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(Citation)
Oncology Letters,27(3):136

(Issue Date)
2024-03

(Resource Type)
journal article

(Version)
Version of Record

(URL)
https://hdl.handle.net/20.500.14094/0100486353

Inflammation-based prognostic markers of metastatic pancreatic cancer using real-world data in Japan: The Tokushukai REAl-world Data (TREAD) project

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Received November 4, 2023; Accepted January 10, 2024

DOI: 10.3892/ol.2024.14269

Abstract. Inflammation-based prognostic markers based on a combination of blood-based parameters, including the modified Glasgow prognostic score (mGPS), have been associated with clinical outcomes in patients with various types of cancer. The present study aimed to evaluate and compare the accuracy of these previously reported markers in patients with metastatic pancreatic cancer receiving first-line chemotherapy. A total of 846 patients were identified between April 2010 and March 2020 as part of a nationwide real-world study from 46 Tokushukai medical group hospitals in Japan. Blood laboratory data collected within 14 days of starting first-line chemotherapy assessed 17 inflammation-based prognostic markers. Information from patients with no missing data was used to compare the accuracy and performance of the inflammation-based prognostic markers. A total of 487 patients were eligible for this supplemental analysis. The 17 inflammation-based markers demonstrated significant prognostic value. Among them, the concordance rate with overall survival (OS) was highest for mGPS. The median OS time of patients with mGPS 0, 1 and 2 was 8.2, 6.0 and 2.9 months, respectively. Compared with mGPS 0, mGPS 1 and 2 showed hazard ratios of 1.39 (95% confidence interval, 1.07-1.81) and 2.63 (2.00-3.45), respectively. The present real-world data analysis showed that various previously reported inflammation-based markers had significant prognostic value in patients with metastatic pancreatic cancer. Among these markers, the mGPS demonstrated the highest level of accuracy. This trial has been registered in the University Hospital Medical Information Network Clinical Trials Registry as UMIN000050590 on April 1, 2023.

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Abbreviations: AIC, akaike information criterion; BMI, body mass index; CALLY, CRP albumin lymphocyte index; CAR, CRP-to-albumin ratio; CIs, confidence intervals; dNLR, derived neutrophil-to-lymphocyte ratio; FOLFIRINOX, fluorouracil, folic acid, oxaliplatin, and irinotecan; GPS, Glasgow prognostic score; HRs, hazard ratios; LIPI, lung immune prognostic index; LMR, lymphocyte-to-monocyte ratio; LMS, lymphocyte-monocyte score; mGPS, modified Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; NLS, neutrophil-lymphocyte score; NPS, neutrophil-platelet score; OS, overall survival; PI, prognostic index; PLR, platelet-to-lymphocyte ratio; PLS, platelet-lymphocyte score; PNI, prognostic nutritional index; S-1, tegafur/gimeracil/oteracil; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; TREAD, tokushukai real-world data; UMIN, university hospital medical information network

Key words: inflammation-based prognostic markers, metastatic pancreatic cancer, real-world data, OS, mGPS

Introduction

Pancreatic cancer is the fourth leading cause of cancer death and has one of the poorest prognoses, with a very low 5-year survival rate of about 10% in Japan and the United States (1-3). Its incidence is increasing (1,3), and most cases (~80%) are unresectable at diagnosis. FOLFIRINOX (including fluorouracil, folinic acid, oxaliplatin, and irinotecan) (4-6) and gemcitabine plus nab-paclitaxel (7) have been reported as the standard first-line therapies for advanced/recurrent pancreatic cancer, but the prognosis remains poor with median overall survival (OS) of 9-12 months in clinical trials (4,7). Conversely,

Table I. Systemic inflammation-based prognostic scores and ratios.

Definition	Score or ratio
PNI	
PNI; Onodera *et al* (16)	
10 x albumin (g/dl) + 0.005 x lymphocyte count (/dl)	≥45
10 x albumin (g/dl) + 0.005 x lymphocyte count (/dl)	<45
GPS	
GPS; original (17)	
C-reactive protein ≤1.0 (mg/dl) and albumin ≥3.5 (g/dl)	0
C-reactive protein >1.0 (mg/dl) or albumin <3.5 (g/dl)	1
C-reactive protein >1.0 (mg/dl) and albumin <3.5 (g/dl)	2
J-mGPS (20)	
C-reactive protein ≤0.5 (mg/dl) and albumin ≥3.5 (g/dl)	0
C-reactive protein >0.5 (mg/dl) or albumin <3.5 (g/dl)	1
C-reactive protein >0.5 (mg/dl) and albumin <3.5 (g/dl)	2
CAR (18)	
C-reactive protein (mg/dl)/albumin (g/dl)	≤0.22
C-reactive protein (mg/dl)/albumin (g/dl)	>0.22
NLR (19)	
Neutrophil count (/μl)/lymphocyte count (/μl)	<3
Neutrophil count (/μl)/lymphocyte count (/μl)	≥3-<5
Neutrophil count (/μl)/lymphocyte count (/μl)	≥5
PLR (20)	
Platelet count (/μl)/lymphocyte count (/μl)	≤150
Platelet count (/μl)/lymphocyte count (/μl)	>150
LMR (21)	
Lymphocyte count (/μl)/monocyte count (/μl)	≥2.40
Lymphocyte count (/μl)/monocyte count (/μl)	<2.40
dNLR (22)	
Neutrophil count (/μl)/(leukocyte count (/μl)-neutrophil count (/μl))	<3
Neutrophil count (/μl)/(leukocyte count (/μl)-neutrophil count (/μl))	≥3-<5
Neutrophil count (/μl)/(leukocyte count (/μl)-neutrophil count (/μl))	≥5
NPS (23)	
Neutrophil count ≤7,500 (/μl) and platelet count ≤400,000 (/μl)	0
Neutrophil count >7,500 (/μl) or platelet count >400,000 (/μl)	1
Neutrophil count >7,500 (/μl) and platelet count >400,000 (/μl)	2
NLS (24,25)	
Neutrophil count ≤7,500 (/μl) and lymphocyte count ≥1,500 (/μl)	0
Neutrophil count >7,500 (/μl) or lymphocyte count <1,500 (/μl)	1
Neutrophil count >7,500 (/μl) and lymphocyte count <1,500 (/μl)	2
PLS (24,25)	
Platelet count ≤400,000 (/μl) and lymphocyte count ≥1,500 (/μl)	0
Platelet count >400,000 (/μl) or lymphocyte count <1,500 (/μl)	1
Platelet count >400,000 (/μl) and lymphocyte count <1,500 (/μl)	2
LMS (24,25)	
Lymphocyte count ≥1,500 (/μl) and monocyte count ≤800 (/μl)	0
Lymphocyte count <1,500 (/μl) or monocyte count >800 (/μl)	1
Lymphocyte count <1,500 (/μl) and monocyte count >800 (/μl)	2
PI (23)	
C-reactive protein ≤1.0 (mg/dl) and leukocyte count ≤11,000 (/μl)	0
C-reactive protein >1.0 (mg/dl) or leukocyte count >11,000 (/μl)	1
C-reactive protein >1.0 (mg/dl) and leukocyte count >11,000 (/μl)	2

Table I. Continued.

Definition	Score or ratio
SII (26)	
Neutrophil count (/μl) x 10 x platelet count (/μl)/lymphocyte count (/μl)	<300
Neutrophil count (/μl) x 10 x platelet count (/μl)/lymphocyte count (/μl)	≥300-<600
Neutrophil count (/μl) x 10 x platelet count (/μl)/lymphocyte count (/μl)	≥600-<1,000
Neutrophil count (/μl) x 10 x platelet count (/μl)/lymphocyte count (/μl)	≥1,000
SIRI (27)	
Neutrophil count (/μl) x monocyte count (/μl)/lymphocyte count (/μl)	<500
Neutrophil count (/μl) x monocyte count (/μl)/lymphocyte count (/μl)	≥500-<1,000
Neutrophil count (/μl) x monocyte count (/μl)/lymphocyte count (/μl)	≥1,000-<2,000
Neutrophil count (/μl) x monocyte count (/μl)/lymphocyte count (/μl)	≥2,000
LIPI (28)	
dNLR ≤3 and lactate dehydrogenase ≤245 (U/l)	0
dNLR >3 or lactate dehydrogenase >245 (U/l)	1
dNLR >3 and lactate dehydrogenase >245 (U/l)	2
CALLY (29)	
Albumin (g/dl) x lymphocyte count (/μl)/C-reactive protein (mg/dl)	<5
Albumin (g/dl) x lymphocyte count (/μl)/C-reactive protein (mg/dl)	≥5

PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; J-mGPS, Japanese-modified GPS; CAR, C-reactive protein-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; dNLR, derived NLR; NPS, neutrophil-platelet score; NLS, neutrophil-lymphocyte score; PLS, platelet-lymphocyte score; LMS, lymphocyte-monocyte score; PI, prognostic index; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; LIPI, lung immune prognostic index; CALLY, CRP albumin lymphocyte index; CRP, C-reactive protein.

our real-world study, encompassing 846 cases of metastatic pancreatic cancer initially treated between 2010 and 2020, revealed a median OS of just 6.8 months (8).

Even in cases with unfavorable prognoses, an accurate prediction of the clinical outcomes is crucial. The usefulness of inflammation-based and nutritional markers in patients with cancer has been widely reported (9). Historically, various prognostic markers and their correlation with outcomes in cancer patients have been reported since the 1980s (10-12). To date, numerous markers have been investigated for their utility in diverse scenarios, and due to their convenience, they are widely utilized in actual clinical practice. Nonetheless, data on their direct comparisons are limited. It's essential to validate the most suitable markers for each specific clinical setting.

The objective of this study is to conduct a direct comparison of the various inflammation-based prognostic markers reported to date, utilizing the aforementioned dataset (8), in order to identify the most accurate markers for assessing prognosis in metastatic pancreatic cancer.

Patients and methods

Study overview. The Tokushukai Real-world Data (TREAD) project is a retrospective cohort study conducted at Tokushukai Medical Group hospitals. Tokushukai Medical Group is a leading medical group in Japan, encompassing 71 general hospitals nationwide. The study utilizes a shared medical record system across these hospitals. (e-Karte and Newtons2; Software Service Inc., Osaka, Japan) and chemotherapy protocol system (srvApmDrop; Software Service Inc., Osaka, Japan), the details of which can be found in a separate article (13). The project adhered to the ethical guidelines for medical and biological research involving human subjects in Japan (14) and followed the principles of the Declaration of Helsinki. Approval for the study was obtained from the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024). Patients were informed about the opt-out method, and the study was registered in the UMIN Clinical Trial Registry under the number UMIN000050590.

Patients. We identified 846 patients with pathologically or radiologically confirmed primary metastatic pancreatic cancer who underwent first-line chemotherapy at Tokushukai Medical Group hospitals between April 1, 2010, and March 31, 2020 (8). Briefly, the patients were treated with gemcitabine, S-1, gemcitabine plus S-1, gemcitabine plus nab-paclitaxel, or FOLFIRINOX as their first-line treatment. Patients with pathological diagnoses of adenocarcinoma, adenosquamous carcinoma, and carcinoma/malignant neoplasms were included in the analysis. Patients with active double cancer, inadequate treatment history, and missing fundamental patient data were excluded from the study.

Data collection. As separately described, information on patients, tumor-related factors, study period (A: 2010-2013, B: 2014-2016, C: 2017-2020), hospital volume (high- and low-volume hospitals), hospital type (government-designated cancer hospital, prefecture-designated cooperative cancer

Table II. Medical and demographic characteristics of patients.

Characteristic	No. of patients	
	All cases (n=846)	Analyzed cases (n=487)
Age, years		
Median (quantile)	70 (36, 64, 70, 76, 90)	71 (37, 65, 71, 76, 90)
≥75, n (%)	266 (31.4)	166 (34.1)
Sex, n (%)		
Male	503 (59.5)	279 (57.3)
Female	343 (40.5)	208 (42.7)
PS, n (%)		
0	232 (27.4)	124 (25.5)
1	290 (34.3)	188 (38.6)
2	53 (6.3)	36 (7.4)
N/A	271 (32.0)	139 (28.5)
BMI, kg/m^2		
Median (quantile)	19.7 (11.2, 17.4, 19.7, 21.9, 35.4)	19.7 (11.2, 17.4, 19.7, 21.9, 35.4)
Smoking status, n (%)		
Current or former (BI >0)	217 (25.7)	125 (25.7)
Never smoked (BI=0)	562 (66.4)	333 (68.4)
N/A	67 (7.9)	29 (5.9)
Pathology, n (%)		
Yes	745 (88.1)	435 (89.3)
Adenocarcinoma	418 (49.4)	243 (49.9)
Adenosquamous carcinoma	7 (0.8)	4 (0.8)
Carcinoma/malignant neoplasm	320 (37.8)	188 (38.6)
No (Radiological diagnosis only)	101 (11.9)	52 (10.7)
Primary disease site, n (%)		
Pancreas head	359 (42.5)	199 (40.9)
Pancreas body	232 (27.4)	140 (28.7)
Pancreas tail	220 (26.0)	129 (26.5)
Not evaluable	35 (4.1)	19 (3.9)
Previous procedures, n (%)		
Surgery	123 (14.5)	47 (9.7)
Endoscopic procedure	44 (5.2)	19 (3.9)
Radiotherapy	47 (5.6)	25 (5.1)
Study period, n (%)		
Period A (2010-2013)	268 (31.7)	135 (27.7)
Period B (2014-2016)	251 (29.6)	159 (32.7)
Period C (2017-2020)	327 (38.7)	193 (39.6)
Hospital scale, n (%)		
High volume (n ≥50)	509 (60.2)	303 (62.2)
Low volume (n <50)	337 (39.8)	184 (37.8)
Hospital type, n (%)		
Government-designated cancer hospital	218 (25.7)	137 (28.1)
Prefectural designated cancer hospital	316 (37.4)	181 (37.2)
General hospital	312 (36.9)	169 (34.7)
First-line systemic therapy, n (%)		
Gemcitabine monotherapy	302 (35.7)	167 (34.3)
S-1 monotherapy	197 (23.3)	102 (20.9)
Gemcitabine plus S-1	66 (7.8)	38 (7.8)
Gemcitabine plus nab-paclitaxel	229 (27.1)	146 (30.0)
FOLFIRINOX	52 (6.1)	34 (7.0)

PS, performance status; BMI, body mass index; N/A, not accessed; BI, Brickman index.

Table III. Overall survival summary statistics for each score.

Score/ratio	n (%)	Events	Median overall survival (95% CI)	Hazard ratio (95% CI)	P-value
PNI					
≥45	200 (41.1)	139	7.4 (6.4-9.1)	Reference	-
<45	287 (58.1)	230	3.9 (3.0-5.1)	1.82 (1.47-2.27)	<0.0001
GPS					
0	184 (37.8)	129	7.4 (6.6-9.1)	Reference	-
1	157 (32.2)	118	5.7 (4.1-7.9)	1.33 (1.03-1.71)	0.0286
2	146 (30.0)	122	2.7 (1.8-4.6)	2.40 (1.86-3.11)	<0.0001
mGPS					
0	137 (28.1)	91	8.2 (7.2-9.9)	Reference	-
1	185 (38.0)	143	6.0 (4.8-8.3)	1.39 (1.07-1.81)	0.0150
2	165 (33.9)	135	2.9 (1.9-4.6)	2.63 (2.00-3.45)	<0.0001
CAR					
≤0.22	216 (46.4)	147	8.3 (7.2-10.5)	Reference	-
>0.22	271 (55.6)	222	4.5 (3.2-5.5)	2.06 (1.65-2.57)	<0.0001
NLR					
<3	177 (24.0)	119	8.3 (7.2-10.7)	Reference	-
≥3-<5	152 (31.2)	115	5.9 (4.8-7.4)	1.76 (1.35-2.29)	<0.0001
≥5	158 (32.4)	135	3.3 (2.8-4.6)	2.67 (2.07-3.44)	<0.0001
PLR					
≤150	203 (41.7)	151	7.1 (5.6-8.7)	Reference	-
>150	284 (58.3)	218	4.8 (4.0-6.4)	1.35 (1.09-1.67)	0.0056
LMR					
≥2.40	329 (67.6)	237	7.1 (6.0-8.6)	Reference	-
<2.40	158 (32.4)	132	3.9 (2.8-5.1)	1.83 (1.47-2.28)	<0.0001
dNLR					
<3	326 (66.9)	233	7.2 (6.0-8.7)	Reference	-
≥3-<5	114 (23.4)	94	3.9 (3.0-5.2)	2.02 (1.58-2.58)	<0.0001
≥5	47 (9.7)	42	2.2 (1.0-4.8)	2.05 (1.46-2.88)	<0.0001
NLS					
0	157 (32.2)	112	8.3 (7.2-10.6)	Reference	-
1	273 (56.1)	204	5.0 (4.0-6.8)	1.60 (1.26-2.03)	0.00011
2	57 (11.7)	53	3.4 (2.8-4.8)	2.46 (1.75-3.47)	<0.0001
PLS					
0	172 (35.3)	125	7.4 (6.4-9.1)	Reference	-
1	307 (63.0)	238	4.8 (3.9-6.0)	1.48 (1.18-1.84)	0.00066
2	8 (1.6)	6	4.7 (0.8-N/A)	1.54 (0.64-3.69)	0.33526
LMS					
0	174 (35.7)	125	7.9 (6.6-9.5)	Reference	-
1	293 (60.2)	224	4.8 (4.0-6.1)	1.52 (1.21-1.90)	<0.0001
2	20 (4.1)	20	1.6 (1.0-4.6)	4.34 (2.64-7.15)	<0.0001
NPS					
0	386 (79.3)	286	6.5 (5.3-8.1)	Reference	-
1	88 (18.1)	72	4.1 (2.9-5.3)	1.56 (1.18-2.05)	0.00155
2	13 (2.7)	11	3.7 (1.9-N/A)	3.32 (1.78-6.18)	<0.0001
PI					
0	235 (48.3)	166	7.9 (6.9-9.6)	Reference	-
1	195 (40.0)	152	5.1 (4.1-6.6)	1.58 (1.26-1.99)	<0.0001
2	57 (11.7)	51	1.9 (1.6-3.9)	3.35 (2.39-4.72)	<0.0001

Table III. Continued.

Score/ratio	n (%)	Events	Median overall survival (95% CI)	Hazard ratio (95% CI)	P-value
SII					
<300	40 (8.2)	30	8.7 (7.2-13.0)	Reference	-
≥300-<600	131 (26.9)	94	8.0 (6.7-10.9)	1.10 (0.72-1.66)	0.6690
≥600-<1,000	121 (24.8)	87	6.0 (4.8-8.7)	1.76 (1.15-2.70)	0.0089
≥1,000	195 (40.0)	158	3.9 (3.0-4.9)	2.50 (1.68-3.72)	<0.0001
SIRI					
<500	39 (8.0)	27	9.6 (8.6-15.5)	Reference	-
≥500-<1,000	120 (24.6)	84	7.2 (5.3-10.1)	1.60 (1.03-2.50)	0.0370
≥1,000-<2,000	140 (28.7)	99	7.1 (5.1-8.7)	1.96 (1.26-3.03)	0.00266
≥2,000	188 (38.6)	159	3.7 (2.9-4.9)	3.37 (2.20-5.17)	<0.0001
LIPI					
0	267 (54.8)	184	7.9 (7.1-9.9)	Reference	-
1	153 (31.4)	126	4.2 (3.6-6.1)	1.86 (1.47-2.34)	<0.0001
2	67 (13.8)	59	2.2 (1.5-4.3)	3.33 (2.45-4.53)	<0.0001
CALLY					
<5	431 (88.5)	332	5.1 (4.2-6.6)	Reference	-
≥5	56 (11.5)	37	10.3 (8.2-13.9)	0.50 (0.35-0.70)	<0.0001

Data were analyzed using log-rank test.PNI, prognostic nutritional index; GPS, Glasgow Prognostic Score; mGPS, modified GPS; CAR, CRP-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; NLS, neutrophil-lymphocyte score; PLS, platelet-lymphocyte score; LMS, lymphocyte-monocyte score; NPS, neutrophil-platelet score; PI, prognostic index; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; LIPI, lung immune prognostic index; CALLY, CRP albumin lymphocyte index; CRP, C-reactive protein; CI, confidence interval.

hospital, or non-designated general hospital), and first-line chemotherapy regimens was extracted from the medical record system, the chemotherapy protocol system, and the National Cancer Registry Data in Japan (15).

For supplemental analysis, blood laboratory data for different parameters [white blood cells, neutrocytes, lymphocytes, monocytes, hemoglobin, platelets, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), γ-glutamyl transpeptidase, alkaline phosphatase, creatinine, creatinine clearance, c-reactive protein (CRP), albumin, glucose, hemoglobin A1c, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)] collected within 14 days of first-line treatment were extracted from the electronic medical record, and levels of inflammation-based prognostic markers were calculated (16-29). The markers used in this study are listed in Table I. For the markers, previously defined cutoff values were used, but for those that were not defined, we referred to previous studies (24,25).

Statistical analysis. Patients with complete data available were evaluated. The primary endpoint evaluated in the current study was OS, defined as the time from the start date of initial palliative chemotherapy to the date of death or final survival confirmation.

Basic statistics (absolute and relative frequencies for categorical variables; quartiles, maximum values, minimum values, means, or medians for continuous variables) were obtained to summarize the distribution of variables related to patient background factors, complications, other prognostic factors, and primary and secondary endpoints. Survival analyses were performed using OS as the primary endpoint. The censored cases included patients who were alive at the end date of the study or had dropped out of the study for any reason.

Kaplan-Meier curves (univariate analyses) were obtained for each inflammation-based prognostic markers associated with OS, and the log-rank test was utilized to compare survival curves. We compared the predictive quality of markers against OS using the Cox regression analysis concordance (rate) and the Akaike Information Criterion (AIC). Concordance was defined as follows. Assuming that (si, yi) is a pair of observed survival time (y) and scores (s), a pair of observations (i, j) was considered 'concordant' if (yi > yj, si < sj) or (yi < yj, si >sj), as these conditions are symmetrical. Conversely, it was considered 'discordant' if the conditions (yi < yj, si < sj) or (yi > yj, si > sj) applied. If c, d, and t_s are counts of pairs that are concordant, discordant, or tied when using score s, then concordance C is defined as $C=(c + t_s/2)/(c + d + t_s)$ using the proportion of concordant pairs. Although the above definition of 'concordant' and 'discordant' pairs appears to be reversed, survival is inversely correlated with the height of the hazard, and this definition has validity.

All analyses were performed using R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

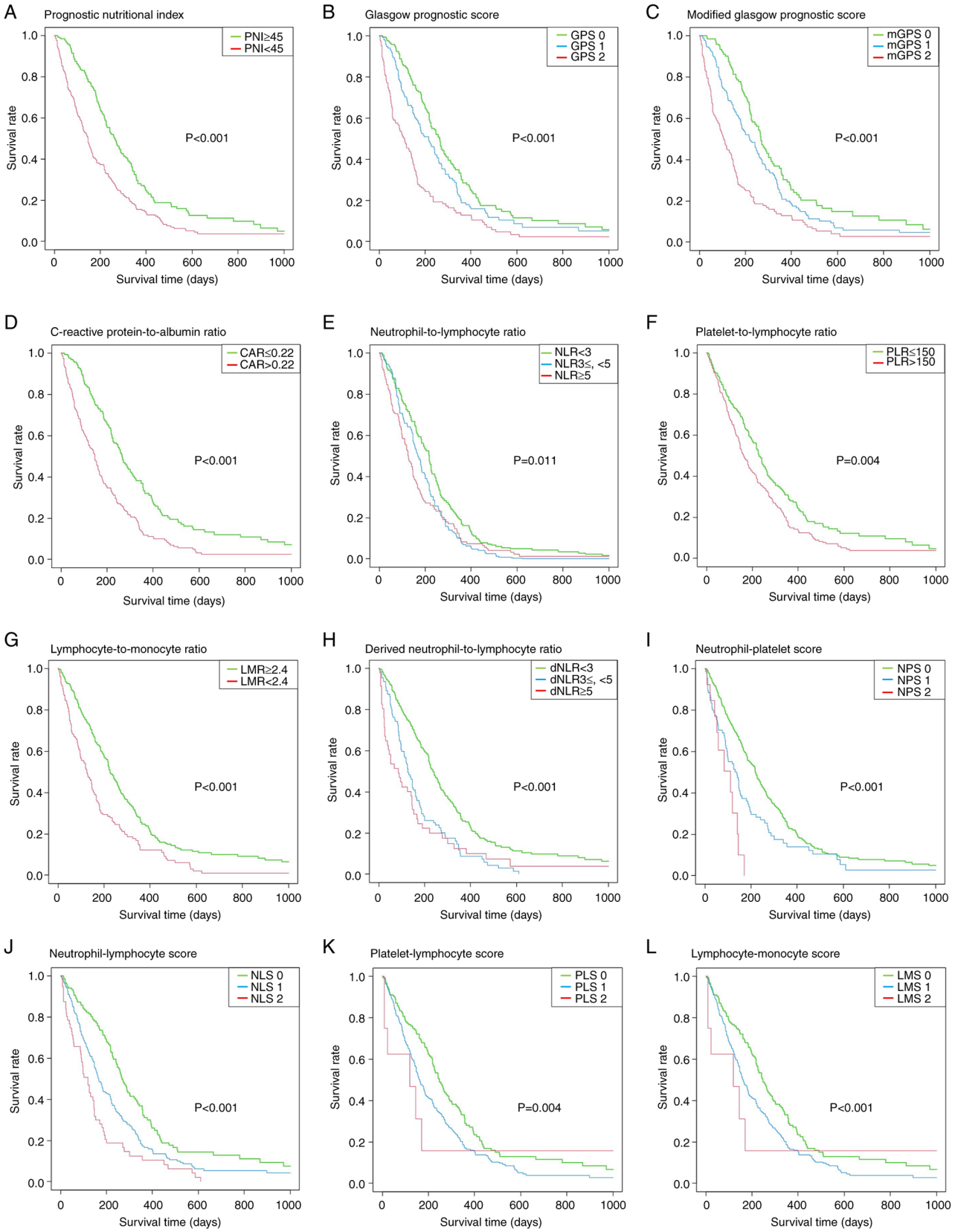

Figure 1. Continued.

All statistical assessments were conducted as two-sided, and significance was determined with a threshold of P<0.05. All statistical analyses were two-sided, and P<0.05 was considered to indicate a statistically significant difference.

Results

Patients' characteristics. Among the 846 patients initially identified for this study, a total of 487 individuals were selected

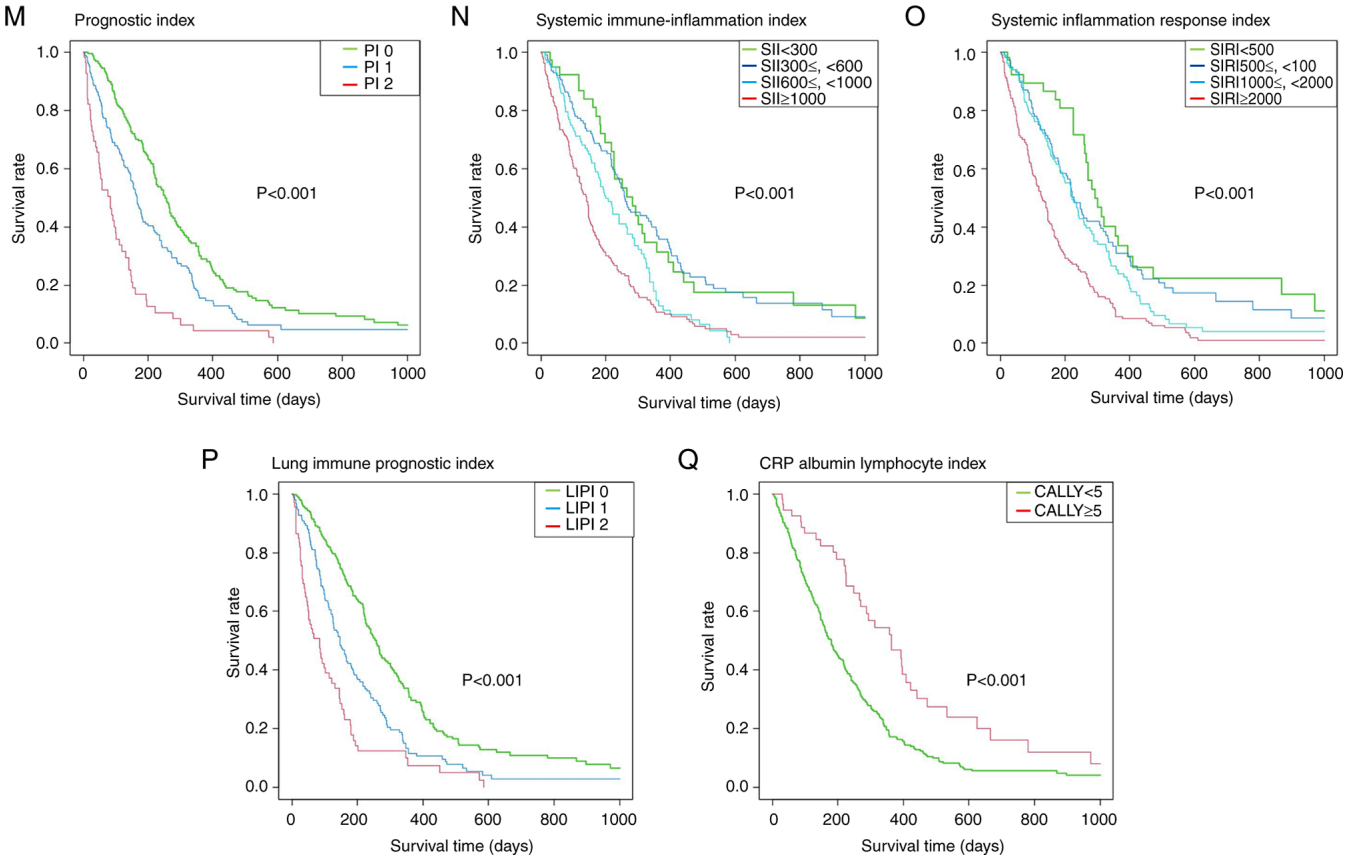

Figure 1. Overall survival based on the different scores/ratios. A log-rank test was used to calculate significance. (A) Prognostic nutritional index, (B) Glasgow prognostic score, (C) modified Glasgow prognostic score, (D) C-reactive protein-to-albumin ratio, (E) neutrophil-to-lymphocyte ratio, (F) platelet-to-lymphocyte ratio, (G) lymphocyte-to-monocyte ratio, (H) derived neutrophil-to-lymphocyte ratio, (I) neutrophil-platelet score, (J) neutrophil-lymphocyte score, (K) platelet-lymphocyte score, (L) lymphocyte-monocyte score, (M) prognostic index, (N) systemic immune-inflammation index, (O) systemic inflammation response index, (P) lung immune prognostic index and (Q) CRP albumin lymphocyte index. CRP, C-reactive protein.

in the analysis due to the availability of complete data. Table II displays the characteristics of both the entire patient cohort and the subset included in the analysis. The two populations showed similar characteristics.

Comparison of the ratios and scores. Table III summarizes the OS statistics by 17 inflammation-based prognostic markers. All markers had statistically significant prognostic value. In addition, when comparing ratios computed as continuous variables with scores determined using categorical variables employing specific cutoff values, it was evident that similar hazard ratio (HR)s were observed. For instance, when we analyzed the HRs and their corresponding 95% confidential intervals for NLR (<3 compared to ≥3-<5 and ≥5) and NLS (0 compared to 1 and 2), the outcomes were as follows: 1.76 (1.35-2.29) and 2.67 (2.07-3.44) for NLR, and 1.60 (1.26-2.03) and 2.46 (1.75-3.47) for NLS, respectively.

Kaplan-Meier curves. The Kaplan-Meier curves for OS by each inflammation-based prognostic marker are shown in Fig. 1. Each marker alone showed a significant correlation with prognosis. Additionally, for the majority of markers, each increment in the numerical value was linked to a gradual deterioration in prognosis.

Comparison of the inflammation-based prognostic markers. The concordance rates and AICs calculated for the 17 inflammation-based prognostic markers are shown in Table IV. The concordance values ranged from 0.616 to 0.679, and the AIC values ranged from 3784 to 3836. Among them, the mGPS correlated best with OS, followed by GPS and lung immune prognostic index (LIPI).

Discussion

In this study, we compared inflammation-based prognostic markers helpful in predicting prognosis in patients undergoing chemotherapy for metastatic pancreatic cancer using real-world data from the Tokushukai medical database. While numerous prognostic and predictive markers have been reported, to the best of our knowledge, this study represents the most comprehensive comparison of inflammation-based prognostic markers to date. All 17 markers we evaluated demonstrated significant prognostic value, irrespective of whether they were ratio-based or scored systems. Among them, the mGPS, GPS, and LIPI emerged as the most accurate in predicting prognosis following first-line treatment of metastatic pancreatic cancer.

GPS is probably the most widely used prognostic score, with numerous reports supporting its usefulness. It was defined and reported by Forrest *et al* (17) in 2003 as CRP and albumin levels in patients with unresectable non-small cell lung cancer. According to multivariate analyses, the combined score of CRP and albumin was identified as an independent prognostic

Table IV. Prognostic scores/ratios, and their concordance rates and AIC for overall survival.

Score	Concordance	AIC
mGPS	0.679	3,796
GPS	0.672	3,802
LIPI	0.669	3,784
PI	0.666	3,799
CAR	0.666	3,801
NLR	0.665	3,788
SIRI	0.657	3,797
SII	0.653	3,801
dNLR	0.650	3,808
PNI	0.650	3,814
LMR	0.645	3,817
NLS	0.642	3,816
LMS	0.632	3,814
NPS	0.628	3,827
CALLY	0.626	3,825
PLS	0.618	3,834
PLR	0.616	3,836

AIC, Akaike Information Criterion; mGPS, modified GPS; GPS, Glasgow Prognostic Score; LIPI, lung immune prognostic index; PI, prognostic index; CAR, CRP-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic immune-inflammation index; dNLR, derived neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; LMR, lymphocyte-to-monocyte ratio; NLS, neutrophil-lymphocyte score; LMS, lymphocyte-monocyte score; NPS, neutrophil-platelet score; CALLY, CRP albumin lymphocyte index; PLS, platelet-lymphocyte score; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein.

factor, and a validation study was subsequently reported in 2004 (30). The validity of the GPS has been reported in the Glasgow Inflammation Outcome Study (18,19), and the GPS is now widely used as an inflammation-based prognostic marker (11). In addition, several modifications of the GPS with adjusted cutoff values have been reported with improved accuracy. In studies of patients with colorectal cancer, low albumin levels did not correlate with poor prognosis because few patients have low albumin levels without elevated CRP levels. Thus, low albumin level alone looked less associated with poor prognosis (31), and a modified GPS that partially excludes the albumin level has been suggested (11). In a study examining the correlation between the mGPS and prognosis in Japanese patients with colorectal cancer, the best cutoff value of 0.5 mg/dl was reported for CRP based on its receiver operating characteristic curve (32).

LIPI, another recently reported score, is based on a combination of dNLR and LDH scores. The prognostic correlation of LIPI was reported by Mezquita *et al* in 2018 in patients treated with immune checkpoint inhibitors for advanced non-small cell lung cancer (28). LIPI has been developed as a prognostic score because dNLR and LDH level were independent prognostic factors in two large retrospective studies of patients with metastatic melanoma treated with ipilimumab (33) or pembrolizumab (34). The combination of these two factors has been reported to be of prognostic value in patients treated with immune checkpoint inhibitors for lung cancer (35,36), urothelial carcinoma (37), or solid tumors in general (38). Although the LIPI score was developed for patients treated with immune checkpoint inhibitors, the present study shows it is also a useful prognostic indicator in metastatic pancreatic cancer. The literature examining the usefulness of LIPI is still limited, and further studies are needed to determine whether it is reproducible in other cancers.

This study has a few limitations. First, due to the retrospective design, a number of patients had deficiencies in blood tests such as CRP, albumin, and LDH, which are not essential for chemotherapy induction. Accordingly, fewer patients qualified for the complete analysis. Second, new inflammation-based prognostic markers are introduced each year, and not all of them are included in this study. Third, this study included only Japanese subjects. Hence, its external validity may be limited in non-Asian populations. However, a nationwide study conducted in the Netherlands on metastatic pancreatic cancer identified CA19-9, albumin, CRP, LDH, C-reactive protein-to-albumin ratio, and GPS/mGPS as easily measurable prognostic biomarkers (39). Additionally, a systematic review from 2013 confirmed the prognostic potential of GPS/mGPS and NLR (40). Hence, it is safe to assume that at least GPS/mGPS are applicable prognostic biomarkers for both Asian and non-Asian patients with metastatic pancreatic cancer.

Lastly, additional parameters such as hemoglobin, CEA, and CA19-9 may also hold prognostic significance. Despite these limitations, the robustness of this study lies in the incorporation of a sizable cohort and the simultaneous assessment of real-world data for numerous inflammation-based prognostic markers. Our future research will evaluate each laboratory parameter and develop a novel prognostic score.

In conclusion, our real-world data analysis demonstrated that 17 inflammation-based markers that previously reported held significant prognostic value for patients with metastatic pancreatic cancer. Among these markers, the mGPS exhibited the highest accuracy.

Acknowledgements

The authors would like to thank Dr Shinnichi Higashiue (chair of the Medical Corporation Tokushukai, Tokyo, Japan and General Incorporated Association Tokushukai, Tokyo, Japan) and Dr Hisaaki Afuso (chief advisor of the Medical Corporation Tokushukai, Tokyo, Japan) for their support in conducting clinical research within the Tokushukai Group, and Mr. Katsuhiko Ozaki (President of Tokushukai Information System, Inc., Osaka, Japan) for their assistance in using the medical database.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RS, YI and MO made substantial contributions to the study design and conception. RS, YF, MS and MH were responsible for data acquisition. RS and YI interpreted the data and drafted the manuscript. KU, TM, KO, NS and HM provided advice on research design and aided in the critical interpretation of this research for critical content. RS and YI confirm the authenticity of all the raw data. NS and HM comprehensively reviewed and approved the final version of this manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The project adhered to the ethical guidelines for medical and biological research involving human subjects in Japan and followed the principles of The Declaration of Helsinki. Approval for the study was obtained from the Ethics Committee of the Tokushukai Group in April 2020 (approval no. TGE01427-024), and the study was registered in the UMIN Clinical Trial Registry under the number UMIN000050590. Patients were provided with information using opt-out methods and no patient declared not to participate.

Patient consent for publication

Patient consent for publication was obtained through opt-out methods.

Competing interests

The authors declare that they have no competing interests.

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