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RESEARCH

Lack of association between SLFN11 expression and treatment efficacy or survival outcomes in patients with pancreatic ductal adenocarcinoma

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Abstract

Purpose Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis. Despite the use of aggressive combination chemotherapy regimens, outcomes remain unsatisfactory. Schlafen family member 11 (SLFN11) has been reported to regulate the DNA damage response and influence tumor sensitivity to certain chemotherapeutic agents. This study aimed to investigate the expression of SLFN11 in PDAC and its potential as a biomarker for predicting treatment efficacy and survival outcomes.

Methods This retrospective observational cohort study included 158 patients with unresectable or borderline resectable PDAC who received palliative chemotherapy. Patients were classified into three groups: metastatic, locally advanced, and borderline resectable PDAC. Immunohistochemical staining for SLFN11 was performed on biopsy specimens, and expression levels were quantified using the histo-score (H-score). Associations between SLFN11 expression and clinical outcomes, including progression-free survival and overall survival, were analyzed using Kaplan–Meier methods and Cox regression models.

Results SLFN11 expression was observed in 54.4% of PDAC tissues. The median H-score for SLFN11 expression was higher in metastatic cases than in locally advanced and borderline resectable cases. However, no significant association was found between SLFN11 expression and the efficacy of chemotherapy or clinical outcomes.

Conclusion Despite the hypothesized role of SLFN11 as a predictive biomarker for chemotherapy efficacy, no significant association was found between SLFN11 expression and clinical outcomes in PDAC. Further studies with larger cohorts and more detailed staging are needed to clarify the potential utility of SLFN11 as a therapeutic biomarker in PDAC.

Keywords Pancreatic ductal adenocarcinoma · SLFN11 · Immunohistochemistry · Chemotherapy · Biomarker · Prognosis

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the malignancies with the poorest prognosis, with a 5-year survival rate persistently < 10% (Siegel et al. 2022). Surgical resection is the only curative treatment for PDAC; however, many patients are diagnosed at an advanced stage, which makes them initially ineligible for surgery. Even among patients who undergo curative-intent surgery, recurrence occurs in approximately 80% of cases (Parikh et al. 2016; Groot et al. 2018). Recent guidelines have expanded surgical indications, recommending neoadjuvant therapy followed by surgical exploration for borderline resectable and

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some initially unresectable cases (National Comprehensive Cancer Network 2025). Recurrence is frequently observed even in resectable cases. Palliative chemotherapy becomes the sole recourse for patients with PDAC ineligible for surgical intervention, with 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and gemcitabine plus nab-paclitaxel and more recently, liposomal irinotecan-based combinations such as NALIRIFOX, being the preferred chemotherapeutic agents for the general PDAC population (Conroy et al. 2011; Von Hoff et al. 2013; Wainberg ZA et al. 2023; Nichetti F et al. 2024). Despite these advances, the prognosis remains unfavorable, with median overall survival generally limited to approximately 11–12 months in real-world settings. Furthermore, no clinically useful biomarkers are available to guide the selection of chemotherapy regimens, predict their efficacy, or forecast outcomes.

In the 2010s, Schlafen family member 11 (SLFN11) garnered attention as a marker for predicting the prognosis and effectiveness of chemotherapy in various cancers, including small cell lung cancer, ovarian cancer, Ewing sarcoma, and triple-negative breast cancer (Barretina et al. 2012; Murai et al. 2016; Zoppoli et al. 2012). High SLFN11 expression has been reported to correlate with increased sensitivity to DNA-damaging agents (DDAs), leading to better treatment responses, whereas low SLFN11 expression is associated with chemotherapy resistance and poorer survival outcomes in these cancers (Coussy et al. 2020; Lok et al. 2017; Takashima et al. 2021b). The SLFN family of proteins is expressed in mammals, and five SLFNs have been identified in humans, which are involved in regulating cell proliferation, inducing immune responses, and regulating viral replication (Liu et al. 2018). SLFN11, a member of this protein family, is expressed only in humans and has 901 amino acid residues and a putative DNA/RNA helicase domain at the C-terminus (Liu et al. 2018). Its expression is positively associated with the efficacy of DDAs, including platinum-based drugs, topoisomerase I and II inhibitors, alkylating agents, and DNA synthesis inhibitors, in breast cancer, lung cancer, ovarian cancer, gastric cancer, and colorectal cancer (Coussy et al. 2020; Shee et al. 2019; Takashima et al. 2021b; Tian et al. 2014). SLFN11 has also been reported in prostate cancer cell lines with respect to increased sensitivity to radiotherapy (Kaur et al. 2019). DDAs include drugs used for treating pancreatic cancer, such as oxaliplatin, irinotecan, and gemcitabine (Murai et al. 2019). Several independent groups have reported a correlation between SLFN11 expression, assessed by immunohistochemistry, and increased sensitivity to DDAs in various cancers. These findings highlight the utility of immunohistochemical evaluation for predicting chemotherapy response (Ballestrero et al. 2017; Coussy et al. 2020; Deng et al. 2015; Hamada et al. 2022; Kagami et al. 2020; Lok et al. 2017; Takashima et al. 2021a, b; Taniyama et al. 2022; Winkler et al. 2021).

SLFN11 expression is absent in normal pancreatic tissue but is observed in approximately 24% of patients with PDAC (Takashima et al. 2021a). The reason for this selective expression pattern is unclear. SLFN11 may be upregulated during tumorigenesis in specific subtypes of PDAC or in response to microenvironmental factors. Some studies have shown that epigenetic regulation, such as promoter methylation, may suppress SLFN11 expression in various cancers. This could explain the low detection rate in PDAC (Lok et al. 2017; Takashima et al. 2021b). Given that SLFN11 expression is associated with chemotherapy sensitivity in multiple cancers, determining whether its expression affects PDAC prognosis is crucial. Therefore, this study aimed to evaluate the clinical significance of SLFN11 expression in PDAC.

Materials and methods

Patients

This was a single-center, retrospective, observational cohort study that included patients with unresectable metastatic (UR-M), unresectable locally advanced (UR-LA), and borderline resectable (BR) pancreatic cancer, classified according to the National Comprehensive Cancer Network guidelines (National Comprehensive Cancer Network 2025). The patients had preserved tissue or surgical remnant specimens obtained via endoscopic ultrasound-guided fine-needle aspiration or tumor biopsy before the initiation of chemotherapy or chemoradiotherapy (CRT) as the initial treatment at Hokkaido University Hospital between January 2012 and December 2021.

Immunohistochemical staining

Eligible specimens were subjected to immunohistochemical staining at a 1:50 dilution using an anti-SLFN11 mouse monoclonal antibody (D-2, #sc-515071, Santa Cruz Biotech, USA). Detailed information about the staining procedure employed in this study is provided in Supplemental Table 1.

Immunohistochemical analysis

SLFN11 expression levels were assessed semiquantitatively by a gastroenterologist and a pathologist who were blinded to the clinicopathological data and patient outcomes. The expression levels were quantified using the histo-score (H-score), which was calculated as follows: H-score = (%

of cells 3+) × 3 + (% of cells 2+) × 2 + (% of cells 1+) (Supplementary Fig. 1). Interobserver discrepancies were resolved through consensus review. Cases were considered to have SLFN11 expression if the median H-score was ≥ 1.

Survival analysis

The association between H-scores and patient outcomes, specifically overall survival (OS) and progression-free survival (PFS), was analyzed. OS was defined as the number of days from the initiation of therapy to death from any cause, and PFS was defined as the number of days from treatment initiation until documented disease progression or death from any cause.

Statistical analysis

The relationships between clinicopathological factors and SLFN11 expression levels were assessed using Mann–Whitney's U, chi-squared, or Fisher's exact test. PFS and OS, along with their 95% confidence intervals (CI), were estimated using the Kaplan–Meier method. Between-group differences were evaluated with the log-rank test. Cox regression analysis was performed to determine the hazard ratios (HR). All statistical analyses were performed using JMP Pro version 17.0.0 software (SAS Institute Inc., Cary, NC, USA), with p-values < 0.050 indicating statistical significance.

Ethics

The study protocol received approval from the Institutional Review Board of Hokkaido University Hospital, Sapporo, Japan (Approval No: 020–0503), and it was publicly announced on the hospital's website (https://www.huhp.hokudai.ac.jp/). The requirement for informed consent was waived due to the retrospective nature of the study. This research was conducted in accordance with the Declaration of Helsinki and the STROBE statement.

Results

Clinicopathological backgrounds

A total of 158 patients with pancreatic cancer were included in this study. Of the 158 cases, 85 were classified as unresectable metastatic (UR-M), 15 as borderline resectable (BR), and 58 as unresectable locally advanced (UR-LA) (Figs. 1 and 2). Detailed clinicopathological data for each group are presented in Tables 1 and 2.

Immunohistochemical staining

In total, 158 samples from metastatic and locally advanced cases were immunostained. Consistent with prior studies, our results revealed nonstained regions in normal pancreatic gland tissues, with staining observed exclusively in tumor gland ducts. Staining was present in 54.4% of cases, with a median H-score of 1 (range: 0–280) (Supplementary Fig. 2). H-scores were compared among the three groups to assess their association with disease progression (Fig. 3). The results showed that the H-score was significantly higher in metastatic cases, corresponding to more advanced disease progression.

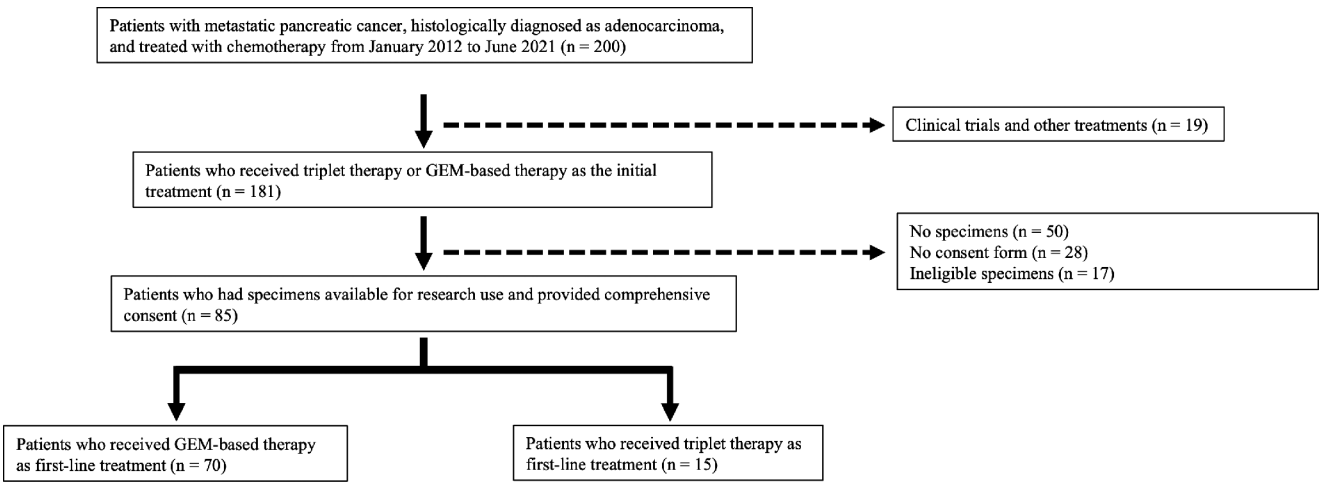

Fig. 1 Diagram of unresectable metastatic (UR-M) cases. A total of 85 patients with metastatic pancreatic cancer were included. Among them, 70 patients were treated with GEM-based therapy (including gemcitabine monotherapy, erlotinib combination therapy, and nab-paclitaxel combination therapy) as first-line treatment, and 15 patients received triplet therapy (including FOLFIRINOX and OX-IRIS) as first-line treatment. FOLFIRINOX: 5-fluorouracil, irinotecan, and oxaliplatin; OX-IRIS: S-1, irinotecan, and oxaliplatin

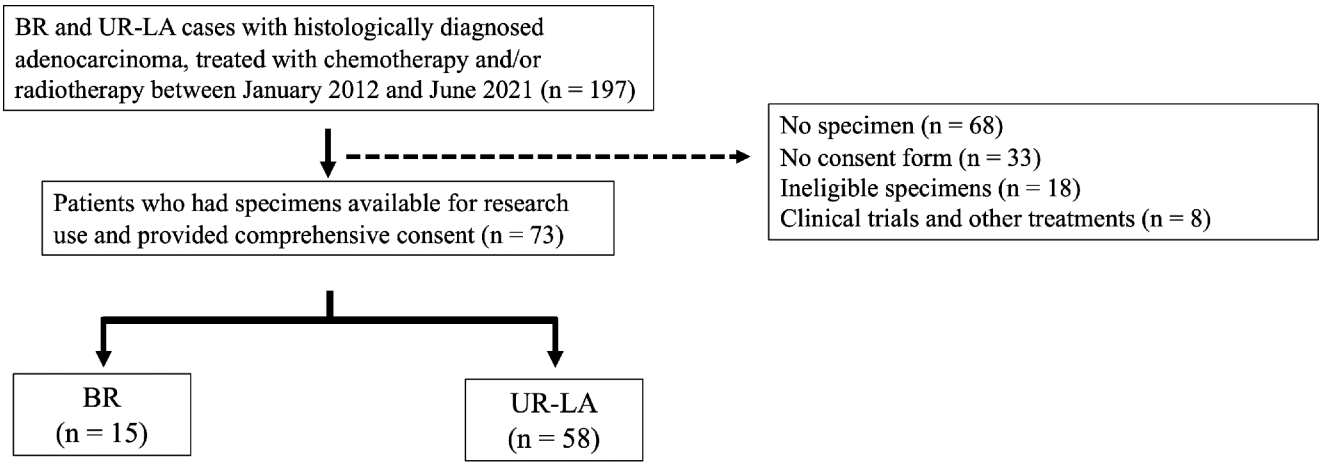

Fig. 2 Diagram of borderline resectable (BR) and unresectable locally advanced (UR-LA) cases. A total of 15 BR and 58 UR-LA cases were included

Table 1 Characteristics of metastatic cases

		GEM-based therapy, *n* (%)			Triplet therapy, *n* (%)		
		SLFN11-positive *N*=37	SLFN11-negative *N*=33	*p*-value	SLFN11-positive *N*=11	SLFN11-negative *N*=4	*p*-value
Age	Median (range)	71 (39–80)	68 (49–80)	0.104	67 (41–72)	65 (56–74)	0.744
Sex	Male	20 (54.1)	12 (36.4)	0.138	7 (63.6)	3 (75.0)	0.680
	Female	17 (46.0)	21 (63.6)		4 (36.4)	1 (25.0)	
First-line regimen	GEM	10 (27.0)	5 (15.1)	0.177	-	-	1.00
	GEM+Erlo	-	2 (6.1)		-	-	
	GEM+nab-PTX	27 (73.0)	26 (78.8)		-	-	
	FOLFIRINOX	-	-		7 (63.6)	2 (50.0)	
	OX-IRIS	-	-		4 (36.4)	2 (50.0)	
ECOG PS	0	16 (43.2)	11 (33.3)	0.559	7 (63.6)	3 (75.0)	1.00
	1	19 (51.4)	20 (60.6)		4 (36.4)	1 (25.0)	
	2	2 (5.4)	1 (3.0)		0 (0)	0 (0)	
	3	-	1 (3.0)		0 (0)	0 (0)	
Primary tumor lesion	Head	13 (35.1)	17 (51.5)	0.227	3 (27.3)	3 (75.0)	0.2352
	Body and tail	24 (64.9)	16 (48.5)		8 (72.7)	1 (25.0)	
Method of collection	Fine-needle aspiration	36 (97.3)	33 (100.0)	1.000	10 (90.9)	4 (100.0)	1.00
	Biopsy forceps	1 (2.7)	0 (0)		0 (0)	0 (0)	
	Surgery	0 (0)	0 (0)		1 (9.1)	0 (0)	

Abbreviations GEM, gemcitabine; Erlo, erlotinib; nab-PTX, nanoparticle albumin-bound paclitaxel; FOLFIRINOX, 5-fluorouracil, irinotecan, and oxaliplatin; OX-IRIS, S-1, irinotecan, and oxaliplatin; ECOG, Eastern Cooperative Oncology Group

Effect of the H-score on the treatment of metastatic cases

To examine the correlation between progression-free survival (PFS) and overall survival (OS) in patients with metastatic PDAC, cases were stratified by the H-score. The median PFS was 3.9 months (95% CI 2.7–5.3) in the SLFN11-positive group and 4.5 months (95% CI 2.5–6.2) in the SLFN11-negative group. The hazard ratio (HR) was 0.84 (95% CI 0.53–1.35) with a *p*-value of 0.47 (Fig. 4a). The median OS was 8.8 months (95% CI 6.1–14.5) in the SLFN11-positive group and 9.0 months (95% CI 6.4–14.0) in the SLFN11-negative group. The HR was 0.71 (95% CI 0.45–1.14) with a *p*-value of 0.16 (Fig. 4b).

The patients were then divided into two groups based on their treatment regimen: the gemcitabine group, which received gemcitabine alone or in combination with nanoparticle albumin-conjugated paclitaxel or erlotinib, and the triplet group, which received fluoropyrimidine, oxaliplatin, and irinotecan. The effects of each regimen on H-score expression were examined.

In the gemcitabine group, the median PFS was 3.9 months (95% CI 2.1–5.5) in the SLFN11-positive group and 4.5 months (95% CI 1.9–6.2) in the SLFN11-negative group. The HR was 0.90 (95% CI 0.54–1.51), with a *p*-value of 0.70 (Fig. 4c). The median OS was 8.1 months (95% CI 4.9–13.0) in the SLFN11-positive group and 9.0 months (95% CI 6.4–14.0) in the SLFN11-negative group. The HR was 0.78

Table 2 Characteristics of borderline resectable (BR) and unresectable locally advanced (UR-LA) cases

		BR			UR-LA		
		SLFN11-positive *N*=5	SLFN11-negative *N*=10	*p*-value	SLFN11-positive *N*=22	SLFN11-negative *N*=36	*p*-value
Age	Median (range)	68 (51–82)	69.5 (46–73)	0.854	66 (52–72)	69 (33–83)	0.008
Sex	Male	2 (40.0)	7 (70.0)	0.329	13 (59.1)	23 (63.9)	0.784
	Female	3 (60.0)	3 (30.0)		9 (40.9)	13 (36.1)	
First-line regimen	CRT arm	4 (80.0)	5 (50.0)		7 (31.8)	17 (47.2)	
	Chemotherapy	1 (20.0)	5 (50.0)	1.00	15 (68.2)	19 (52.8)	0.0045
	S-1	-	1 (20.0)		-	-	
	GEM	-	-		-	8 (42.1)	
	GEM + nab-PTX	1 (100)	4 (80.0)		10 (66.7)	10 (52.6)	
	FOLFIRINOX	-	-		3 (20)	1 (5.3)	
	OX-IRIS	-	-		2 (13.3)	-	
ECOG PS	0	2 (40.0)	8 (80.0)	0.251	12 (54.5)	17 (47.2)	0.920
	1	3 (60.0)	2 (20.0)		10 (45.5)	17 (47.2)	
	2	-	-		-	1 (2.8)	
	3	-	-		-	1 (2.8)	
Primary tumor lesion	Head	4 (80.0)	7 (70.0)	1.00	15 (68.2)	22 (61.1)	0.779
	Body and tail	1 (20.0)	3 (30.0)		7 (31.8)	14 (38.9)	
Method of collection	Fine-needle aspiration	5 (100)	10 (100)	1.00	22 (100)	36 (100)	1.00

Abbreviations BR, borderline resectable; UR-LA, unresectable locally advanced; CRT, chemoradiotherapy; GEM, gemcitabine; nab-PTX, nanoparticle albumin-bound paclitaxel; FOLFIRINOX, 5-fluorouracil, irinotecan, and oxaliplatin; OX-IRIS, S-1, irinotecan, and oxaliplatin; ECOG, Eastern Cooperative Oncology Group

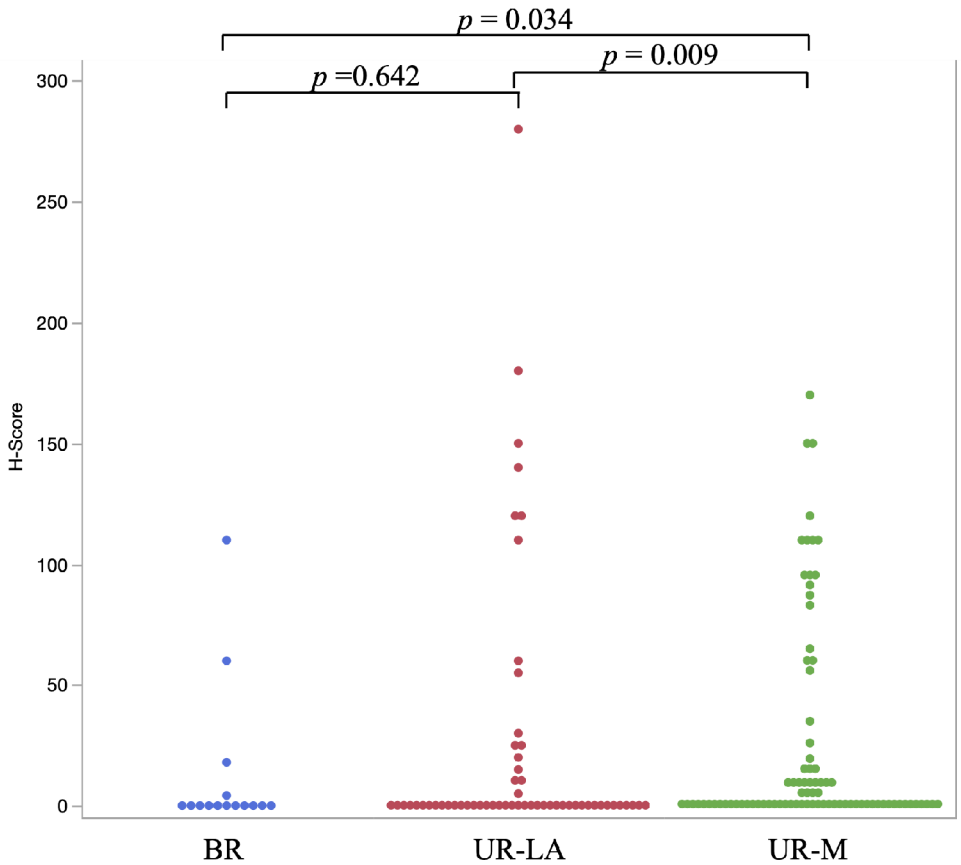

Fig. 3 Distribution of the H-scores. The H-scores of SLFN11 expression were compared among UR-M, BR, and UR-LA cases. A trend toward higher SLFN11 expression was observed in UR-M cases

(95% CI 0.47–1.31) with a *p*-value of 0.35 (Fig. 4d). In the triplet therapy group, the median PFS was 4.1 months (95% CI 1.5–16.3) in the SLFN11-positive group and 6.6 months (95% CI 0.7–13.8) in the SLFN11-negative group. The HR for this comparison was 0.64 (95% CI 0.18–2.21), with a *p*-value of 0.47 (Fig. 4e). The median OS was 14.9 months (95% CI 4.3–21.8) in the SLFN11-positive group and 14.5 months (95% CI 0.7–17.7) in the SLFN11-negative group.

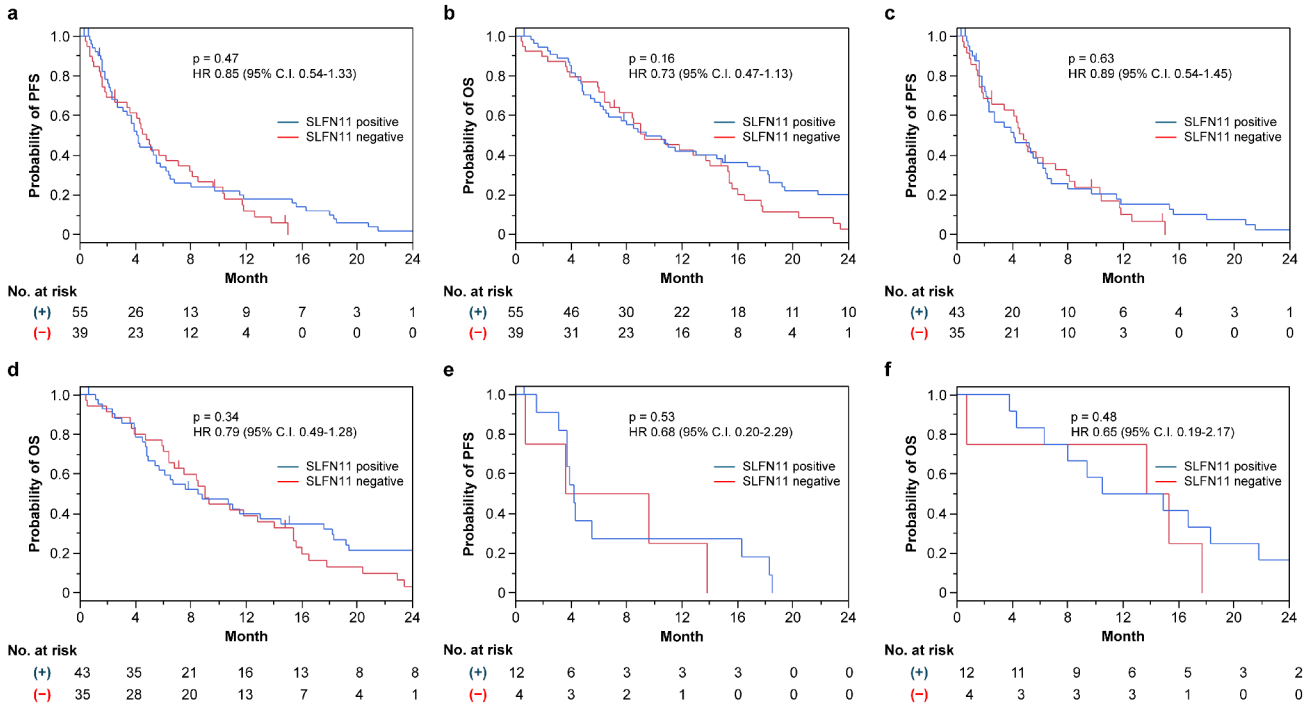

Fig. 4 Effect of the H-score on the treatment of UR-M cases. (**a**–**b**) Kaplan–Meier curves of the PFS for primary therapy and OS in 85 patients (48 in the SLFN11-positive group and 37 in the SLFN11-negative group) with metastatic pancreatic cancer. (**c**–**d**) Kaplan–Meier curves of the PFS for primary therapy and OS in 70 patients with metastatic pancreatic cancer (37 in the SLFN11-positive group and 33 in the SLFN11-negative group) who received GEM-based therapy as first-line treatment. (**e**–**f**) Kaplan–Meier curves of the PFS for primary therapy and OS in 15 patients with metastatic pancreatic cancer (11 in the SLFN11-positive group and 4 in the SLFN11-negative group) who received triplet therapy as the primary therapy

The HR was 0.59 (95% CI 0.17–2.02) with a *p*-value of 0.39 (Fig. 4f).

Effect of the H-score on treatment in UR-LA and BR cases

The PFS of patients who received CRT before the first disease progression was calculated, including the chemotherapy and surgeries performed until tumor progression. Owing to the limited number of BR cases, this study predominantly presents data on UR-LA cases. This analysis includes PFS and OS outcomes, stratified by the H-score, in a cohort of 58 patients with UR-LA.

The median PFS for all patients with UR-LA pancreatic cancer was 9.7 months (95% CI 5.2–14.9) in the SLFN11-positive group and 12.7 months (95% CI 8.8–22.9) in the SLFN11-negative group. The HR was 1.47 (95% CI 0.81–2.68), with a *p*-value of 0.20 (Fig. 5a). The median OS was 19.0 months (95% CI 10.0–24.6) in the SLFN11-positive group and 28.8 months (95% CI 10.0–32.1) in the SLFN11-negative group. The HR was 1.29 (95% CI 0.72–2.29) with a *p*-value of 0.39 (Fig. 5b). Given the limited number of patients in each treatment regimen, only data from the gemcitabine group were reported. In these patients, the median PFS was 9.3 months (95% CI 3.9–13.7) in the SLFN11-positive group and 11.8 months (95% CI 2.1–22.9) in the SLFN11-negative group. The HR was 1.60 (95% CI 0.64–3.98), with a *p*-value of 0.31 (Fig. 5c). The median OS was 15.3 months (95% CI 8.0–21.6) in the SLFN11-positive group and 12.7 months (95% CI 5.3–40.4) in the SLFN11-negative group. The HR was 0.35 (95% CI 0.65–3.37), with a *p*-value of 0.35 (Fig. 5d). Supplementary Fig. 3 shows additional Kaplan–Meier analyses for PFS and OS in all BR patients and those who received CRT for UR-LA and BR. No significant differences in survival outcomes were observed between the SLFN11-positive and SLFN11-negative groups in any of these subgroups (all *p*-values > 0.1). Although SLFN11-positive cases exhibited a trend toward longer OS in some analyses, the small sample size and wide CI preclude definitive conclusionss.

Discussion

Expression of SLFN11 in PDAC

This study represents the first investigation into SLFN11 expression in pancreatic cancer utilizing immunostaining

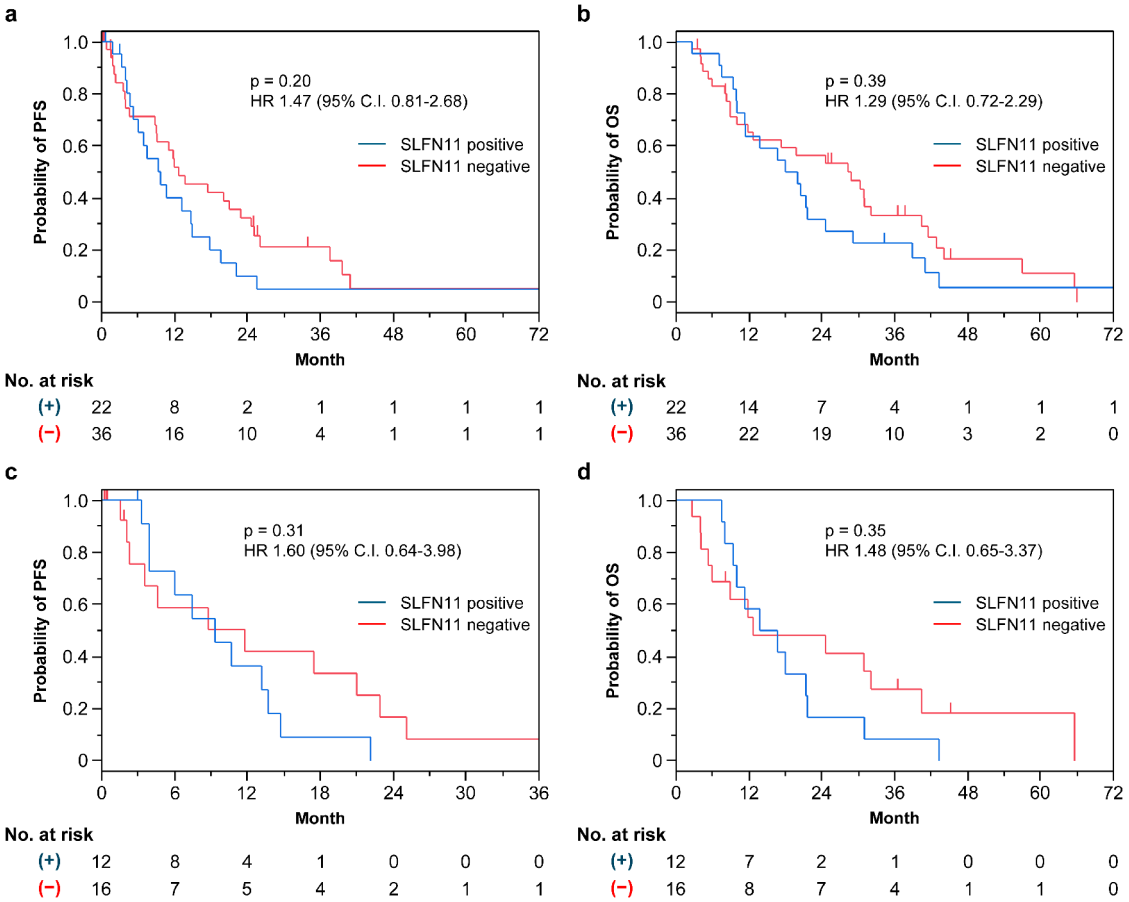

Fig. 5 Effect of the H-score on the treatment of UR-LA cases. (**a**–**b**) Kaplan–Meier curves of the PFS for primary therapy and OS in 58 patients (22 in the SLFN11-positive group and 36 in the SLFN11-negative group) with UR-LA pancreatic cancer. (**c**–**d**) Kaplan–Meier curves of the PFS for primary therapy and OS in 28 patients with UR-LA pancreatic cancer (12 in the SLFN11-positive group and 16 in the SLFN11-negative group) who received GEM-based therapy as first-line treatment

on clinical specimens and examining its correlation with chemotherapy efficacy. Most samples were derived from endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and few were obtained through other methods, yet the H-score validation was achievable. Consistent with previous studies, SLFN11 expression was not detected in normal pancreatic tissue in this study, with positivity confined solely to tumor regions (Takashima et al. 2021a). Notably, our analysis revealed that SLFN11 expression was higher in UR-M cases compared to BR and UR-LA cases, as indicated by the higher median H-score in metastatic samples. These findings suggest a potential association between increased SLFN11 expression and disease progression. The absence of SLFN11 expression in normal pancreatic tissue, as confirmed by previous studies and this investigation, supports the hypothesis that SLFN11 expression may evolve dynamically with cancer progression, potentially influencing disease trajectory and therapeutic response. A previous study on gastric cancer cell lines demonstrated an upregulation of SLFN11 expression during tumorigenesis, indicating that SLFN11 expression escalates as the cancer advances (Takashima et al. 2021b). In our study, SLFN11 expression was observed in 55.7% of PDAC cases, which is higher than the previously reported prevalence of 24% (Takashima et al. 2021a). This discrepancy may be due to differences in immunohistochemical techniques, antibody sensitivity, or patient cohort characteristics. Importantly, our study included a larger number of patients than the previous report, which strengthens the statistical reliability of our findings and provides a more comprehensive estimate of SLFN11 prevalence in PDAC. Alternatively, the previous study was based on surgical cases, while the increase in the H-score in relation to stage in our study could have led to a higher positivity rate. Further validation using alternative methods, such as mRNA expression analysis and DNA methylation profiling, may help clarify the true prevalence of SLFN11 expression in PDAC. Since SLFN11 expression has been reported to be associated with increased sensitivity to DNA-damaging agents (DDAs) in various cancers, we hypothesized that SLFN11 expression in PDAC would

correlate with improved chemotherapy efficacy. However, contrary to our expectations, no significant correlation was observed between SLFN11 expression and OS or PFS. These findings suggest that additional factors, such as tumor heterogeneity and alternative mechanisms of drug resistance, may play a critical role in determining treatment outcomes in PDAC. This study did not establish a clear predictive role for SLFN11 in chemotherapy response in PDAC.

Relevance of SLFN11 in the PDAC treatment

The predominant treatment protocols for pancreatic cancer currently include FOLFIRINOX and gemcitabine plus nab-paclitaxel regimens, which utilize chemotherapeutic agents such as oxaliplatin, irinotecan, and gemcitabine. A previous study suggested that SLFN11 expression may predict the effectiveness of DDAs, such as platinum compounds, topoisomerase inhibitors, and gemcitabine (Shee et al. 2019). However, in this study, no significant correlation was observed between SLFN11 expression and treatment efficacy, indicating that SLFN11 may not serve as a predictive biomarker in PDAC for these agents. This discrepancy highlights the need for further investigations into the role of SLFN11 as a predictive biomarker in the treatment of pancreatic cancer.

Previous reports have indicated that SLFN11 expression is typically low or absent in PDAC compared with other carcinomas, as observed in mRNA studies using preclinical models (Winkler et al. 2021). In the present study, the median H-score for SLFN11 was also low, with a median of 1, suggesting the absence of a significant correlation with favorable chemotherapy outcomes. Notably, higher H-scores were observed in metastatic cases, implying that increased SLFN11 expression might correlate with advanced disease stages. However, this study did not assess the detailed stages of the disease or enumerate metastases, which remain a critical area for future investigation.

Although the potential for SLFN11 to modulate the efficacy of poly(ADP-ribose) polymerase (PARP) inhibitors has been suggested in ovarian cancer (Willis et al. 2021), we cannot evaluate the relationship among SLFN11 expression, PARP inhibitor response, and breast cancer susceptibility (*BRCA*) mutations because of the recent approval of olaparib for PDAC. Consequently, the implications of SLFN11 for the therapeutic efficacy of PARP inhibitors in pancreatic cancer remain unknown.

Limitations

This single-center, retrospective study analyzed a small number of cases, which may introduce selection bias. In addition, the use of small specimens primarily collected via EUS-FNA raises concerns that only a portion of the tumor mass was sampled. This approach could potentially miss subclonal variations among tumors because these may not be fully represented in the samples obtained (Willis et al. 2021). Furthermore, SLFN11 staining could not be performed on all tumor sections due to the sample acquisition method, limiting the assessment of intratumoral heterogeneity. Additionally, SLFN11 expression was detected in 55.7% of the cases, which limited the statistical power to evaluate its correlation with clinical outcomes, such as OS and PFS. The heterogeneity of the patient cohort, including differences in tumor stage (locally advanced, borderline resectable, and metastatic PDAC) and treatment regimens (FOLFIRINOX, gemcitabine-based therapy, and CRT), may have influenced OS and PFS independently of SLFN11 expression. Moreover, treatment duration and potential adverse effects were not fully accounted for in our analysis, which could impact survival outcomes.

Another important limitation is the small number of patients who received FOLFIRINOX. FOLFIRINOX contains two DDAs (oxaliplatin and irinotecan), making it particularly relevant for evaluating the predictive value of SLFN11. However, our ability to assess the relationship between SLFN11 expression and the efficacy of this regimen was limited due to the relatively low number of patients treated with FOLFIRINOX in this cohort. Future studies with a larger number of patients treated with FOLFIRINOX are needed to determine whether SLFN11 can serve as a predictive biomarker for response to this treatment.

Additionally, the wide variability in treatment regimens among patients in this study might have contributed to the difficulty in establishing a clear correlation between SLFN11 expression and survival outcomes. Differences in treatment duration, intensity, and potential adverse effects were not fully accounted for. These factors may have confounded the relationship between SLFN11 expression and patient prognosis. Future prospective studies with a more homogeneous cohort and standardized treatment protocols are needed to minimize these confounding variables. Additionally, many patients were excluded due to unavailable tissue specimens or lack of consent, which may have introduced selection bias and affected the generalizability of the results.

However, it is notable that all biopsy specimens were obtained before treatment initiation, ensuring that SLFN11 expression was not influenced by prior chemotherapy or other therapeutic interventions. Future studies with larger, more homogeneous cohorts and prospective designs are

needed to further elucidate the role of SLFN11 as a predictive biomarker in PDAC.

Conclusion

To the best of our knowledge, this is the first study to evaluate SLFN11 expression intensity in PDAC using FNA biopsies to examine its correlation with prognosis and pharmacological outcomes. Despite the limited sample size inherent to FNA, these small clinical specimens proved adequate for SLFN11 evaluation. However, this study did not reveal any significant association between SLFN11 expression levels and clinical outcomes in pancreatic cancer, challenging the potential utility of SLFN11 as a prognostic or therapeutic biomarker. Although other carcinomas have shown a positive correlation between SLFN11 expression and the efficacy of DAAs, a larger, more comprehensive study is warranted to substantiate these findings in PDAC.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval This study was approved by the Institutional Review Board of Hokkaido University Hospital, Sapporo, Japan (Approval No: 020–0503).

Consent to participate The requirement for informed consent was waived by the Institutional Review Board of Hokkaido University Hospital, Sapporo, Japan, due to the retrospective nature of the study.

Consent to publish Not applicable.

Competing interests The authors declare no competing interests.

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