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Systemic inflammation response index correlates with survival and predicts oncological outcome of resected pancreatic cancer following neoadjuvant chemotherapy

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ABSTRACT

Background: The Systemic Inflammation Response Index (SIRI) has been used to predict the prognosis of various cancers. This study examined SIRI as a prognostic factor in the neoadjuvant setting and determined whether it changing after chemotherapy is related to patient prognosis.
Methods: Patients who underwent pancreatic surgery following neoadjuvant chemotherapy for pancreatic cancer were retrospectively analyzed. To establish the cut-off values, SIRIpre-neoadjuvant, SIRIpost-neoadjuvant, and SIRIquotient (SIRIpost-neoadjuvant/SIRIpre-neoadjuvant) were calculated and significant SIRI values were statistically determined to examine their effects on survival rate.
Results: The study included 160 patients. Values of SIRIpost-neoadjuvant $\geq$ 0.8710 and SIRIquotient <0.9516 affected prognosis (hazard ratio [HR], 1.948; 95% confidence interval [CI], 1.210–3.135; **P = 0.006; HR, 1.548; 95% CI, 1.041–2.302; **P = 0.031). Disease-free survival differed significantly at values of SIRIpost-neoadjuvant < 0.8710 and SIRIpost-neoadjuvant $\geq$ 0.8710 (P = 0.0303). Overall survival differed significantly between SIRIquotient <0.9516 and SIRIquotient $\geq$0.9516 (P = 0.0368).
Conclusions: SIRI can predict the survival of patients with pancreatic ductal adenocarcinoma after resection and neoadjuvant chemotherapy. Preoperative SIRI value was correlated with disease-free survival, while changes in SIRI values were correlated with overall survival.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC), a lethal disease and the fourth leading cause of cancer-related deaths in the United States [1], has an overall 5-year survival rate of 15–20% [2–4]. It is expected to become the second leading cause of cancer-related death by 2030 [5].

Margin-negative resection is the most effective treatment for PDAC. However, because most cases are diagnosed at advanced stages, only 15–20% of cases can be treated surgically [1]. Chemotherapy is a treatment option for the remaining 80–85% of cases, and some patients switch to surgery. Many studies have examined the benefits of chemotherapy before surgery [6–8].

The National Comprehensive Cancer Network (NCCN) guidelines recommend neoadjuvant chemotherapy for borderline resectable pancreatic cancer [9], and some reports have even described its potential role in resectable pancreatic cancer [10–12]. It is necessary to predict the response to and prognosis after neoadjuvant chemotherapy to effectively administer it before surgery.

The Systemic Inflammation Response Index (SIRI), which reflects cancer-association inflammation [13,14], is calculated using neutrophil, monocyte, and lymphocyte counts [15]. In malignancy, inflammatory cells in the peripheral venous blood might influence tumor carcinomatosis, progression, and metastasis [13,14]. White blood cells (neutrophils, monocytes, and lymphocytes) and platelets are important inflammatory markers of cancer [16]. The neutrophil-to-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and systemic immune-

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inflammation index (SII) have been proposed as prognostic factors for many malignancies [17–20]. SIRI especially reflects the balance between host inflammation and immune status using neutrophil, monocyte, and lymphocyte counts [16].

Several studies have investigated the SIRI as a prognostic factor for predicting survival and oncologic outcomes of patients with pancreatic cancer [15,16,21–23]. Qi et al. initially introduced it to predict the survival of patients with metastatic pancreatic cancer [15], while Pacheco-Barcia et al. studied its use for predicting the survival of patients with metastatic pancreatic cancer receiving modified fluorouracil/leucovorin/irinotecan/oxaliplatin (FOLFIRINOX) [23].

To the best of our knowledge, no studies to date have examined the use of SIRI to predict the survival of patients with resected pancreatic cancer following neoadjuvant chemotherapy. Therefore, this study aimed to examine whether SIRI is a significant prognostic factor in the neoadjuvant setting and whether its changes after neoadjuvant chemotherapy can predict patient prognosis.

2. Material and methods

2.1. Data collection

The medical records of patients who underwent pancreatic surgery after neoadjuvant chemotherapy for PDAC in 2006–2019 were retrospectively analyzed using the tumor, node, and metastasis staging system based on the American Joint Committee on Cancer 8th edition [24]. Resectability (resectable, borderline resectable, locally advanced) was assessed using the NCCN consensus-based guidelines [9]. Resection status was classified as R0/R1/R2. R1 resection was defined as a tumor within 1 mm of the circumferential or transection margin [25]. Neoadjuvant chemotherapy regimens without radiation therapy in this study were gemcitabine-based, fluorouracil-based (FL-based), capecitabine, tegafur/gimeracil/oteracil, tegafur/uracil, and FOLFIRINOX.

Patients with cancer routinely undergo blood tests at the time of diagnosis and after neoadjuvant chemotherapy to evaluate their systemic condition and response to treatment. In general, neoadjuvant chemotherapy is initiated within one week of the cancer diagnosis, while surgery is performed one month after the end of the neoadjuvant chemotherapy. Therefore, the laboratory data collected within one week of neoadjuvant chemotherapy initiation and one month of termination were analyzed in this study.

A total of 172 patients underwent pancreatic resection following neoadjuvant chemotherapy performed by multiple surgeons. Owing to the lack of laboratory data, 12 patients were excluded from this retrospective study. Clinical and pathological data, laboratory findings, and oncological outcomes of all 160 patients were investigated. The median follow-up period was 30 months. The American Society of Anesthesiologists (ASA) classification was used to assess pre-anesthesia medical comorbidities [26]. This study was approved by the Institutional Review Board of Sincheon Severance Hospital (approval number 4-2020-0809) and conducted in accordance with the Declaration of Helsinki.

2.2. Systemic Inflammation Response Index

The SIRI value was calculated by multiplying the neutrophil and monocyte counts and dividing them by the lymphocyte count as previously described (SIRI = neutrophil count × monocyte count/lymphocyte count) [15]. To confirm SIRI values before versus after neoadjuvant chemotherapy, neutrophil, monocyte, and lymphocyte counts were checked in blood samples drawn nearest to the start of neoadjuvant chemotherapy and the subsequent surgery. In this study, for convenience, the SIRI value before neoadjuvant chemotherapy is indicated as $SIRI^{pre\text{-}neoadjuvant}$, while that after neoadjuvant chemotherapy is $SIRI^{post\text{-}neoadjuvant}$. The change in SIRI after neoadjuvant chemotherapy, $SIRI^{quotient}$, was calculated as $SIRI^{post\text{-}neoadjuvant}/SIRI^{pre\text{-}neoadjuvant}$.

2.3. Statistical analysis

To establish the cut-off SIRI values and their changes, subtraction, division, average, and geometric mean as well as $SIRI^{pre\text{-}neoadjuvant}$ and $SIRI^{post\text{-}neoadjuvant}$ were calculated. Among the calculated SIRI values, significance was determined using statistical techniques to examine their effect on survival rate.

Contal and O'Quigely's method was used to establish a statistically significant cut-off value for SIRI. This method obtains a new statistical value, called the Q-statistic, by weighting the point of the greatest difference in the Kaplan-Meier curves, with which the log-rank test value is the most significant. The SIRI value at which this Q-statistic peaks is defined as the cut-off point. In each analysis, when death was an event, the $SIRI^{post\text{-}neoadjuvant}$ significant cut-off value was 0.8710; when recurrence was an event, the $SIRI^{quotient}$ significant cut-off value was 0.9516. Further details are provided in **Supplement 1**.

The patients were divided into groups based on their $SIRI^{post\text{-}neoadjuvant}$ and $SIRI^{quotient}$ values. Group A included patients with a $SIRI^{post\text{-}neoadjuvant}$ of <0.8710, while Group B included patients with a $SIRI^{post\text{-}neoadjuvant} \geq 0.8710$. Group C included patients with a $SIRI^{quotient}$ of ≥0.9516, while Group D included patients with a $SIRI^{quotient}$ of <0.9516. Details of the clinical and pathological features of the four groups are provided in **Supplement 2.**

Continuous variables are expressed as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. Student's t-test and the Mann-Whitney *U* test were used to compare continuous variables, while the chi-squared and Fisher's exact tests were used to examine categorical variables. A Cox proportional hazards regression model was used, and significant variables in the univariate analysis were included in the multivariate analysis. The simple contrast method was used to examine categorical multiple variables in the Cox regression analysis. Each predictor category was compared to the reference category. Statistical significance was defined as $P < 0.05$. Median survival was estimated using the Kaplan-Meier method. Statistical analyses were performed using SAS (version 9.4; SAS Inc., Cary, NC, USA) and the R package (version 3.4.3; http://www.R-project.org).

3. Results

3.1. General characteristics of patients with resected pancreatic cancer following neoadjuvant chemotherapy

A total of 160 patients were included in this study. The mean patient age was 61.81 ± 8.90 years, and there was a male predominance (57.5% [n = 92]). The mean body mass index (BMI) was 22.82 ± 2.85 kg/m^2. An ASA score of 2 was the most common in all patients (55.0%). A total of 87 patients (54.4%) underwent preoperative biliary drainage (endoscopic retrograde biliary drainage or percutaneous transhepatic biliary drainage) and catheter insertion. The mean preoperative carbohydrate antigen 19-9 (CA 19-9) level was 710.71 ± 1847.88 U/mL and the mean tumor size was 2.14 ± 1.41 cm. There were 84 patients with resectable status, 64 with borderline resectable status, and 12 with locally advanced status. In terms of cancer staging, yT1 (46.9%) and yN0 (65.0%) were the most common stages among all patients. The majority of patients (83.8%) had no lymphovascular invasion (yLi), whereas perineural invasion was found in 84 patients (52.5%). There were 147 patients with R0 status, 13 patients with R1 status, and none with

R2 status. A total of 111 patients (69.4%) received adjuvant chemotherapy postoperatively (Table 1).

The clinicopathological characteristics of the groups were compared according to $SIRI^{post\text{-}neoadjuvant}$ and $SIRI^{quotient}$ values. There were no statistically significant differences in any variable between Groups A ($SIRI^{post\text{-}neoadjuvant} < 0.8710$) and B ($SIRI^{post\text{-}neoadjuvant} \geq 0.8710$). There were also no statistically significant differences in any variables between Groups C ($SIRI^{quotient} \geq 0.9516$) and D ($SIRI^{quotient} < 0.9516$) except that the latter had more patients with yPi than the former (**Supplement 2**).

3.2. Prognostic factors of resected pancreatic cancer following neoadjuvant chemotherapy

In terms of disease-free survival, age (hazard ratio [HR], 0.973; 95% confidence interval [CI], 0.991–0.996; $*P = 0.019$), tumor size (HR, 1.339; 95% CI, 1.151–1.557; $*P = 0.0002$); yT3 stage (HR, 3.708; 95% CI, 1.806–7.615; $*P = 0.0004$), yN2 stage (HR, 2.974; 95% CI, 1.396–6.332; $*P = 0.0047$), R1 status (HR, 2.120; 95% CI, 1.158–3.879; $*P = 0.015$), FL-based neoadjuvant chemotherapy (HR, 0.414; 95% CI, 0.248–0.689; $*P = 0.0007$), and adjuvant chemotherapy (HR, 0.662; 95% CI, 0.441–0.994; $P* = 0.0465$) all significantly affected the prognosis of patients in the univariate analysis. In the multivariate analysis, age (HR, 0.971; 95% CI, 0.948–0.994; $P** = 0.013$), yN2 stage (HR, 4.080; 95% CI, 1.746–9.531; $**P = 0.001$), FL-based neoadjuvant chemotherapy (HR, 0.348; 95% CI, 0.206–0.589; $**P = 0.001$), and adjuvant chemotherapy (HR, 0.534; 95% CI, 0.341–0.837, $*P = 0.006$) significantly affected disease-free survival. A $SIRI^{post\text{-}neoadjuvant}$ value ≥ 0.8710 affected patient prognosis on univariate (HR, 1.541; 95% CI, 1.039–2.286; $*P = 0.317$) and multivariate (HR, 1.948; 95% CI, 1.210–3.135; $**P = 0.006$) analyses (Table 2).

In terms of overall survival, tumor size (HR, 1.291; 95% CI, 1.113–1.498; $*P = 0.0007$), yT3 stage (HR, 3.557; 95% CI, 1.722–7.349; $*P = 0.0006$), yN2 stage (HR, 4.714; 95% CI, 2.288–9.712; $*P < 0.0001$), yLi (HR, 1.732; 95% CI, 1.018–2.947; $*P = 0.0429$), R1 status (HR, 1.953; 95% CI, 1.040–3.664; $*P = 0.037$), FL-based neoadjuvant chemotherapy (HR, 0.591; 95% CI, 0.351–0.996; $*P = 0.0482$) and adjuvant chemotherapy (HR, 0.556; 95% CI, 0.374–0.827; $*P = 0.0037$) significantly affected patient prognosis on the univariate analysis. Tumor size (HR, 1.261; 95% CI, 1.085–1.467; $*P = 0.003$) and adjuvant chemotherapy (HR, 0.490; 95% CI, 0.328–0.732; $**P = 0.001$) significantly affected overall survival on the multivariate analysis. A $SIRI^{quotient} < 0.9516$ affected prognosis on the univariate (HR, 1.517; 95% CI, 1.023–2.249; $*P = 0.0380$) and multivariate (HR, 1.548; 95% CI, 1.041–2.302; $**P = 0.031$) analyses (Table 2).

3.3. $SIRI^{post\text{-}neoadjuvant}$ and $SIRI^{quotient}$ stratify disease-free/overall survival

Patients with $SIRI^{post\text{-}neoadjuvant}$ values < 0.8710 were significantly more likely to survive disease-free than those with values ≥ 0.8710 ($P = 0.0303$) (Fig. 1). Patients with $SIRI^{quotient}$ values ≥ 0.9516 were significantly more likely to survive overall than those with values < 0.9516 ($P = 0.0368$) (Fig. 2).

Table 1
Clinical and pathological characteristics of the study participants.

Variable	N = 160
Age, years, mean ± SD	61.81 ± 8.90
Sex, male/female, n (%)	92 (57.5)/68 (42.5)
BMI[a], kg/m^2, mean ± SD	22.82 ± 2.85
ASA[b], n (%)	
1	29 (18.1)
2	88 (55.0)
3	39 (24.4)
4	4 (2.5)
Preoperative BD[c], N[d]/Y[e], n (%)	73 (45.6)/87 (54.4)
Preoperative CA 19-9[f], U/mL, mean ± SD	710.71 ± 1847.88
Resectability at diagnosis, n (%)	
Resectable	84 (52.5)
Borderline resectable	64 (40.0)
Locally advanced	12 (7.5)
Tumor size, cm, mean ± SD	2.14 ± 1.41
yT stage (8th edition), n (%)	
yT1	75 (46.9)
yT2	62 (38.8)
yT3	10 (6.3)
yT4	1 (0.6)
Unknown	12 (7.5)
yLN stage (8th edition), n (%)	
yN0	104 (65.0)
yN1	46 (28.8)
yN2	10 (6.3)
yLymphovascular invasion, N/Y, n (%)	134 (83.8)/26 (16.3)
yPerineural invasion, N/Y, n (%)	76 (47.5)/84 (52.5)
R[g] status, n (%)	
R0	147 (91.9)
R1	13 (8.1)
R2	0 (0.0)
Adjuvant chemotherapy, N/Y, n (%)	49 (30.6)/111 (69.4)

[a] Body mass index.
[b] American Society of Anesthesiologists classification score.
[c] Biliary drainage.
[d] No.
[e] Yes.
[f] Carbohydrate antigen 19-9.
[g] Resection status.

4. Discussion

This study found that $SIRI^{post\text{-}neoadjuvant} \geq 0.8710$ and $SIRI^{quotient} < 0.9516$ significantly affected the prognosis of patients with pancreatic cancer who underwent resection following neoadjuvant chemotherapy. Disease-free survival differed significantly between patients with a $SIRI^{post\text{-}neoadjuvant} < 0.8710$ versus $SIRI^{post\text{-}neoadjuvant} \geq 0.8710$, while overall survival differed significantly between patients with a $SIRI^{quotient} < 0.9516$ and $SIRI^{quotient} \geq 0.9516$.

Despite surgery being the only curative treatment method, only about 15–20% of patients are surgical candidates at the time of the pancreatic cancer diagnosis [1]. Most of the remaining 80–85% of patients also have systemic diseases, so it is difficult to expect curative resection. Of them, only some can undergo surgery after chemotherapy. Studies have shown that patients who receive neoadjuvant chemotherapy prior to surgery have better oncological outcomes than those who undergo surgery alone [27,28]. Versteijne et al. reported that the preoperative chemoradiation therapy group had a higher R0 resection rate and better median disease-free survival than the immediate surgery group (71% vs. 40%, $P < 0.001$; 8.1 months versus 7.7 months, $P = 0.032$, respectively) [8]. Jang et al. reported that the R0 resection rate and median survival were significantly better in the neoadjuvant chemoradiation group than in the upfront surgery group (51.8% vs. 26.1%, $P = 0.004$; 21 vs. 12 months, $P = 0.028$, respectively) [29]. Several factors affect the treatment outcomes of neoadjuvant chemotherapy, including anticancer drug type and duration, tumor resectability, whether radiation therapy is added, and surgical timing [30]. Therefore, further research on the therapeutic effects of neoadjuvant chemotherapy are required in various fields.

The decision regarding switching from neoadjuvant chemotherapy to surgery is often difficult due to a lack of clear criteria, especially when tumor characteristics (changes in imaging and tumor markers) do not differ significantly after neoadjuvant chemotherapy. Therefore, it is important to understand the

Table 2
Prognostic factors of survival of resected pancreatic cancer after neoadjuvant chemotherapy.

Variable	Disease-free survival				Overall survival			
	HR[a]	95% CI[b]	*P[c]	**P[d]	HR	95% CI	*P	**P
Age	0.973	0.951–0.996	0.019	0.013	0.993	0.970–1.017	0.5573	NS[e]
Sex								
Male	1	–	–	–	1	–	–	–
Female	0.747	0.503–1.11	0.1492	NS	0.673	0.448–1.010	0.0559	NS
ASA[f]								
1	1	–	–	–	1	–	–	–
2	1.23	0.741–2.043	0.4233	NS	1.194	0.728–1.960	0.4825	NS
3	0.916	0.497–1.686	0.7775	NS	0.87	0.458–1.649	0.6694	NS
4	0.709	0.165–3.048	0.6443	NS	1	0.232–4.305	0.9997	NS
PBD[g]								
No	1	–	–	–	1	–	–	–
Yes	0.839	0.571–1.232	0.3711	NS	0.918	0.624–1.350	0.6643	NS
PCA 19-9[h]	1	1.0–1.0	0.7822	NS	1	1.0–1.0	0.9542	NS
Resectability								
Resectable	1		–		1			
Bordeline	0.955	0.640–1.423	0.820	NS	0.895	0.597–1.342	0.592	NS
Locally advanced	0.795	0.361–1.750	0.569	NS	1.145	0.544–2.412	0.722	NS
Tumor size	1.339	1.151–1.557	0.0002	0.666	1.291	1.113–1.498	0.0007	0.1337
yT stage								
yT1	1	–	–	–	1	–	–	–
yT2	0.987	0.647–1.507	0.9519	NS	0.984	0.646–1.499	0.9402	NS
yT3	3.708	1.806–7.615	0.0004	NS	3.557	1.722–7.349	0.0006	NS
yT4	0	–	NS	NS	0	.	0.9872	NS
Unknown	0.431	0.175–1.0161	0.067	NS	0.396	0.157–1.004	0.0509	NS
yLN stage								
yN0	1	–	–	–	1	–	–	–
yN1	1.322	0.863–2.024	0.1991	0.547	1.369	0.889–2.106	0.1536	NS
yN2	2.974	1.396–6.332	0.0047	0.001	4.714	2.288–9.712	<.0001	NS
R[i] status								
R0	1	–	–	–	1	–	–	–
R1	2.120	1.158–3.879	0.015	0.316	1.953	1.040–3.664	0.037	0.177
R2	0	–	NS	NS	0		NS	NS
yLI[j]								
No	1	–	–	–	1	–	–	–
Yes	1.082	0.623–1.880	0.7788	NS	1.732	1.018–2.947	0.0429	0.081
yPI[k]								
No	1	–	–	–	1	–	–	–
Yes	1.235	0.835–1.826	0.2911	NS	1.263	0.852–1.873	0.2446	NS
ND[l]								
GEM[m]	1	–	–	–	1	–	–	–
FL[n]	0.414	0.248–0.689	0.0007	0.001	0.591	0.351–0.996	0.0482	NS
Capecitabine[o]	0.803	0.439–1.468	0.4758	0.080	0.959	0.522–1.762	0.8919	NS
TS-1[p]	0.79	0.286–2.185	0.6502	0.249	0.714	0.259–1.968	0.5145	NS
UFT[q]	2.012	0.859–4.713	0.1076	0.521	2.077	0.881–4.899	0.0950	NS
FOLFIRINOX[r]	1.076	0.389–2.975	0.8879	0.787	0.445	0.108–1.830	0.2618	NS
AC[s]								
No	1	–	–	–	1	–	–	–
Yes	0.662	0.441–0.994	0.0465	0.006	0.556	0.374–0.827	0.0037	0.001
SIRI[post-neoadjuvant][t]								
<0.8710	1	–	–	–	–	–	–	–
≥0.8710	1.541	1.039–2.286	0.0317	0.006	–	–	–	–
SIRI[quotient][u]								
≥0.9516	1	–	–	–	1	–	–	–
'< 0.9516	0.844	0.571–1.246	0.3929	0.241	1.517	1.023–2.249	0.0380	0.031

[a] Hazard ratio.
[b] Confidence interval.
[c] Univariate analysis.
[d] Multivariate analysis.
[e] Not significant.
[f] American Society of Anesthesiologists classification score.
[g] Preoperative biliary drainage.
[h] Preoperative carbohydrate antigen 19-9.
[i] Resection status.
[j] Lymphovascular invasion.
[k] Perineural invasion.
[l] Neoadjuvant drugs.
[m] Gemcitabine.
[n] Fluorouracil.
[o] Capecitabine.
[p] Tegafur/gimeracil/oteracil.
[q] Tegafur/uracil.
[r] Fluorouracil/leucovorin/irinotecan/oxaliplatin.
[s] Adjuvant chemotherapy.

[t] SIRI value after neoadjuvant chemotherapy.
[u] Change of Systemic Inflammation Response Index (SIRI) after neoadjuvant chemotherapy ($SIRI^{post\text{-}neoadjuvant}/SIRI^{pre\text{-}neoadjuvant}$).

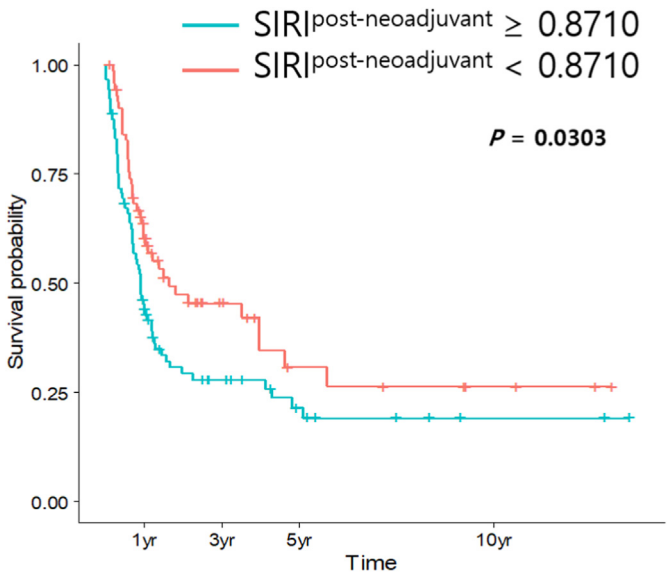

Fig. 1. Kaplan-Meier curve of disease-free survival based on $SIRI^{post\text{-}neoadjuvant}$
$SIRI^{post\text{-}neoadjuvant}$ is the SIRI value after neoadjuvant chemotherapy. The statistical cut-off value of $SIRI^{post\text{-}neoadjuvant}$ was 0.8710. SIRI, Systemic Inflammation Response Index.

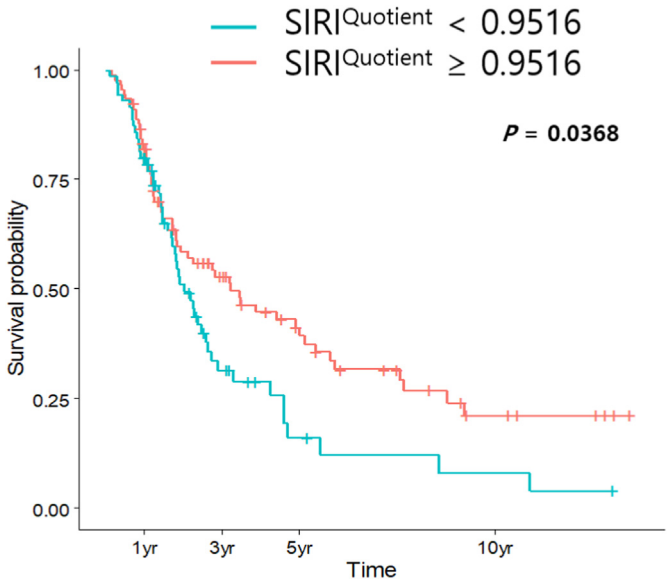

Fig. 2. Kaplan-Meier curve of overall survival based on $SIRI^{quotient}$
$SIRI^{quotient}$ is the change in SIRI after neoadjuvant chemotherapy ($SIRI^{post\text{-}neoadjuvant}/SIRI^{pre\text{-}neoadjuvant}$). The statistical cut-off value of $SIRI^{quotient}$ was 0.9516. SIRI, Systemic Inflammation Response Index.

preoperative prognostic factors that can predict pancreatic cancer outcomes and neoadjuvant chemotherapy responses, which increases our understanding of prognosis as well as surgical timing.

Studies have examined various prognostic predictors in patients with pancreatic cancer. CA 19-9 [31,32], prognostic nutritional index (PNI) [33], hemoglobin-albumin-lymphocyte-platelet score, NLR [32,34], LMR [35,36], PLR [37], SII [20], and others are prognostic predictors after resection in these patients. In particular, studies of the association between immunological indicators such as NLR, LMR, and SIRI and tumors have been actively conducted. Qi et al. initially introduced the SIRI as a prognostic predictor in patients with locally advanced pancreatic cancer [15]. In the palliative chemotherapy setting, patients with a SIRI ≥1.8 had a shorter time to progression (TTP) (HR, 2.348; 95% CI, 1.559–3.535; $P = 0.003$) and shorter overall survival (HR, 2.789; 95% CI, 1.897–4.121; $P < 0.001$) than those with a SIRI < 1.8[15]. In the multivariate analysis, SIRI was an independent prognostic predictor of both TTP and overall survival [15]. Pacheco-Barcia et al. reported that an elevated SIRI ($\geq 2.3 \times 10^9$/L) is an independent prognostic factor for patients with metastatic pancreatic cancer who received modified FOLFIRINOX therapy [23]. SIRI can also predict the outcomes of other malignancies, such as breast [16,38], thyroid [39], lung [40], stomach [41], and liver [42].

Many studies have investigated the prognostic factors of pancreatic cancer, such as NLR, LMR, PLR, and SII. Among them, NLR is known to be particularly highly correlated with prognosis [43]. However, other studies showed that neither NLR nor PLR predicted survival in patients who underwent pancreatectomy for PDAC [44]. We aimed to confirm the association between SIRI, a combination of neutrophil, lymphocyte, and monocyte counts, a more complex combination that includes all of the elements of NLR and LMR, and pancreatic cancer prognosis. Moreover, studies on SIRI (lymphocyte, monocyte, and neutrophil counts) are rare. Above all, we focused on the fact that no studies have demonstrated an association with SIRI in patients with pancreatic cancer who underwent neoadjuvant chemotherapy. Therefore, we attempted to confirm the relationship between the SIRI and prognosis in patients who underwent preoperative chemotherapy.

Immune cells that comprise the tumor microenvironment include myeloid lineage (macrophages, TIE-2-expressing monocytes [TEMs], neutrophils, mast cells, myeloid-derived suppressor cells) and lymphoid lineage (natural killer [NK] cells, $CD4^+$ helper T cells, regulatory T cells, $CD8^+$ cytotoxic T cells, and B cells) [45]. Of these, only elements related to SIRI (monocyte, neutrophil, and lymphocyte counts) were considered in detail. TEMs express TIE-2, a tyrosine kinase receptor for the angiogenic growth factor angiopoietin [46]. A higher number of TEMs are present in the bloodstream and infiltrate neoplastic tissue in cancer [46]. Although TEMs have been implicated in various aspects of tumorigenesis, they are best known for their role in promoting tumor angiogenesis [47]. Neutrophil granulocytes, which play an early role in inflammation by rapidly defending against microbes at the infection site, flock to tumor cells in response to cytokines and chemoattractants [48]. Neutrophils can be divided into N1 and N2 phenotypes. N1-type neutrophils elicit an anti-tumoral response [49], while N2-type neutrophils promote tumorigenesis [49,50]. Neutropenia is most common side effect of chemotherapy. Although neutropenia increases a patient's risk of infection, a retrospective analysis reported that neutropenia in response to chemotherapy is correlated with improved overall survival [51]. NK cells are cytotoxic lymphocytes that play an important role in both the innate and adaptive immune responses. It is generally recognized that NK cells provide an anti-tumorigenic immune response [52]. Indeed, reduced NK cell levels in patients with cancer were correlated with decreased overall survival [53]. $CD4^+$ helper T cells, which play diverse roles in cancer development, can be subdivided into phenotypically divergent TH1 and TH2 lineages [54]. TH1 cells exhibit direct cytotoxic functions by releasing granules that directly kill tumor cells in their microenvironment [55], while TH2 cells elicit pro-tumorigenic effects by inhibiting $CD8^+$ T cell cytotoxicity and immunosuppression to promote tumor growth [55]. The

infiltration of cytotoxic $CD8^+$ T cells, which are lymphocytes that kill tumor cells, is associated with prolonged overall survival [56].

The SIRI was established by combining three important inflammatory indicators and host immune factors that influence tumor development. However, no studies have examined SIRI in the neoadjuvant setting. This is the first study to analyze the potential oncologic association between SIRI and prognosis after resected pancreatic cancer in a neoadjuvant setting. Our multivariate analysis confirmed that patients with a $SIRI^{post\text{-}neoadjuvant} < 0.8710$ had increased disease-free survival, while patients with a $SIRI^{quotient} \geq 0.9516$ had increased overall survival. This shows that SIRI values after neoadjuvant chemotherapy are likely associated with postoperative recurrence, while changes in SIRI values after neoadjuvant chemotherapy are likely associated with overall survival.

In summary, generally decreased neutrophil and monocyte counts and increased lymphocyte counts may be associated with a good prognosis, meaning that a low SIRI value can show a relatively better prognosis than a high SIRI value. To prove this theory, it is necessary to obtain cancer cell tissue or blood samples before and after chemotherapy and check the neutrophil, monocyte, and lymphocyte phenotypes to confirm and prove the level changes. It is also necessary to check for differences in the composition of the immune cells in the circulation and tumor tissues.

Additional studies are needed to demonstrate the clinical application of SIRI. According to the current NCCN guidelines, it is necessary to check whether the same results are obtained when neoadjuvant chemotherapy is administered to patients with borderline resectable pancreatic cancer. Further research is needed to determine whether neoadjuvant chemotherapy is administered to patients with resectable pancreatic cancer. In addition, for SIRI to be useful in actual clinical practice, it is necessary to verify how SIRI values change with each chemotherapy cycle and whether the same results are obtained even when external validation is performed. Therefore, we plan to examine the relationship between tumor oncologic characteristics and immunological factors such as SIRI in future studies.

This study had several limitations related to its retrospective nature and small sample size. First, inflammation may be affected by a systemic condition or concomitant infection, such as cholangitis, which may act as a bias. Second, the types of anticancer drugs used for neoadjuvant chemotherapy were different and their effects were not considered. In particular, the high number of patients with a high SIRI after Xeloda in our data requires further study (**Supplement 2**). Third, the cut-off SIRI value was confirmed by statistical analysis. Although the results of this study are difficult to generalize, the possibility of SIRI acting as an independent prognostic factor in a neoadjuvant setting has been illustrated. If a clear algorithm is discovered, it can be used to predict the prognosis of cancer using specific criteria. Fourth, this study did not reflect tumor regression status. This retrospective study included data collected from 2006 to 2019. There are no reports of tumor regression status in past data. However, there was no statistically significant association between the change in tumor size and CA19-9 values according to the SIRI (**Supplement 3**). Further research should reflect the tumor regression status expected to yield more accurate results will be obtained. Only the data of the patients who underwent surgery were reviewed. There are no data on patients who did not undergo surgery due to disease progression during chemotherapy.

In summary, this study showed that SIRI values after neoadjuvant chemotherapy are likely to be associated with recurrence after surgery, and that changes in SIRI before and after neoadjuvant chemotherapy are likely to be associated with overall survival. Based on studies regarding the prognostic value of PNI and inflammatory and immunologic factors, including SIRI, in order to improve the prognosis of pancreatic cancer patients, it is necessary to study tumor biology, as well as overall patient-related factors. This could lead to an increase in the effectiveness of immunotherapy for pancreatic cancer in the future, and further research is needed on this topic.

This study found that the SIRI can be used to predict the survival of patients with PDAC after neoadjuvant chemotherapy and resection. Preoperative SIRI was found to correlate with disease-free, and the change in SIRI after neoadjuvant chemotherapy was found to correlate with overall survival. When considering surgery in these patients, the prognosis must be evaluated not only from an oncological point of view, but also from patient-related factors, such as SIRI, and future studies that can help improve prognosis by incorporating these factors are needed. Further research is needed to study the effects of different anticancer drugs on patient immune factors.

Declaration of competing interest

The authors declare no conflicts of interest regarding this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.08.009.

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