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ORIGINAL ARTICLE

Retrospective Study

Stromal secreted protein acidic and rich in cysteine expression: A potential target for improved prognosis in patients with pancreatic cancer

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Abstract

BACKGROUND

Pancreatic cancer tissues mainly consist of fibrotic and dense stroma, which limits their therapeutic efficacy. The stromal fibroblasts of pancreatic tumors frequently express the secreted protein acidic and rich in cysteine (SPARC).

AIM

To assess the impact of SPARC and its oncological relevance in patients undergoing pancreatic cancer resection.

METHODS

Ninety-one pancreatic ductal adenocarcinoma specimens were obtained from patients with curative resection between January 2009 and December 2015 as a retrospective study. SPARC expression patterns were analyzed using immunohistochemistry. Oncological outcomes were analyzed based on SPARC expression

patterns. Oncological outcomes, based on SPARC expression, were analyzed in The Cancer Genome Atlas-Pancreatic Adenocarcinoma cohort (retrieved from a public database).

RESULTS

Patients with stromal SPARC expression (sSPARC+) had poorer overall survival than that in those without it (sSPARC-) (P = 0.035). However, among patients who received adjuvant treatment, no difference was observed in survival between the sSPARC+ and the sSPARC- groups (P = 0.14). In The Cancer Genome Atlas-Pancreatic Adenocarcinoma samples, the high SPARC expression group exhibited noticeably lower overall survival than that in the low expression group (cutoff: 14.1295, P = 0.0222). Furthermore, SPARC expression was strongly correlated with the percentage the CD10+ stromal component (R^2 = 0.804, P < 0.001).

CONCLUSION

Adjuvant chemotherapy improves survivals in sSPARC+ pancreatic cancer patients, indicating suggesting sSPARC expression as a prognostic biomarker and potential indicator for neoadjuvant treatment planning.

Key Words: Pancreatic ductal adenocarcinoma; Secreted protein acidic and rich in cysteine; Tumor microenvironment; Stroma; Survival

Core Tip: This retrospective study investigated the prognostic significance of stromal secreted protein acidic and rich in cysteine (SPARC) expression in resected pancreatic ductal adenocarcinoma. High stromal SPARC expression is associated with inferior recurrence-free and overall survival, particularly in patients without adjuvant chemotherapy. External validation using The Cancer Genome Atlas-Pancreatic Adenocarcinoma cohort further supported the association between unfavorable prognosis and high SPARC expression. These findings suggest that stromal SPARC may serve as a meaningful prognostic biomarker and potential therapeutic target for pancreatic ductal adenocarcinoma.

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INTRODUCTION

Currently, three treatment options are available for pancreatic cancer: Radiation therapy, chemotherapy, and surgery. Complete surgical excision has long been the only curative option for improving overall survival[1]. However, approximately 20% of pancreatic adenocarcinomas are surgically resectable[2,3]. Even if surgical resection is possible, > 50% of patients experience cancer recurrence within 1-2 years after surgery[4]. The 5-year survival rate is ≤ 20%-30% after surgical resection. Even after undergoing surgical resection, 10% of pancreatic cancer patients develop fatal gastrointestinal cancer, which is associated with a dismal 5-year survival rate. Recently, surgical resection with neoadjuvant therapy has been considered an option for curative treatment[5,6]. Even though new chemotherapy regimens and surgical techniques have improved patient outcomes, survival rates remain low[7-10].

Treatment outcomes for pancreatic cancer have improved due to the development of effective chemotherapeutic drugs. Patients with resected pancreatic cancer[11], locally advanced pancreatic cancer[12], and metastatic pancreatic cancer[13] now have better long-term survival rates owing to chemotherapy regimens such as FOLFIRINOX treatment. Additionally, in patients with advanced pancreatic cancer, combination therapy with gemcitabine plus nab-paclitaxel (GEM-NAB) increases survival rates[14,15]. However, a comparison of these two chemotherapeutic regimens, in a randomized control trial, has not been reported. A recent meta-analysis[16] that included 3813 patients (2123 patients treated with GEM-NAB and 1690 patients treated with FOLFIRINOX) from 16 retrospective studies found a longer median overall survival with FOLFIRINOX treatment. However, the overall risk of cancer progression and death was similar between the GEM-NAB and FOLFIRINOX treatment groups, suggesting an important role for systemic chemotherapy in treatment of pancreatic cancer.

The secret to improving survival outcomes is early intervention. Identifying biomarkers that can reliably diagnose pancreatic cancer at an early stage or detect its causes is crucial for effective treatment. The pancreatic cancer stroma, which consists of dense and fibrotic tissues, causes hypovascularity and hypoxia, thereby playing a key role in disease progression and creating a major obstacle for drug delivery. Pancreatic cancer induces hypoxic physiological responses by creating a favorable hypovascular tumor microenvironment (TME) that promotes tumor growth. For decades, oncological efforts have focused on understanding the significance of the microenvironment in pancreatic carcinogenesis. However, pancreatic ductal adenocarcinoma patients who receive immunotherapy experience only modest impro-

vements[17-20].

The etiology of various diseases, including human carcinogenesis, is significantly influenced by secreted protein acidic and rich in cysteine (SPARC). SPARC influences TME cell cycle processes such as apoptosis, differentiation, and division. Additionally, it affects cancer cell motility, adhesion, and invasion, thereby influencing cancer metastasis. Studies aimed at identifying the other roles and effects of SPARC expression in carcinogenesis are currently underway[21]. SPARC functions to negatively regulate cell proliferation in breast, stomach, colon, leukemia, lung, neuroblastoma, and ovarian cancers[22-29].

Ongoing research explores SPARC expression in pancreatic cancer. Stromal fibroblasts frequently express SPARC in pancreatic cancer. However, the majority of pancreatic cancer cells do not express SPARC. In pancreatic mouse models, SPARC overexpression occurs more frequently in the stroma than in tumor cells[30-33]. Gundewar *et al*[34] and Mantoni *et al*[35] proposed that stromal SPARC (sSPARC) expression could serve as a potential target for directed therapy and as a prognostic factor. Therefore, understanding the role of SPARC in carcinogenesis is crucial[36].

This study set out to evaluate the significance of SPARC expression in tumors of individuals whose pancreatic cancer had been removed and the potential oncological implications of this finding. Analysis of The Cancer Genome Atlas-Pancreatic Adenocarcinoma (TCGA-PAAD) cohort data allowed for the validation of values related to SPARC expression findings. To identify specific cell types linked to SPARC expression, deconvolution of cell type-specific gene expression and the relative fraction of TME components was performed.

MATERIALS AND METHODS

Patient and external validation data

Records of patients at Severance Hospital who received curative resection for pancreatic ductal adenocarcinoma between January 2009 and December 2015 were examined retrospectively. Analyses were performed on 91 resected samples. For the purpose of describing the SPARC expression patterns, immunohistochemistry was used. Based on SPARC expression, oncological outcomes were compared. TCGA-PAAD SPARC expression cohort data, retrieved from a public database (http://portal.gdc.cancer.gov/), was used to assess oncologic outcomes. The Institutional Review Board of Severance Hospital gave their approval to this study, No. 4-2017-1029. As this was a retrospective study, informed consent was not required. Ethical principles from the 2013 World Medical Association Declaration of Helsinki's were adhered throughout the investigation.

Immunohistochemistry

Sections of the tissue that were 4 μm thick were cut off. Tissue samples were deparaffinized, rehydrated, and washed twice. To reduce background staining from endogenous peroxidases, the slides were washed four times in buffer after treatment with hydrogen peroxide block for 10 minutes. As per the guidelines provided by the manufacturer, tissue slices were incubated with a primary SPARC monoclonal antibody (ON1-1, 1:1000, Thermo Fisher Scientific, Rockford, IL, United States) at 4 °C. The slides were washed four times. Following exposure to a primary antibody enhancer, all slides underwent a 20-minute incubation period at room temperature before being rinsed four times with buffer. The tissue sections were rinsed four times with buffer after treatment with the horseradish peroxidase polymer for 30 minutes at room temperature. Next, the sections were incubated with hematoxylin, cleaned four times with deionized water, and counterstained for chromogen detection.

The proportion of tumor cells with cytoplasmic staining was used to assess cytoplasmic SPARC (cSPARC) expression. The staining intensity was graded as negative (0), weak (1), moderate (2), or strong (3) (Figure 1). In accordance with the criteria described by Sinn *et al*[37], cSPARC positivity was defined as either > 50% of tumor cells with moderate to strong intensity or > 10% of tumor cells with strong intensity (immunoreactive score ≥ 3). The SPARC antibody showed high and homogeneous stromal staining in fibroblasts, as reported by Hidalgo *et al*[38]. sSPARC expression was assessed based on the percentage of fibroblasts exhibiting strong cytoplasmic staining, as described by Hidalgo *et al*[38]. Based on the distribution of stromal staining patterns and in line with previous literature, sSPARC positivity was defined as strong staining in ≥ 50% of stromal fibroblasts (Figure 2), whereas sSPARC negativity was defined as staining in < 50% stromal fibroblasts (Figure 2).

Two experienced pathologists independently evaluated the immunostaining results and any discordant or ambiguous cases were resolved by consensus to minimize interobserver variability instead of quantifying interobserver agreement using a kappa statistic. The selection of these thresholds is consistent with previous literature and further supported by statistical principles of cutoff optimization using survival or receiver operating characteristic (ROC)-based methods, as proposed by Budczies *et al*[39]. In addition, we categorized the patients into four groups according to expression of SPARC. Patients who had cancer cells that expressed SPARC were placed in the cSPARC+ group, while those who did not have cancer cells that expressed SPARC were placed in the cSPARC- group. Patients who showed positive staining of SPARC in stromal tissue were assigned to the sSPARC+ group, and patients with negative staining of SPARC in stromal tissue were assigned to the sSPARC- group.

Assessment of SPARC mRNA expression and survival analysis using the TCGA-PAAD cohort

To externally validate the oncologic significance of SPARC, mRNA expression data were retrieved from the TCGA-PAAD cohort using the University of California, Santa Cruz Xena browser. SPARC expression levels were compared according to recurrence and survival status using the Mann-Whitney *U* test. Its predictive potential was evaluated using ROC curve analysis. The best cut-off value for SPARC expression was determined using the Cox proportional hazards model,

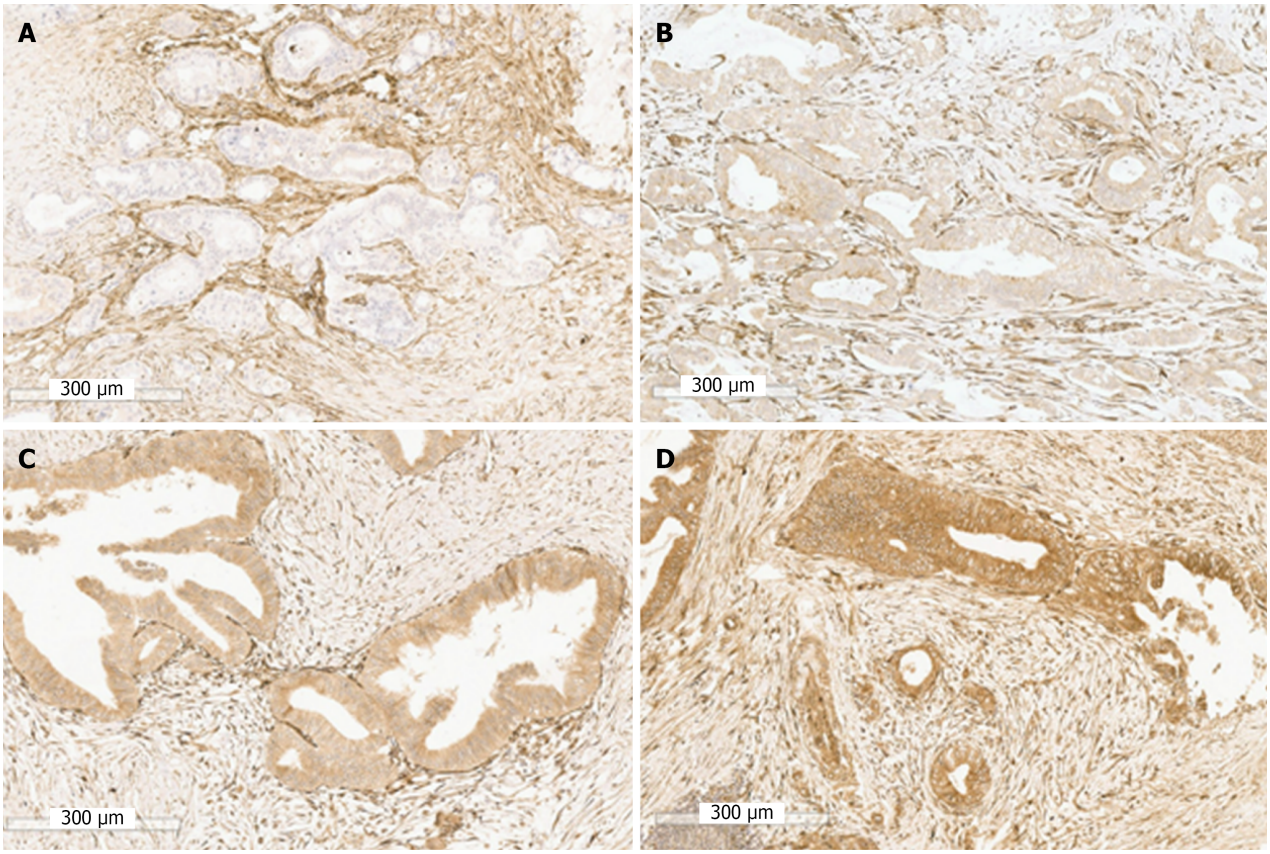

Figure 1 Representative immunohistochemical secreted protein acidic and rich in cysteine staining intensity in the cancer component (× 100, scale bar: 300 μm). This figure is provided as a representative case without quantitative statistical comparison. A: Secreted protein acidic and rich in cysteine (SPARC) cancer negative (0); B: SPARC cancer weak (1); C: SPARC cancer moderate (2); D: SPARC cancer strong (3).

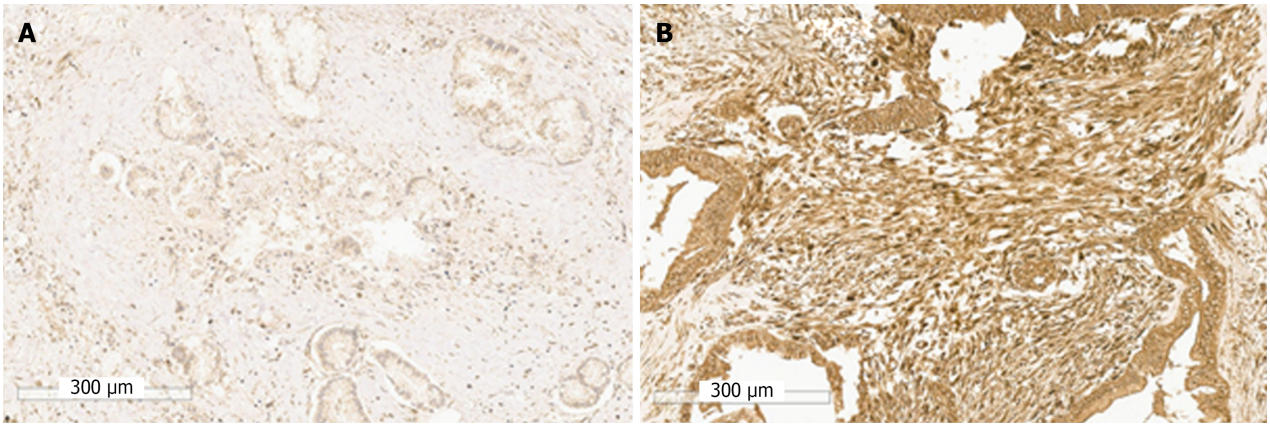

Figure 2 Representative immunohistochemical secreted protein acidic and rich in cysteine staining in the stromal component (× 100, scale bar: 300 μm). This figure is provided as a representative case without quantitative statistical comparison. A: Stromal negative secreted protein acidic and rich in cysteine; B: Stromal positive secreted protein acidic and rich in cysteine.

specifically applying the maxstat algorithm implemented in the survminer R package. Based on this threshold, patients were stratified into high- and low- expression groups, and log-rank tests were used to compare recurrence-free and overall survival between the two groups.

Statistics analysis

SPSS statistics software, version 26 (IBM Corporation, Armonk, NY, United States), was used for all statistical analyses. The duration from entry to local or distant disease relapse was defined as disease-free survival (DFS). The time from study enrolment to death from any cause was defined as overall survival. A *P* value adjustment was necessary as multiple comparisons were performed[40]. χ^2 tests were used to evaluate the associations between SPARC expression and clinicopathological tumor characteristics. For univariate survival analysis, the Kaplan-Meier method with log-rank testing

was employed. Cox regression models were used for multivariate analyses. *P* values were typically two-sided and values below 0.05 were considered as statistically significant. For subgroup survival outcome comparisons involving more than two groups, Bonferroni correction was applied to adjust for multiple comparisons. Adjusted *P* values are reported in the results and figures. The significance threshold was adjusted and $P < 0.05$ was considered statistically significant. Only patients with complete clinicopathological and immunohistochemical data were included in the analysis; therefore, there were no missing data requiring statistical imputation. Because this was a retrospective study, only patients with available long-term follow-up data were included in the analysis. Therefore, loss to follow-up was not applicable. Sensitivity analyses were performed by externally validating SPARC expression using the TCGA-PAAD dataset and by stratifying patients according to cSPARC and sSPARC expression levels to assess the robustness of the prognostic associations.

Deconvolution of relative proportion and cell-type-specific gene expression

The CIBERSORTx algorithm (https://cibersortx.stanford.edu/), which estimates the relative fractions of TME components, was used to quantify cell-specific gene expression[41]. The TR4 signature matrix was used to deconvolute cell-specific molecular features of the TME, including CD10 (stromal component), CD31 (endothelial cell component), CD45 (immune cell component), and epithelial cell adhesion molecule (tumor component). Bulk transcriptomic data obtained from the TCGA-PAAD cohort were used to calculate SPARC expression in the stromal component of the TME and the relative fractions of all TME components.

RESULTS

Characteristics of patients who have had resected pancreatic cancer

Data on patients ($n = 91$), who underwent curative pancreatic resection for pancreatic cancer were retrospectively collected. Median follow-up duration was 43.0 ± 6.5 months (range, 2.0-94.0 months). Patients characteristics were as follows: Mean age, 63.7 ± 9.3 years (range, 35-83 years); males, 51 (56%), females, 40 (44%). At that time, pancreatic ductal adenocarcinoma was histologically confirmed in all the patients. Preoperative radiologic analysis revealed that 57 patients (62.3%) had pancreatic head cancer and 34 (37.3%) had pancreatic body or tail cancer. Of these, 58 (63.7%) underwent pylorus-preserving pancreaticoduodenectomy, 31 (34.1%) distal pancreatectomy, and two (2.2%) underwent total pancreatectomy. Adjuvant chemotherapy was administered to 73 patients (80.2%) who underwent curative resection (Table 1). Most patients ($n = 56$, 76.9%) received up to six cycles (spaced 4 weeks apart) of gemcitabine-based adjuvant chemotherapy (Table 2)[42,43].

Clinicopathological differences in SPARC expression in resected pancreatic cancer tissue

Of the 91 pancreatic cancer cases, 41 (45.1%) were positive for sSPARC+ (Figure 3A and B). The remaining 50 patients (54.9%) did not exhibit sSPARC- (Figure 3C and D). Additionally, cSPARC+ patterns were observed (Figure 3A) in 27 of the 41 sSPARC+ patients (65.9%). In contrast, cancer cells from the 14 remaining sSPARC+ patients (34.1%) did not exhibit the cSPARC+ patterns (Figure 3B). Of the 50 sSPARC- patients, only 31 (62%) exhibited cSPARC+ expression (Figure 3C), and 19 (38%) produced negative SPARC signals (Figure 3D). Between the sSPARC+ and sSPARC- groups, no significant variations were found in the general clinical features ($P > 0.05$). Based on the pathologic outcome, the biological cancer behavior did not differ significantly ($P > 0.05$). sSPARC expression pattern had no effect on cancer stage or adjuvant chemotherapy. In the sSPARC+ and sSPARC- groups, 33 (80.5%) and 40 (80.0%) patients underwent adjuvant chemotherapy ($P > 0.999$; Table 3), respectively.

Oncologic effect of SPARC expression in resected pancreatic cancer

Based on univariate analysis, no statistically significant difference was seen in overall survival between the cSPARC+ and cSPARC- groups ($P = 0.369$; Figure 4A). However, it was shown that there was a statistically significant ($P = 0.035$) difference in overall survival between the sSPARC+ and sSPARC- groups (Figure 4B). According to SPARC expression, there was no variation in survival in the sSPARC- group ($P = 0.42$; Figure 5A). *P* indicates Bonferroni-corrected *P* value in Figure 5. [a]*P* value less than 0.05, indicates a significant difference in this survival analysis[40]. According to sSPARC expression, no significant difference was observed in the survival rate of the cSPARC- group ($P = 1.0$; Figure 5A). However, according to sSPARC expression, a significant variation was observed in the overall survival rate of the cSPARC+ group ([a]$P = 0.04$; Figure 5A).

sSPARC expression as an independent predictor for patients with resected pancreatic cancer

Pathological N-stage ($P = 0.040$), postoperative adjuvant chemotherapy ($P < 0.001$), and SPARC-stromal expression pattern ($P = 0.007$) were significant predictive variables in univariate analysis. Additionally, it was also discovered that N1 stage [hazard ratio (HR) = 3.137, 95% confidence interval (CI): 1.527-6.444, $P = 0.002$], adjuvant chemotherapy (HR = 0.151, 95%CI: 0.074-0.306, $P < 0.001$), and SPARC-stromal expression pattern (HR = 2.726, 95%CI: 1.441-5.158, $P = 0.002$) were all independent predictors of prognosis in patients with resected pancreatic cancer after multivariate analysis. To assess whether the effect of SPARC-stromal expression on prognosis differed by adjuvant chemotherapy status, we incorporated an interaction term between SPARC and adjuvant therapy into the multivariate Cox regression model. The interaction term was not statistically significant ($P = 0.637$), suggesting that the prognostic impact of SPARC expression was not significantly modified by adjuvant chemotherapy, respectively (Table 4).

Table 1 General characteristics of the patients, *n* (%)/mean ± SD

Variables, *n* = 91		Frequency
Age (years)		63.7 ± 9.3
Gender	Male/female	51 (56)/40 (44)
Tumor location	Head/body + tail	57 (62.3)/34 (37.4)
Radiologic tumor size (cm)		2.75 ± 1.30
Preoperative CA19-9		509.0 ± 1565.7
Operation	PPPD/DPS/TP	58 (63.7)/31 (34.1)/2 (2.2)
Tumor differentiation	Well/moderate/poor	14 (15.4)/66 (72.5)/11 (12.1)
LVI	Yes/no	29 (31.9)/62 (68.1)
PNI	Yes/no	67 (73.6)/24 (26.4)
pT stage[1]	T1/T2/T3	29 (31.9)/55 (60.4)/7 (7.7)
pN stage	N0/N1/N2	39 (42.9)/40 (44.0)/12 (13.2)
Retrieved LN number		19.4 ± 10.0
Metastatic LN number		1.4 ± 2.0
Adjuvant therapy	Yes/no	73 (80.2)/18 (19.8)

[1]Tumor stage was assessed according to the tumor-node-metastasis classification, the American Joint Committee on Cancer 8th edition.
CA19-9: Carbohydrate antigen 19-9; LVI: Lymphovascular invasion; PNI: Perineural invasion; LN: Lymph node; PPPD: Pancreaticoduodenectomy, preserving the pancreatic head; DPS: Disease progression score; TP: Total protein.

Table 2 Adjuvant chemotherapy regimen, *n* (%)

Variables	Frequency (*n* = 73)
Gemcitabine	56 (76.9)
Fluorouracil	3 (4.1)
Tegafur-uracil	3 (4.1)
Fluorouracil-cisplatin	4 (5.4)
Fluorouracil-leucovorin	2 (2.7)
Fluorouracil-epirubicin-cisplatin	3 (4.1)
Follow up loss	2 (2.7)

Impact of sSPARC expression in postoperative adjuvant chemotherapy in resected pancreatic cancer

Subgroup analysis limited to patients with adjuvant chemotherapy (n = 73) demonstrated that sSPARC expression still remained a significant prognostic factor in both univariate (HR = 3.010, 95%CI: 1.360-6.662, P = 0.007) and multivariate analyses (HR = 2.604, 95%CI: 1.258-5.391, P = 0.010; Supplementary Table 1). Correlation analysis of the oncologic effect revealed that postoperative adjuvant chemotherapy improved survival in patients with sSPARC-resected pancreatic cancer (median 59.521 ± 7.348 months, 95%CI: 45.119-73.924). The patients' survival rates with adjuvant chemotherapy were higher than patients' survival rates without receiving adjuvant chemotherapy (median 24.04 ± 8.445 months, 95%CI: 7.488-40.592; ^aP = 0.040; Figure 5B). P indicates Bonferroni-corrected P value in Figure 5. ^aP value is less than 0.05, indicating a significant difference in this survival analysis[40].

The survival advantage of adjuvant chemotherapy in patients with sSPARC+ resected pancreatic cancer (median 35.455 ± 4.263 months, 95%CI: 27.099-43.811) was attenuated. The survival outcome in the sSPARC+ group, without adjuvant chemotherapy, was poor (median 13.00 ± 7.533 months, 95%CI: 0.00-27.765; ^aP = 0.028; Figure 5B). The results indicated that the survival rate of patients with sSPARC+ who underwent surgical resection and did not received postoperative adjuvant chemotherapy was poorer than that of patients who underwent surgical resection and received postoperative adjuvant chemotherapy (^aP < 0.001; Figure 5B). However, patients who received adjuvant chemotherapy following surgery had similar survival benefits, regardless of sSPARC expression (P = 0.14; Figure 5B).

Table 3 Clinic-pathological characteristics according to secreted protein acidic and rich in cysteine expression, *n* (%)/mean ± SD

	Variables	SPARC stroma (+) (*n* = 41)	SPARC stroma (-) (*n* = 50)	*P* value
Age (years)		64.4 ± 9.0	63.1 ± 9.7	0.236
Gender	Male/female	22 (53.7)/19 (46.3)	29 (58.0)/21 (42.0)	0.832
Tumor location	Head/body + tail	23 (56.1)/18 (43.9)	34 (68.0)/16 (32.0)	0.281
Radiologic tumor size (cm)		2.82 ± 1.61	2.69 ± 0.98	0.639
Preoperative CA19-9		293.3 ± 512.0	685.8 ± 2053.7	0.236
Operation	PPPD/DPS/TP	23 (56.1)/17 (41.5)/1 (2.4)	35 (70.0)/14 (28.0)/1 (2.0)	0.491
Tumor differentiation	Well/moderate/poor	9 (22.0)/29 (70.7)/3(7.3)	5 (10.0)/37 (74.0)/8 (16.0)	0.198
LVI	Yes/no	11 (26.8)/30 (73.2)	18 (36.0)/32 (64.0)	0.376
PNI	Yes/no	30 (73.2)/11 (26.8)	37 (74.0)/13 (26.0)	> 0.999
pT stage	T1/T2/T3	15 (36.6)/22 (53.7)/4 (9.8)	25 (28.0)/33 (66.0)/3 (6.0)	0.477
pN stage	N0/N1/N2	16 (39.0)/20 (48.8)/5 (12.2)	23 (46.0)/20 (40.0)/7 (14.0)	0.768
Retrieved LN number		19.3 ± 10.4	19.4 ± 9.8	0.986
Metastatic LN number		1.4 ± 2.3	1.4 ± 1.7	0.934
Adjuvant therapy	Yes/no	33 (80.5)/8 (19.5)	40 (80.0)/10 (20.0)	> 0.999

SPARC: Secreted protein acidic and rich in cysteine; CA19-9: Carbohydrate antigen 19-9; LVI: Lymphovascular invasion; PNI: Perineural invasion; LN: Lymph node; PPPD: Pancreaticoduodenectomy, preserving the pancreatic head; DPS: Disease progression score; TP: Total protein.

External validation of SPARC expression and its oncologic effect in pancreatic cancer-public database assessment

Comparisons of gene expression for extracellular matrix-related molecules associated with the TME were performed using the TCGA-PAAD cohort. Among the various extracellular matrix components, tissue inhibitors of metalloproteinases and SPARC were the most significantly upregulated molecules. The distribution of gene expression levels was visualized using bot plots. In each plot, the bot represents the interquartile range (25^{th}-75^{th} percentile), with the horizontal line inside indicating the mean expression value. Whiskers denote the 10^{th} and 90^{th} percentiles (Supplementary Figure 1).

Oncologic validation of SPARC expression in the TCGA-PAAD cohort

To evaluate the difference of SPARC expression according to oncologic outcome in terms of recurrence or death, we compared the mean of SPARC expression in the TCGA-PAAD cohort. No significant differences were observed between the two groups (no recurrence *vs* recurrence, $P > 0.05$; no death *vs* death, $P < 0.05$). The Mann-Whitney *U* test was performed to calculate *P* value from the comparisons (Supplementary Figure 2). To further investigate the prediction potential of SPARC expression in the TCGA-PAAD cohort, ROC curve analysis was conducted. The area under the curve values for recurrence and death were 0.526 and 0.517, respectively, indicating limited discriminatory ability (Supplementary Figure 3).

After selecting optimal cut-off using the Cox proportional hazard model, TCGA-PAAD samples were stratified into high and low SPARC expression groups. Kaplan-Meier survival analysis revealed that patients within the lowest 10% of SPARC expression had significantly prolonged recurrence-free survival (cutoff: 14.1575, HR = 2.875, 95%CI: 1.033-8.003, $P = 0.0283$) and overall survival (cut-off: 14.1295, HR = 3.023, 95%CI: 1.223-7.477, $P = 0.0222$), suggesting that low SPARC expression may confer favorable prognosis in a distinct molecular subset (Supplementary Figure 4).

Cell-specific SPARC expression according to TME component

The stromal component (CD10+ cell population) accounted for the largest portion of pancreatic cancer tissue (Supplementary Figure 5A). SPARC expression and the proportion of CD10+ stromal cells were substantially correlated ($R^2 = 0.804$, $P < 0.001$; Supplementary Figure 5B). Compared with other TME components, the CD10+ stromal component showed remarkably high SPARC expression ($P < 0.001$; Supplementary Figure 5C). Poor overall survival and DFS were highly correlated with high SPARC expression (overall survival, $P = 0.0022$; DFS, $P = 0.0015$; Supplementary Figure 5D). The relative CD10+ stromal component fraction also showed significant prognostic difference (overall survival, $P = 0.0032$; DFS, $P = 0.0145$; Supplementary Figure 5D). Groups according to SPARC expression and CD10 relative fraction exhibited prognostic significance. Additionally, the subgroup with a high CD10+ proportion and high SPARC expression was substantially linked to unfavorable survival result (Supplementary Figure 5E).

Table 4 Univariate and multivariate Cox regression analysis of factors affecting overall survival

Variables (*n* = 91)	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Location	0.985 (0.533-1.818)	0.961		
Tumor size				
≤ 3.0	1.00			
> 3.0	1.644 (0.854-3.163)	0.137		
N status		0.040		0.007
N0	1.00		1.0	
N1	2.388 (1.217-4.689)	0.011	3.137 (1.527-6.444)	0.002
N2	1.691 (0.598-4.783)	0.322	1.761 (0.609-5.088)	0.296
CA19-9				
≤ 35	1.00			
> 35	1.228 (0.618-2.441)	0.554		
Cell differentiation		0.250		
Well	1.0			
Moderately	0.553 (0.268-1.138)	0.108		
Poorly	0.734 (0.250-2.153)	0.573		
Lymphovascular invasion	1.009 (0.516-1.972)	0.978		
Perineural invasion	0.806 (0.413-1.573)	0.528		
Adjuvant therapy			1.0	
None	1.0			
Done	0.236 (0.123-0.452)	< 0.001	0.151 (0.074-0.306)	< 0.001
SPARC			1.0	
Stroma (-)	1.0			
Stroma (+)	2.335 (1.255-4.345)	0.007	2.726 (1.441-5.158)	0.002
SPARC adjuvant therapy			1.367 (0.749-2.497)	0.309

SPARC: Secreted protein acidic and rich in cysteine; CA19-9: Carbohydrate antigen 19-9; HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

The microenvironment associated with pancreatic cancer are unique. The stellate cells in the pancreas that constitute the stroma of pancreatic cancer produce excessive stromal substances such as collagen, laminin, and fibronectin, which leads to desmoplasia. Consequently, this in turn results in hypo-vascularization of the microenvironment, which impairs local drug delivery and renders tumors resistant to chemotherapeutic agents[19,44-46]. Individuals with pancreatic cancer metastases have a poor prognosis. The overall 5-year survival rate of overall is less than 1%-2% in advanced stages[47]. In most cases, gemcitabine is administered as palliative chemotherapy. However, these treatments have limited survival benefits. Only a modest prolongation of the 30-day median survival was observed[48]. According to an autopsy sequences of patients with resected pancreatic malignancy, 85%-90% of patients die from recurrent illness, rather than local disease, and systemic recurrence accounts for 70%-85% of all deaths[49,50].

SPARC has attracted a lot of interest, because recent developments regarding the oncological effectiveness of nab-paclitaxel in pancreatic cancer treatment[51]. Nab-paclitaxel promotes the accumulation of chemotherapeutic drugs in tumors by delivering paclitaxel through albumin. During this process, albumin-drug complexes accumulate in SPARC-positive locations because SPARC functions as a high-affinity albumin receptor. In fact, tumor response is correlated with SPARC expression in preclinical and clinical settings of pancreatic cancer, and nab-paclitaxel absorption is higher in SPARC expressing tumors[15,52,53]. Numerous researches have examined the predictive significance of SPARC expression in pancreatic cancer. A meta-analysis by Han *et al*[33], which included 1623 patients from 10 currently accessible articles concluded that: SPARC expression, particularly in the stroma, negatively impact pancreatic cancer prognosis (HR = 1.53, 95%CI: 1.05-2.24, *P* = 0.03).

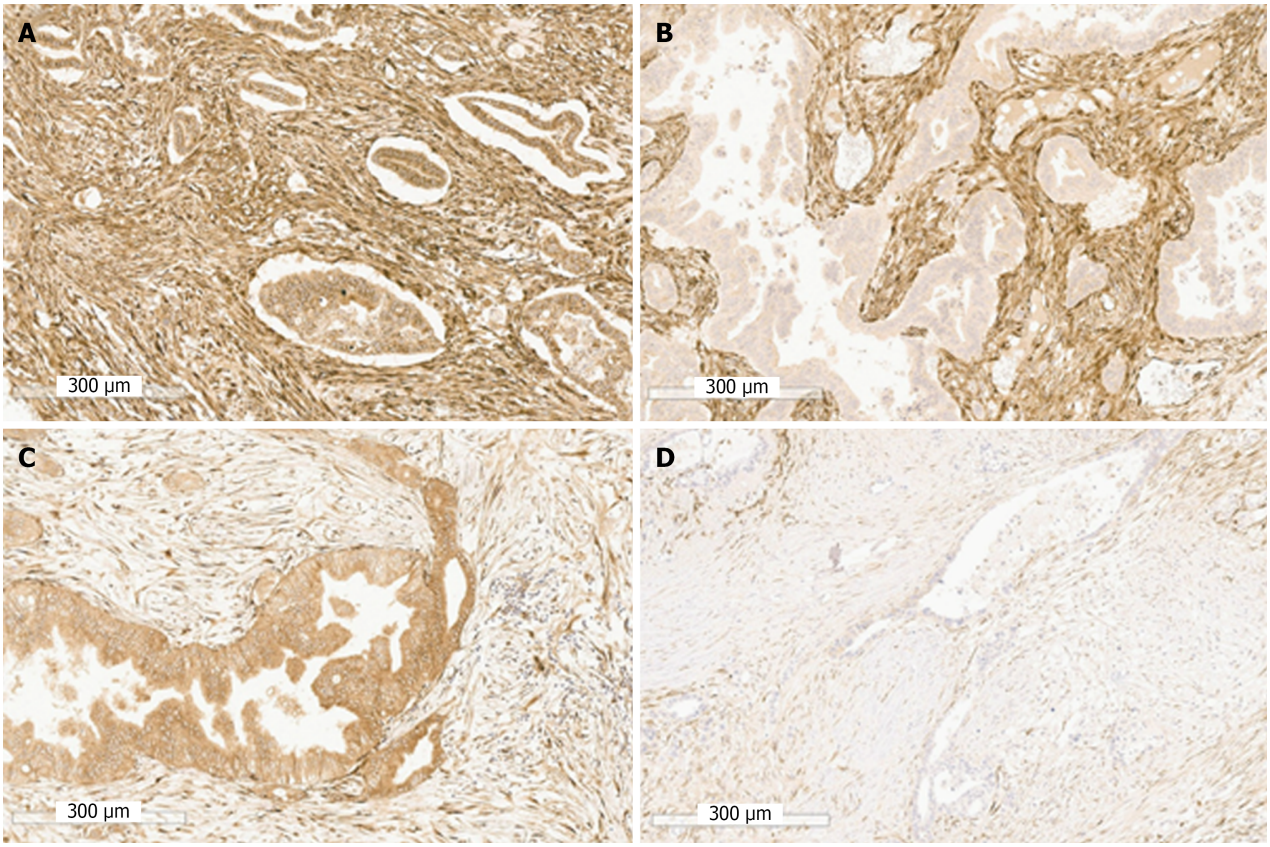

Figure 3 Representative immunohistochemical staining of secreted protein acidic and rich in cysteine in the cancer and stromal components combination (× 100, scale bar: 300 μm). This figure is provided as a representative case without quantitative statistical comparison. A: Secreted protein acidic and rich in cysteine (SPARC) stroma (+) and SPARC cancer (+); B: SPARC stroma (+) and SPARC cancer (-); C: SPARC stroma (-) and SPARC cancer (+); D: SPARC stroma (-) and SPARC cancer (-).

According to recent studies, SPARC expression may have unfavorable implications in patients undergoing surgical resection for pancreatic cancer. Murakawa *et al*[54] examined how SPARC expression affect the survival rate of patients with pancreatic cancer who underwent curative resection and found that the patients' survival rate with positive for SPARC expression (39.1%) was notably lower than those with negative expression (19.8%; $P = 0.0316$). Yu *et al*[55] identified a relationship between a higher proportion of SPARC expression and decreased overall and DFS in primary tumor cells with positive SPARC expression in metastatic lymph nodes compared to normal lymph nodes (32/38 *vs* 0/38) in her study. Shintakuya *et al*[56] found that adjuvant gemcitabine alone or in combination with S-1 decreased the disease-free and overall survival rates of patients with resected pancreatic ductal adenocarcinomas. These findings suggest that lymph node metastasis plays a significant predictive role in resected pancreatic cancer patients.

In this study, we found that tumors with cellular SPARC expression were present in more than half of the patients with resected pancreatic cancer (63.7%). In addition, 45% of the patients exhibited sSPARC expression. As all samples in this study showed strong stromal staining patterns, we categorized the sSPARC+ group based on the density distribution. SPARC expression in stromal cells had a significantly greater impact on prognosis than expression in tumor cells in patients with resected pancreatic cancer. These findings are supported by the TCGA-PAAD cohort results. Additionally, we discovered a substantial correlation between sSPARC expression in pancreatic cancer and the CD10+ cell population. A significant association between stromal CD10+ cells and SPARC expression, which leads to poor prognosis, has also been observed in other malignancies[57,58]. Furthermore, several studies have suggested that CD10+ cancer associated fibroblasts (CAFs) correspond to specific subtypes such as CAF-S1[59-61]. These subtypes exhibit immunosuppressive and pro-tumorigenic functions. Although this study did not classify CAF subtypes, observed correlation between CD10+ and sSPARC expression may indicate a mechanistically relevant subset of fibroblasts. Although the precise molecular pathways remain unclear, these findings suggest that SPARC-expressing CAFs create an immunosuppressive microenvironment that hampers chemotherapeutic efficacy. Therefore, our results suggest that sSPARC expression in resected pancreatic cancer may serve as both a significant prognostic factor and a viable therapeutic target.

Consistent with previously reported findings[54,56,62], we found that sSPARC expression was a distinct prognostic factor in individuals with resected pancreatic cancer. The lack of significant differences in clinicopathological characteristics based on SPARC expression further supports its role as an independent biomarker. While the prognostic role of sSPARC expression was evident, we further evaluated whether its impact was modified by the receipt of adjuvant chemotherapy. We found the lack of a statistically significant interaction between SPARC expression and adjuvant chemotherapy. This result implies that sSPARC could serve as a consistent prognostic marker regardless of systemic treatment. Interestingly, when we solely focused on the patients with adjuvant chemotherapy, sSPARC expression still

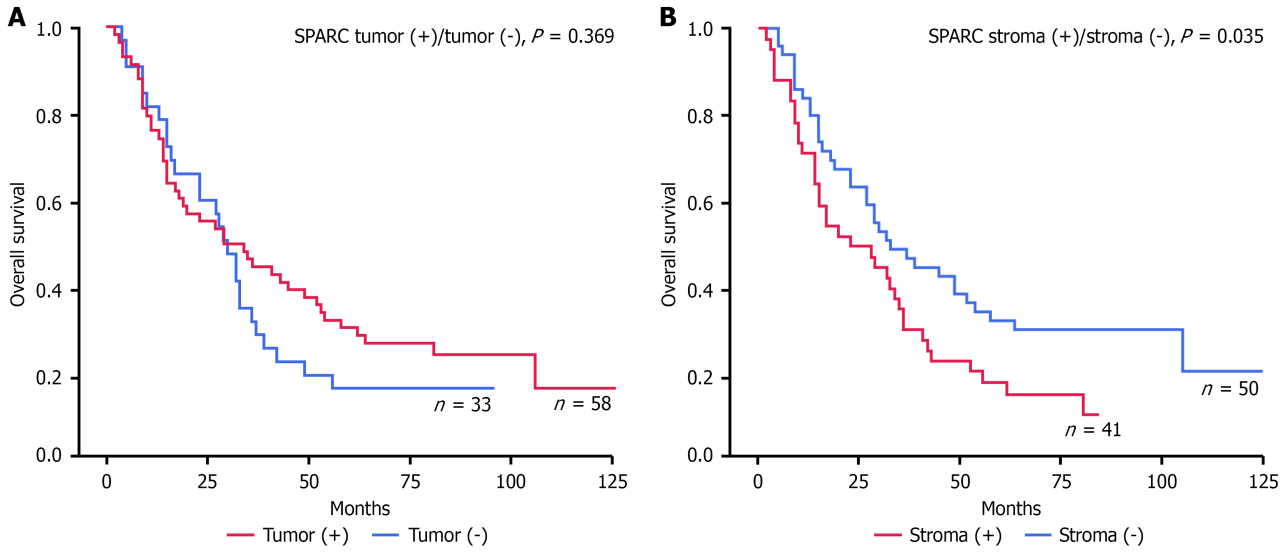

Figure 4 Survival analysis according to secreted protein acidic and rich in cysteine expression in stroma and cancer cell of resected pancreatic tissue. A: Overall survival difference according to secreted protein acidic and rich in cysteine expression in cancer tissue; B: Overall survival difference according to secreted protein acidic and rich in cysteine expression in stroma of the tumor. SPARC: Secreted protein acidic and rich in cysteine.

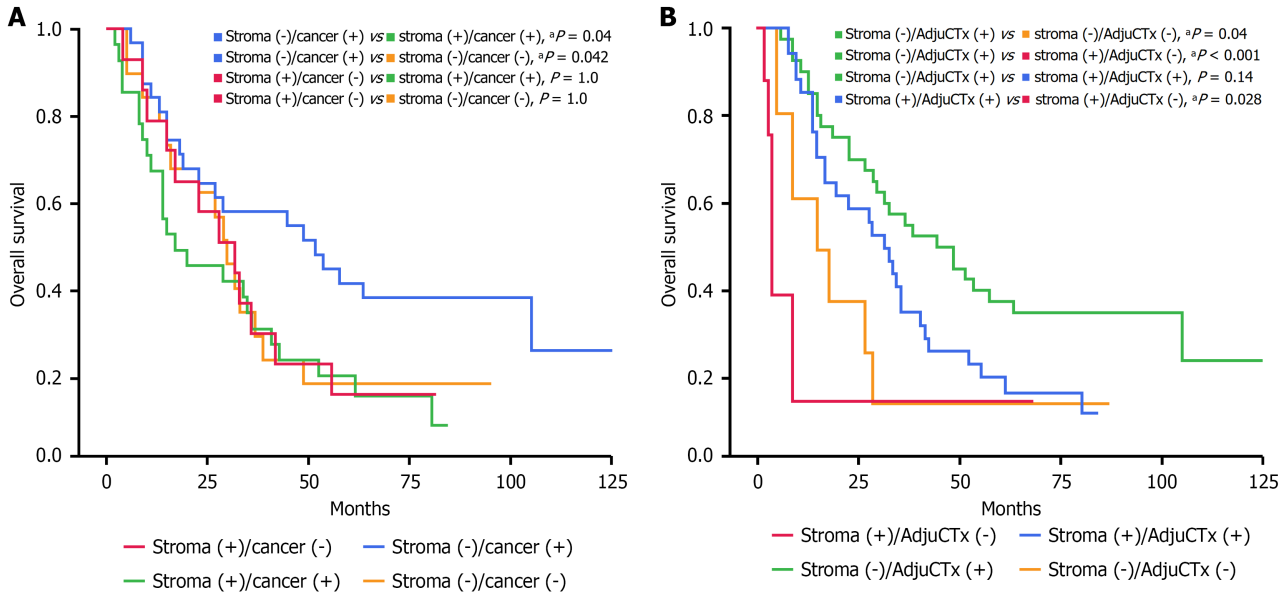

Figure 5 Overall survival difference. A: According to secreted protein acidic and rich in cysteine expression in stroma and cancer cells; B: According to secreted protein acidic and rich in cysteine expression and postoperative adjuvant chemotherapy. *P* indicates Bonferroni-corrected *P* value. $^{a}P < 0.05$ was considered statistically significant. AdjuCTx: Adjuvant chemotherapy.

showed significant association with overall survival. Overall, these results suggest that SPARC mediated mechanisms alone in TME may exert prognostic influence beyond chemotherapy response against pancreatic cancer propagation.

SPARC contributes to malignancy development by influencing processes such as apoptosis, cell proliferation, cell cycle progression, angiogenesis, adhesion, migration, and metastasis[21]. Pancreatic cancer metastasis is associated with SPARC expression. Heeg *et al*[63] found that the E26 transformation-specific transcription factor, ETS variant 1, regulates the growth of stroma and pancreatic cancer metastasis, functionally mediated through SPARC. Seux *et al*[64] observed that tumor protein 53-induced nuclear protein-1 expression may affect cell migration in various pancreatic cancer cell lines; where migration was reduced due to the transcriptional downregulation of SPARC. These findings suggested that SPARC expression is associated with cellular metastasis.

Based on sSPARC expression, we evaluated the impact of postoperative adjuvant chemotherapy in patients with resected pancreatic cancer. In contrast to sSPARC- patients, who appeared to benefit from adjuvant chemotherapy after surgical resection, the survival advantage associated with adjuvant chemotherapy was attenuated in sSPARC+ patients. In particular, sSPARC+ patients who did not receive postoperative adjuvant chemotherapy had poor long-term oncological outcomes. However, when preoperative detection is possible, adjuvant chemotherapy may be beneficial by

mitigating the adverse effects of SPARC expression. Additionally, SPARC, a potential therapeutic target for pancreatic cancer, has the potential to improve patient survival.

This study had some limitations. First, this study had a relatively small sample size, particularly in key subgroups, such as the eight patient who did not receive adjuvant chemotherapy in sSPARC+ subgroup, raising the possibility of small-sample bias in the corresponding survival analysis. Furthermore, it did not include patients who underwent neoadjuvant chemotherapy, because it was a retrospective study based solely on surgically resected specimens. Further prospective studies are required to validate SPARC as a predictive marker in a neoadjuvant setting. Second, although we revealed the independent role of sSPARC expression in patient prognosis, our findings differed from previous studies in that carbohydrate antigen 19-9 (CA19-9) was not included as a significant predictor. This discrepancy may be explained by the known limitations of CA19-9, including high false-positive rate resulting from pancreaticobiliary disease such as cholangitis, pancreatitis, obstructive jaundice, and hepatic cysts, which can interfere with CA19-9 results. In addition, individuals with Lewis-negative blood group lacked CA19-9 expression[65-68]. These potential confounding factors may have affected CA19-9 measurements in our cohort. Therefore, while CA19-9 remains clinically important, our findings suggest that sSPARC expression may provide additional prognostic insight, especially in cases where CA19-9 may be unreliable or equivocal.

Additionally, despite the association between sSPARC expression and clinical outcomes observed in our cohorts, its predictive performance in the TCGA-PAAD dataset was limited, as indicated by area under the curve values close to 0.5 for both recurrence and overall survival. These results suggest that SPARC may not serve as a stable and independent prognostic biomarker in external datasets. Nevertheless, when applying a cut-off derived from our Cox model, patients with low SPARC expression in the TCGA-PAAD cohort showed significantly better survival, providing partial external support for our findings. While the overall predictive performance in TCGA was modest, this stratified analysis highlights the potential utility of SPARC expression in identifying clinically relevant subpopulations. Another limitation of this study is that we did not perform multiplex immunostaining or spatial co-localization analysis of SPARC and CD10. Therefore, we plan to conduct further research with a larger cohort, incorporating digital spatial gene profiling of tumor cells, which may help elucidate the prognostic mechanism associated with SPARC expression. Additionally, we performed co-localization analyses of CD10+ stromal cells and SPARC expression to validate their spatial interaction and potential functional connection.

CONCLUSION

In conclusion, SPARC expression in stromal cells but not in malignant cells, was strongly correlated with survival in patients with pancreatic cancer. Prominent sSPARC expression appears a significant predictive indicator of biological aggressiveness and rapid progression occur in patients. Notably, postoperative chemotherapy partially attenuated the aggressive biological effects of SPARC, suggesting potential therapeutic implications. These results underscore the relevance of SPARC as a candidate biomarker for risk stratification and as a potential molecular target, particularly in the context of preoperative neoadjuvant chemotherapy. Further studies, including larger validation studies with external prospective cohorts, along with *in vitro* studies, and animal studies, are required to confirm these observations. Nevertheless, the development of new biomarkers for SPARC-targeting chemotherapeutic agents or novel therapeutic strategies aimed at modulating SPARC-mediated stromal signaling may be warranted for new opportunities with improved outcomes. This serves as a foundation for the development of molecular anticancer therapeutics for drug-resistant pancreatic cancer. This study provides foundational evidence for the clinical translation of SPARC-targeted therapy in the management of pancreatic ductal adenocarcinoma.

FOOTNOTES

Author contributions: Yang HY, Chong JU, and Kang CM designed the study and obtained the data; Yang HY, Chong JU, Jang M, and Lee SH analyzed data, interpreted the data and results; Yang HY and Chong JU drafted the manuscript and made equal contributions as co-first authors; Yang HY, Lee SH, Kang CM, Hwang HK, and Lee WJ revised the manuscript for intellectual content; all authors contributed significantly to and agree with the content of the manuscript.

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