diagnostic and prognostic value of *ITGA3* expression in pancreatic cancer, and to determine its potential use as a biomarker for pancreatic cancer.

Disclosure

The authors report no conflicts of interest in this work.

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