CANCER DIAGNOSIS & PROGNOSIS
3: 311-319 (2023) doi: 10.21873/cdp.10217

Clinicopathological and Prognostic Relevance of Tumoral Suppression of Tumorigenicity 2 Expression in Patients With Surgically Resected Pancreatic Carcinoma

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Abstract. *Background/Aim: The interleukin (IL)-33/suppression of tumorigenicity 2 (ST2) pathway promotes cancer development and remodels the tumor microenvironment. However, the role of tumoral ST2 expression remains controversial in some solid malignancies. In this study, we have investigated the clinicopathological and prognostic relevance of tumoral ST2 expression in patients with resected pancreatic carcinoma after neoadjuvant chemoradiotherapy. Patients and Methods: We analyzed data from 76 patients with surgically resected pancreatic ductal adenocarcinoma after neoadjuvant chemoradiotherapy, between 2009 and 2018. Tissue microarrays were constructed and immunohistochemical analysis was performed for ST2. Associations between variables were analyzed using chi-square tests. Disease-specific survival (DSS) and disease-free survival (DFS) were analyzed using log-rank tests. Results: High expression of ST2, which was observed in 43 patients (57%), was more frequent in patients with high T status (p=0.002), lymphatic invasion (p=0.049), and ≤50% of tumor cells destroyed by chemoradiotherapy (p=0.043; Evans grade I-IIA vs. IIB). In stage I patients, DFS was significantly lower in patients with high ST2 expression (median, 10.6 months) than in those with low ST2 expression (median, 43.4 months; p=0.046). Conclusion: High tumoral ST2 expression is associated with high T status, lymphatic invasion, and lower histopathological response grade in patients with pancreatic carcinoma after neoadjuvant chemoradiotherapy.*

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Key Words: Suppression of tumorigenicity 2, pancreatic carcinoma, prognosis.

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, is expressed in endothelial cells, fibroblasts, and epithelial cells both during homeostasis and inflammation (1, 2). The human suppression of tumorigenicity 2 (*ST2*) gene encodes for three splice variants; soluble ST2 (sST2), transmembrane ST2 (ST2L), and variant ST2 (ST2V) (1). The IL-33 receptor is a heterodimeric complex consisting of ST2L and IL-1 receptor accessory protein (2). ST2 is expressed on the membrane of a variety of immune cell types, such as T helper (Th)2 lymphocytes, group 2 innate lymphoid cells, macrophages, mast cells, basophils, eosinophils, dendritic cells, and natural killer (NK) cells (3). IL-33/ST2 signaling is crucial for tissue repair, type 2 immunity, allergic and non-allergic inflammation, and viral infection (3).

Recent studies have shown associations between the biological role of the IL-33/ST2 axis and progression of malignant tumors. However, the significance of tumoral ST2 expression remains controversial in some malignancies (4). In this study, we investigated the clinicopathological and prognostic relevance of tumoral ST2 expression in patients with resected pancreatic carcinoma after neoadjuvant chemoradiotherapy.

Patients and Methods

Patients. This retrospective study was approved by the Institutional Review Board of Kagawa University (approval number: 2020-090) and Shimane University (approval number: 20221012-1). All experiments were performed in accordance with relevant guidelines and regulations.

We reviewed records from patients with invasive pancreatic ductal adenocarcinoma who had undergone pancreatic resection after chemoradiotherapy at Kagawa University between 2009 and

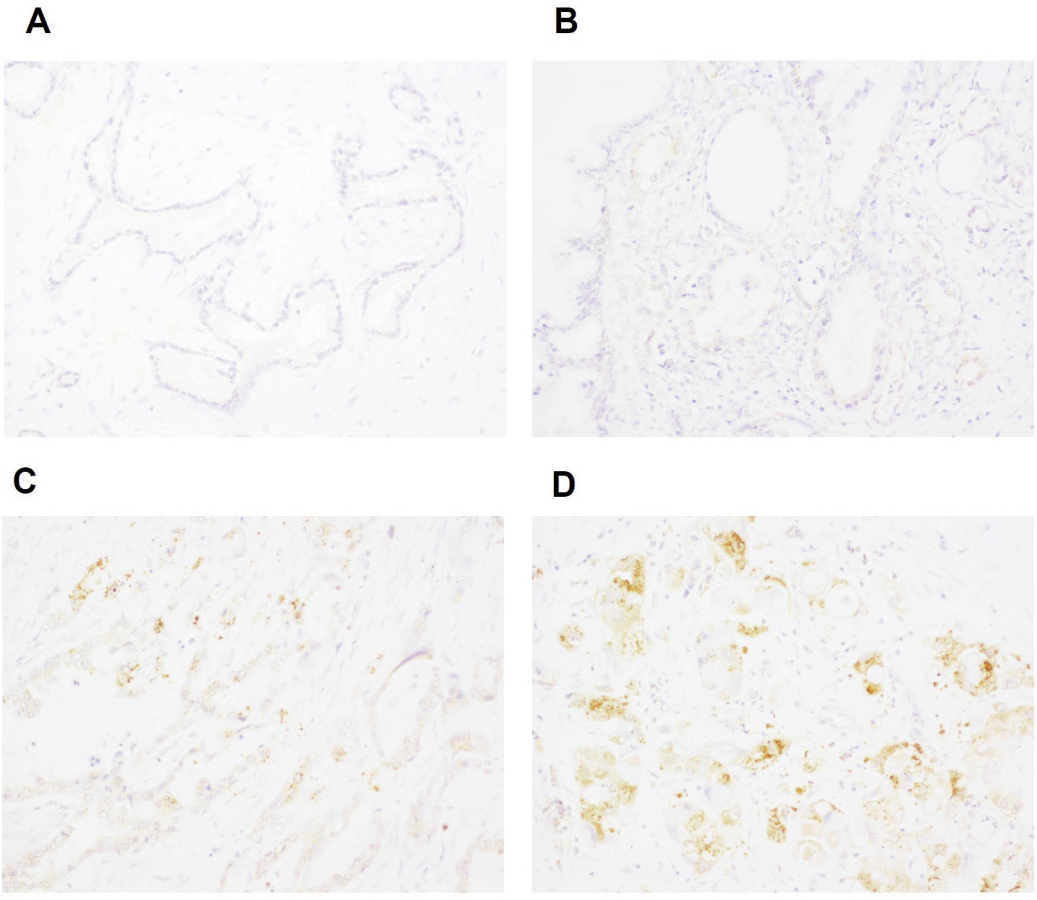


Figure 1. *Evaluation of suppression of tumorigenicity 2 (ST2) expression in pancreatic carcinomas with immunohistochemistry using tissue microarrays. Examples of (A) total score 0, (B) total score 2 (distribution score 1, intensity score 1), (C) total score 4 (distribution score 2, intensity score 2), and (D) total score 6 (distribution score 3, intensity score 3).*

2018 (n=81). After excluding patients with positive surgical margin (n=3) or ≤10% residual tumor after chemoradiotherapy (n=2), 76 patients were eventually included in our analysis. Clinical data were collected from a prospectively maintained pancreatic carcinoma database. Tumor, node, metastasis (TNM) stages were assigned based on the eighth edition of the American Joint Committee on Cancer TNM Staging Manual (5).

Immunohistochemistry using tissue microarrays and scoring. Formalin-fixed, paraffin-embedded tumor specimens from patients who met the inclusion criteria were used for tissue microarray construction. One representative main tumor site was marked on Hematoxylin & Eosin-stained slides. Using a tissue array (Tissue Microprocessor KIN-2, Azumaya, Japan), cylindrical 3-mm tissue cores from the corresponding paraffin block were arrayed on the recipient block.

Four-μm sections from stored formalin-fixed, paraffin-embedded tumor blocks were stained with an anti-ST2 rabbit polyclonal antibody (Proteintech, Rosemont, IL, USA; diluted at 1:100) using a BOND-III automated immunohistochemical slide staining system (Leica Biosystems). We used diaminobenzidine as chromogen and hematoxylin as nuclear counterstain.

Using an Olympus BX53 upright microscope (Olympus Corporation, Tokyo, Japan) with a standard 22-mm-diameter eyepiece, anti-ST2 stained tumor slides were reviewed by a pathologist (M.N.), who was blinded to patient outcomes. Immunohistochemistry scoring was based on the distribution and intensity of the staining in the main tumor. Distribution was scored based on a scale of 0 (0-25%), 1 (26-50%), 2 (51-75%), or 3 (76-100%) according to the percentage of positive cells in each core. Staining intensity was scored as 0 (no expression), 1 (mild expression), 2 (intermediate expression), or 3 (strong expression). Distribution and intensity scores were summed in a total score (0-6) for each patient (Figure 1). The score of ST-2 expression was dichotomized as low or high according to the median value (median: 2, range=0-6). When the score was equal or greater than the median, expression was classified as high.

Statistical analysis. Associations between variables were analyzed using chi-square tests for categorical variables. Disease-specific survival (DSS) was defined as the time from resection to the date of death related to pancreatic carcinoma or last follow-up. Disease-free survival (DFS) was defined as the time from

Table I. *Clinicopathologic characteristics and their associations with ST2 expression.*

Variables	All patients	ST2 expression				*p*-Value	
		Low		High			
	N	N	%	N	%		
Age, years						0.93	
>70	35	15	43	20	57		
≥70	41	18	44	23	56		
Sex						0.67	
Female	39	16	41	23	59		
Male	37	17	46	20	54		
Tumor location						0.40	
Head/neck	50	20	40	30	60		
Body/tail	26	13	50	13	50		
Pathological T category						**0.002**	(T1 *vs*. T2-3)
T1	25	17	68	8	32		
T2	41	12	29	29	71		
T3	10	4	40	6	60		
Pathological N category						0.44	(N0 *vs*. N1-2)
N0	43	17	40	26	60		
N1	28	14	50	14	50		
N2	5	2	40	3	60		
Pathological stage						0.57	(I *vs*. II-III)
Stage I	42	17	40	25	60		
Stage II	29	14	48	15	52		
Stage III	5	2	40	3	60		
Histologic grade						0.19	(G1 *vs*. G2-3)
G1	35	18	51	17	49		
G2	29	11	38	18	62		
G3	12	4	33	8	67		
Lymphatic invasion						**0.049**	
Negative	34	19	56	15	44		
Positive	42	14	33	28	67		
Vascular invasion						0.14	
Negative	11	7	64	4	36		
Positive	65	26	40	39	60		
Perineural invasion						0.42	
Negative	11	6	55	5	45		
Positive	65	27	42	38	58		
Evans' classification						**0.043**	(I-IIA *vs*. IIB)
Grade I	4	2	50	2	50		
Grade IIA	49	17	35	32	65		
Grade IIB	23	14	61	9	39		

Significant *p*-values are shown in bold.

resection to disease recurrence. DSS and DFS were estimated using the Kaplan–Meier method, and non-parametric group comparisons were performed using the log-rank test. All statistical tests were two-sided, with the significance level set at 5%. Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 23.0; IBM, Armonk, NY, USA).

Results

Patient characteristics and association of clinicopathological factors with patient outcomes. The clinicopathological characteristics of all patients who had undergone pancreatic resection after chemoradiotherapy (n=76) are summarized in Table I. During the study period, 52 patients recurred and 33 died from pancreatic carcinoma-related causes. The median duration of follow-up for patients who were alive at the time of the last follow-up was 27 months (range=5-113 months).

Univariate analyses of all patient outcomes (DSS and DFS) with clinicopathological factors are shown in Table II. None of the clinicopathological factors were associated with DSS. High T status (p=0.041), lymph node metastasis (p=0.008), pathological stage (p=0.030), and perineural

Table II. *Association between clinicopathologic characteristics and clinical outcomes in all patients.*

Variables	N	Disease-specific survival			Disease-free survival		
		Median (months)	95%CI	*p*-Value	Median (months)	95%CI	*p*-Value
Age, years				0.60			0.12
>70	35	45.3	32.4-58.3		15.2	11.6-18.7	
≥70	41	58.8	19.5-98.0		23.4	13.2-33.5	
Sex				0.73			0.13
Female	39	45.3	21.1-69.6		13.9	7.7-20.2	
Male	37	46.4	24.8-67.9		19.2	12.0-26.4	
Tumor location				0.68			0.43
Head/neck	50	45.3	23.8-66.9		15.7	11.2-20.2	
Body/tail	26	46.4	21.0-71.8		23.4	12.5-34.2	
T category				0.10			**0.041**
T1	25	57.0	37.5-76.6		24.0	0.6-47.3	
T2-3	51	37.8	30.6-45.2		12.1	7.5-16.7	
N category				0.097			**0.008**
N0	43	58.8	43.2-74.3		26.1	9.5-42.8	
N1-2	33	34.2	25.8-42.6		12.1	7.9-16.2	
Pathological stage				0.22			**0.030**
Stage I	42	57.0	43.9-70.1		24.0	7.9-40.0	
Stage II-III	34	36.2	28.9-43.5		12.1	7.2-16.9	
Histologic grade				0.90			0.27
G1	35	46.4	28.5-64.3		23.4	15.1-31.7	
G2-3	41	37.9	14.2-61.5		15.6	11.2-19.9	
Lymphatic invasion				0.64			0.16
Negative	34	58.8	28.1-89.4		23.7	13.4-34.1	
Positive	42	38.7	26.6-50.7		13.9	9.0-18.9	
Vascular invasion				0.42			0.051
Negative	11	62.3	Not met		44.1	9.8-78.3	
Positive	65	45.3	33.9-56.7		15.7	11.7-19.7	
Perineural invasion				0.10			**0.001**
Negative	11	Not met	Not met		Not met	Not met	
Positive	65	38.7	27.7-49.6		15.6	11.6-19.5	
Evans' classification				0.23			0.17
Grade I-IIA	53	38.7	25.6-51.7		15.7	11.2-20.2	
Grade IIB	23	57.0	19.0-95.0		36.8	0.0-76.0	
ST2 expression				0.70			0.067
Low	33	46.4	28.3-64.5		23.7	16.0-31.5	
High	43	45.3	19.6-71.0		11.7	9.8-13.6	

Significant *p*-values are shown in bold.

invasion (p=0.001) were significantly associated with worse DFS. Univariate analyses of DFS with clinicopathological factors in stage I patients showed that perineural invasion (p=0.004) was significantly associated with worse DFS (Table III).

Association between ST2 expression and patient characteristics. High expression of ST2 was observed in 43 patients (57%). Associations between patient characteristics and ST2 expression are summarized in Table I. High expression of ST2 was more frequent in patients with high pathological T status (T1 *vs*. T2-3; p=0.002), in those with lymphatic invasion (p=0.049), and in those with ≤50% of tumor cells destroyed by chemoradiotherapy compared to those with >50% of tumor cells destroyed (Evans grade I-IIA *vs*. IIB; p=0.043) (Figure 2).

Association between ST2 expression and patient outcome. ST2 expression was not associated with DSS (p=0.70) (Table II). In all patients, DFS was lower in patients with high ST2 expression (median 11.7 months) than in those with low ST2 expression (median 23.7 months) (Figure 3A), although this difference was not statistically significant (p=0.067). In stage I patients, DFS was significantly lower in patients with high ST2 expression (median 10.6 months) than in those with low ST2 expression (median 43.4

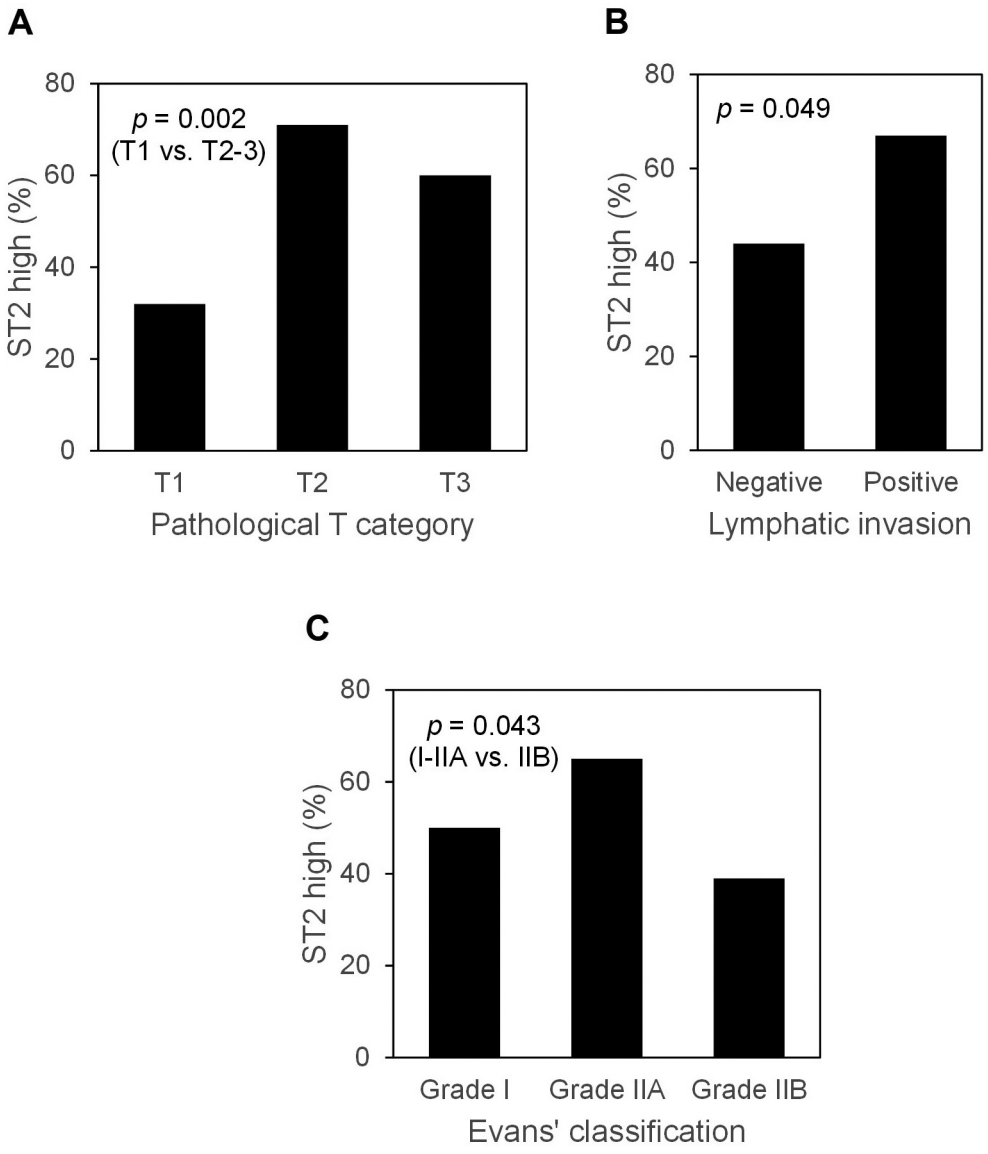


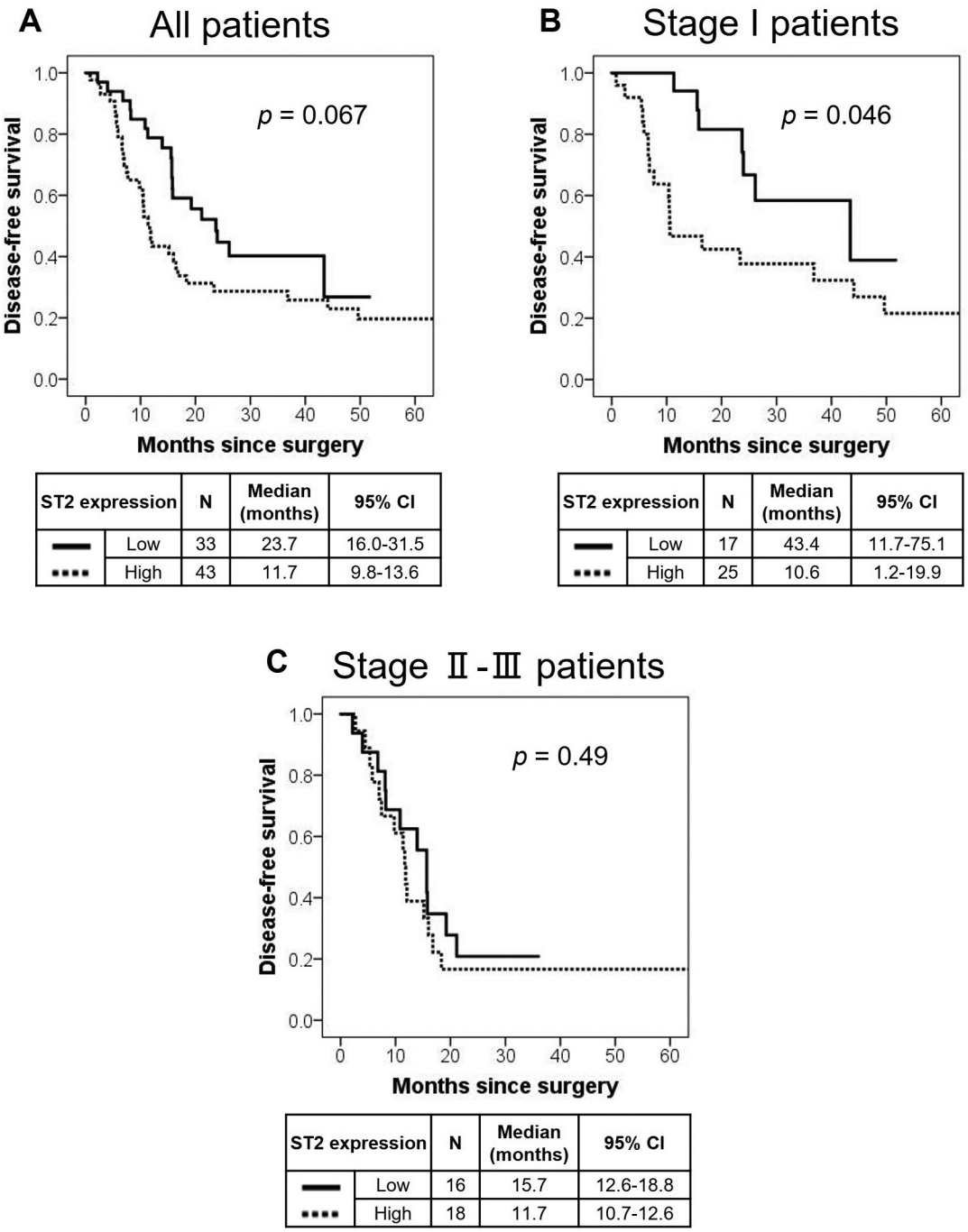
Figure 2. *Association between suppression of tumorigenicity 2 (ST2) expression and patient characteristics in patients with pancreatic carcinoma who underwent neoadjuvant chemoradiotherapy. High expression of ST2 was more frequent in (A) patients with a high pathological T status (T1 vs. T2-3; p=0.002), (B) those with lymphatic invasion (p=0.049), and those with ≤50% of tumor cells destroyed by chemoradiotherapy compared to those with >50% of tumor cells destroyed (Evans grade I-IIA vs. IIB; p=0.043).*

months; p=0.046) (Figure 3B and Table III). In stage II-III patients, ST2 expression was not associated with DFS (p=0.49) (Figure 3C).

Discussion

In this study, immunohistochemical analyses of tumoral ST2 expression were performed with the aim to interrogate its clinicopathological and prognostic relevance in patients with resected invasive pancreatic ductal adenocarcinoma who were submitted to neoadjuvant chemoradiotherapy. We have demonstrated that tumoral ST2 expression was associated with high T status, lymphatic invasion, and lower histopathological response grade after neoadjuvant chemoradiotherapy in patients with pancreatic carcinoma, while it was also associated with lower DFS in stage I patients.

The IL-33/ST2 signaling pathway promotes cancer development and remodels the tumor microenvironment. Therefore, the IL-33/ST2 pathway may be a potential prognostic marker and a possible immunotherapeutic target.



ST2 expression		N	Median (months)	95% CI
▬	Low	33	23.7	16.0-31.5
▪▪▪▪	High	43	11.7	9.8-13.6

ST2 expression		N	Median (months)	95% CI
▬	Low	17	43.4	11.7-75.1
▪▪▪▪	High	25	10.6	1.2-19.9

ST2 expression		N	Median (months)	95% CI
▬	Low	16	15.7	12.6-18.8
▪▪▪▪	High	18	11.7	10.7-12.6

Figure 3. *Association between suppression of tumorigenicity 2 (ST2) expression and disease-free survival (DFS) in patients with pancreatic carcinoma who underwent neoadjuvant chemoradiotherapy. (A) In all patients, DFS was lower in patients with high ST2 expression (median, 11.7 months) than in those with low ST2 expression (median, 23.7 months), although without statistical significance (p=0.067). (B) In stage I patients, DFS was significantly lower in patients with high ST2 expression (median, 10.6 months) than in those with low ST2 expression (median, 43.4 months; p=0.046). (C) In stage II-III patients, ST2 expression was not associated with DFS (p=0.49).*

However, how the IL-33/ ST2 axis is involved in the development of carcinomas remains unclear. ST2 is expressed in various types of immune and tumor cells. IL-33 is secreted from stromal cells, endothelial and epithelial cells, and tumor cells including tumor-initiating cells (4, 6). In some studies, the IL-33/ST2 axis has been reported as a pro-tumoral effector

Table III. *Association between clinicopathologic characteristics and disease-free survival in stage I patients.*

Variables	N	Disease-free survival		
		Median (months)	95%CI	*p*-Value
Age, years				0.48
>70	15	15.6	0.0-32.2	
≥70	27	26.1	8.8-43.5	
Sex				0.22
Female	19	24.0	0.0-49.9	
Male	23	49.6	0.0-100.3	
Tumor location				0.91
Head/neck	29	26.1	4.6-47.7	
Body/tail	13	23.7	0.0-51.0	
T category				0.42
T1	19	43.4	0.0-90.9	
T2-3	23	16.4	0.0-37.3	
Histologic grade				0.99
G1	22	26.1	11.2-41.0	
G2-3	20	16.4	0.0-33.3	
Lymphatic invasion				0.73
Negative	27	24.0	12.4-35.6	
Positive	15	44.1	0.0-90.1	
Vascular invasion				0.074
Negative	10	44.1	42.7-45.4	
Positive	32	23.4	13.9-32.9	
Perineural invasion				**0.004**
Negative	9	Not met	Not met	
Positive	33	23.4	13.2-33.5	
Evans' classification				0.76
Grade I-IIA	28	23.7	13.5-33.9	
Grade IIB	14	36.8	0.0-77.8	
ST2 expression				**0.046**
Low	17	43.4	11.7-75.1	
High	25	10.6	1.2-19.9	

Significant *p*-values are shown in bold.

pathway, by promoting expansion of immune suppressive cells, such as myeloid-derived suppressor cells or regulatory T cells. In contrast, the IL-33/ST2 axis may also promote formation of an antitumoral microenvironment by recruiting immune cells such as CD8+ T and NK cells (4).

Previously, the IL-33/ST2 axis was shown to facilitate proliferation of cancer cells *in vivo*, which was dependent on up-regulation of cyclooxygenase 2/prostaglandin E2 expression through NFκB signaling (7), and to increase expression of IL-6, CXCR4, MMP-2, and MMP-9 in tumor cells, which were essential for enhanced tumor metastasis in rectal carcinoma (8). In contrast, Akimoto *et al*. have reported that sST2 negatively regulated tumor growth and metastatic spread of colorectal carcinoma through modulation of the tumor microenvironment (9). Moreover, Zhang *et al*. suggested that tumor-derived IL-33 modulated the tumor microenvironment, by enhancing recruitment of CD11b+ myeloid cells, to potently promote colon carcinogenesis and liver metastasis (10). In pancreatic carcinoma, clinicopathological and prognostic associations with IL-33/ST2 axis, based on immunohistochemical analyses in human cancer samples, have not yet been well investigated. Takenaga *et al*. have demonstrated that the cancer cell-derived interleukin-33 decoy receptor sST2 enhanced orthotopic tumor growth through up-regulation of CXCL3 *via* inhibition of IL-33/ST2L signaling in the tumor microenvironment in a murine pancreatic cancer model; however, they could not find a consistent association between *IL-33* or *ST2* expression and prognosis, based on analysis of public prognosis databases (11). Induction of IL-33/ST2 signaling results in activation of immune effector cells that leads to recruitment of pro- or anti-oncogenic cells into the tumor microenvironment (12). IL-33/ST2 signaling is negatively regulated by sST2, which acts as a decoy receptor and sequesters IL-33 to block its interaction with ST2L (13). Thus, IL-33 bioactivity is controlled by various factors, such as the balance between ST2L and sST2, and heterogeneous expression in various cell types and immunological conditions, indicating that this complexity may account for the inconsistent literature regarding the prognostic value of ST2 expression in carcinomas.

The incidence of pancreatic carcinoma has been increasing for years. Pancreatic carcinoma is the seventh leading cause of cancer death globally (14). and remains as one of the most lethal malignancies, with a 5-year survival rate of approximately 11% (15). Although radical resection is necessary for patients with pancreatic carcinoma, 80-85% of patients present with advanced unresectable disease (16). Neoadjuvant therapy added to surgery appears to be effective for pancreatic carcinoma. A systematic review and meta-analysis performed by Zhan *et al*. suggested that patients with borderline resectable or locally advanced pancreatic carcinoma may benefit from neoadjuvant therapy (17). Recently, Suto *et al*. have reported that the reduction rate of fluorodeoxyglucose uptake on positron emission tomography and carbohydrate antigen 19-9 levels may serve as pre-operative predictors of therapeutic response to neoadjuvant chemoradiotherapy in patients with resected pancreatic carcinoma, and were associated with better recurrence-free survival (18). However, prediction factors, based on pathological parameters using carcinoma tissues, of therapeutic response and recurrence after neoadjuvant chemoradiotherapy have not been thoroughly investigated in patients with pancreatic carcinoma. In our study, we have demonstrated that tumoral ST2 expression was significantly associated with lower histopathological response grade after neoadjuvant chemoradiotherapy in patients with pancreatic carcinoma and lower DFS in stage I patients. We suggest that ST2 expression may potentially predict response to neoadjuvant chemoradiotherapy and disease recurrence in patients with pancreatic carcinoma. However, we evaluated ST2 expression based on cancer tissues after chemoradiotherapy, but not biopsy specimens before neoadjuvant chemoradiotherapy and surgery,

which may be considered as a limitation of our study; thus, further investigation would be required based on therapy-naïve cancer tissues using pre-operative biopsy. Interestingly, Kieler *et al*. have demonstrated a significant association between high sST2 plasma levels and inferior survival in patients with advanced non-resectable, pancreatic carcinoma undergoing chemotherapy (19), suggesting that sST2 may be a possible predictor of response to chemotherapy, although this finding was not based on surgically resected cases with neoadjuvant treatment.

In conclusion, we have identified tumoral ST2 expression as a marker of biological aggressiveness, such as disease recurrence, higher T status and lymphatic invasion, and as a possible predictor of recurrence and lower histopathological response grade in invasive pancreatic ductal adenocarcinoma after neoadjuvant chemoradiotherapy. These findings suggest that ST2 may serve as a predictor of response to current neoadjuvant therapy or as a therapeutic target in tumor immunotherapy in pancreatic carcinoma. However, the biological role of the IL-33/ST2 pathway in tumor progression is still unclear, although the controversial effects of IL-33/ST2 axis may be attributed to the disparate immunohistochemical detection of IL-33 receptor variants (sST2, ST2L, or other variant ST2), or the heterogeneous expression of ST2 in various cell types (tumor cells *vs*. immune cells in tumor microenvironment) that can be activated by IL-33. Our study was limited by the fact that IL-33 immunohistochemistry was not performed in this cohort, and that interactions between IL-33 and ST2 in tumor cells or tumor immune microenvironment were not investigated. Therefore, future in-depth investigation is warranted based on double staining with anti-IL-33 and anti-ST2 antibodies to confirm the role of IL-33/ST2 axis in the tumor microenvironment.

Conflicts of Interest

All Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

NM, EI, and KK designed the experiments; NM, EI, and KK performed the experiments; NM and KK analyzed the data; NM and KK helped with the discussion; NM and KK wrote the manuscripts; and RH and KO supervised the project. All Authors have reviewed the manuscripts.

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Received March 10, 2023
Revised March 21, 2023
Accepted March 22, 2023