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ORIGINAL ARTICLE

Prognostic value of an inflammation-based nutritional score for patients with initially unresectable pancreatic adenocarcinoma undergoing conversion surgery following chemo-/radiotherapy

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Abstract

Purpose To clarify the prognostic value of the preoperative nutrition status of patients undergoing conversion surgery (CS) for initially unresectable pancreatic adenocarcinoma (UR-PA).

Methods The subjects of this retrospective study were 41 consecutive patients with initially UR-PA treated with chemo-/radiotherapy and subsequent CS between 2007 and 2014, at Tohoku University Hospital. The preoperative Glasgow Prognostic Score (GPS) was 0, conveying normal nutrition, in 25 patients (N group) and 1–2, conveying malnutrition, in 16 patients (M group). The clinicopathological factors influencing overall survival were defined by uni- and multivariate analyses.

Results The M group had a significantly worse prognosis than the N group (median overall survival (mOS) 9.6 vs 40.7 months, $p=0.001$). Multivariate analysis identified a GPS of 1–2 as an independent predictor of worse prognosis [hazard ratio (HR)3.437, $p=0.032$], followed by CA19-9 elevation before CS (HR4.089, $p=0.012$) and pathological lymph node metastases (HR2.314, $p=0.046$). Patients who maintained a favorable nutritional status (GPS 0) during preoperative treatment had a significantly better prognosis, whereas those whose nutritional status deteriorated (elevated to GPS 1–2) had poorer survival (mOS 40.7 vs. 9.7 months, $p=0.003$)

Conclusion Preoperative malnutrition status (GPS 1–2) is considered an independent predictor of a worse prognosis for patients undergoing CS for initially UR-PA.

Keywords Pancreas adenocarcinoma · Inflammation-based score · Conversion surgery

Introduction

Pancreatic adenocarcinoma (PA) is an aggressive malignancy associated with a dismal prognosis of 6.8–9% 5-year overall survival [1, 2]. Surgical resection provides the only chance for cure of this disease; however, fewer than 30% of patients with newly diagnosed PA are candidates for surgical resection [3]. Recently, novel agent and chemotherapy regimens such as gemcitabine plus albumin (Alb)-bound paclitaxel (GnP) and FOLFIRINOX have been introduced for PA, with promising response rates (20%-30%) in clinical trials [4–7]. A multicentric Japanese group reported significantly better efficacy of neoadjuvant chemotherapy using gemcitabine plus S1 (GS) than of conventional upfront surgery for potentially resectable PA [8–10]. Furthermore, despite the radiologic appearance of initially unresectable (UR)-PA with no intent to resect, multidisciplinary non-surgical treatments induce favorable efficacy in the long term and might enable a subsequent surgical option, called "conversion surgery (CS)", in 4.5–29% of patients with UR-PA [11–13]. Those selected patients are likely to benefit from CS, which can improve their prognosis and achieve 31–56 months of median overall survival (OS).

Nutritional disorders in patients with cancer are characterized by loss of skeletal muscle and fat mass, termed recently as "cancer-induced weight loss" or "cachexia" [14–16]. The symptoms of cachexia are mediated by the

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interaction of tumor- and host-derived compounds, leading to progressive functional impairment and an irreversible condition requiring conventional nutritional support. Cachexia negatively affects therapeutic outcomes, such as infectious complications in perioperative management and less responsiveness to systemic chemo-/radiotherapy, resulting in adverse prognoses for esophageal cancer, head and neck cancer, and PA [17–19]. Several scoring systems have been devised to evaluate the inflammation-based nutritional status of patients with cancer, such as the Glasgow Prognostic Score (GPS) based on C-reactive protein (CRP) and serum albumin. The GPS is considered the most useful tool to reflect a systemic immune-inflammatory status and has been validated to define the different stages of cachexia objectively [20]. Previous reports have identified the GPS as a significant factor associated with the survival of esophageal cancer and PA patients [21–23]. In particular, UR-PA patients undergoing CS are likely to be characterized as having a worsened nutrition status following long-term chemo-/radiotherapy; however, few papers have reported the usefulness of preoperative GPS to predict overall survival after CS.

For patients with initially UR-PA, a subsequent surgical option after long-term favorable responses to multimodality therapies provides a potential for a more favorable prognosis; therefore, the patient's total nutritional status after chemo-/radiotherapy must be evaluated to determine patient selection for CS. This study aims to define the prognostic implication of an inflammatory-based nutrition prognostic scoring system, such as the GPS, for patients with initially UR-PA undergoing CS.

Methods

Study design

We collected retrospective data on 42 patients with initially UR-PA, who showed a favorable response to multimodality chemo-/radiotherapy and subsequently underwent CS at Tohoku University Hospital between 2007 and 2017. Patients with tumors other than invasive ductal carcinoma, such as endocrine carcinoma, acinar cell carcinoma, or intraductal papillary mucinous carcinoma were excluded. One patient who received total parenteral nutrition as an intervention before CS for a worsening nutritional status was also excluded from this cohort. The remaining 41 patients did not receive any specific nutritious intervention before CS and were the subjects of this analysis. The present study was performed in accordance with the Declaration of Helsinki and approved by our institutional review board (2019-1-303). Informed consent was waived because of the retrospective nature of this study.

Patient selection for CS

UR-PA was diagnosed by thin-slice abdominal computed tomography according to the NCCN guidelines in all patients who underwent several regimens of chemo-/radiotherapies with no intention of resection [24, 25]. After the chemo-/radiotherapy, if there was a progression-free appearance in the major tumor involvement or distant metastases on radiological imaging or intraoperatively, CS was scheduled as radical surgical resection 6 months or longer in principle after beginning the initial treatment. The decreased value of tumor markers during the preoperative treatment period was considered of greater importance in the decision-making for CS.

In this study, a total of 41 patients with initially UR-PA showed a favorable response to long-term non-surgical treatment and underwent surgical resection (Fig. 1). The tumors in 30 patients with locally advanced UR-PA (UR-LA) appeared to be localized without any newly detectable distant metastases during the preoperative period (Table 1). In 11 patients with UR-PA metastases (UR-M), liver metastasis in one patient and peritoneal cancer cells in one patient disappeared completely after the preoperative treatment. Other liver or peritoneal metastases in 8 patients showed a favorable response to preoperative treatment with PR or SD evaluation according to the Response Evaluation Criteria in Solid Tumors (RECIST) and these 8 patients underwent pancreatectomy combined with partial hepatectomy. The remaining one UR-M patient underwent CS with PD evaluation by RECIST. This patient had a synchronous small liver metastasis initially, which grew slowly during the chemo-/radiotherapy period over 2 years; however, as no new obvious metastases were identified during that period, we performed subsequent pancreatectomy combined with partial liver resection. Unfortunately, early liver recurrence was identified 82 days after CS and the patient died 145 days after CS and 843 days after beginning the initial treatment.

Perioperative management

The type of preoperative chemo-/radiotherapy given to each patient was dependent on their condition and decided by the physician. In the latter period of this study, GS or GnP became the major systemic chemotherapy regimen and radiotherapy was combined with S1 in most cases (Supplemental Table 1). In patients with emerging obvious metastases on radiological investigation, insufficient decrease of the cancer antigen (CA19-9) level, or a high incidence of adverse events, other agents or regimens were administered as second-line therapy. Sixteen

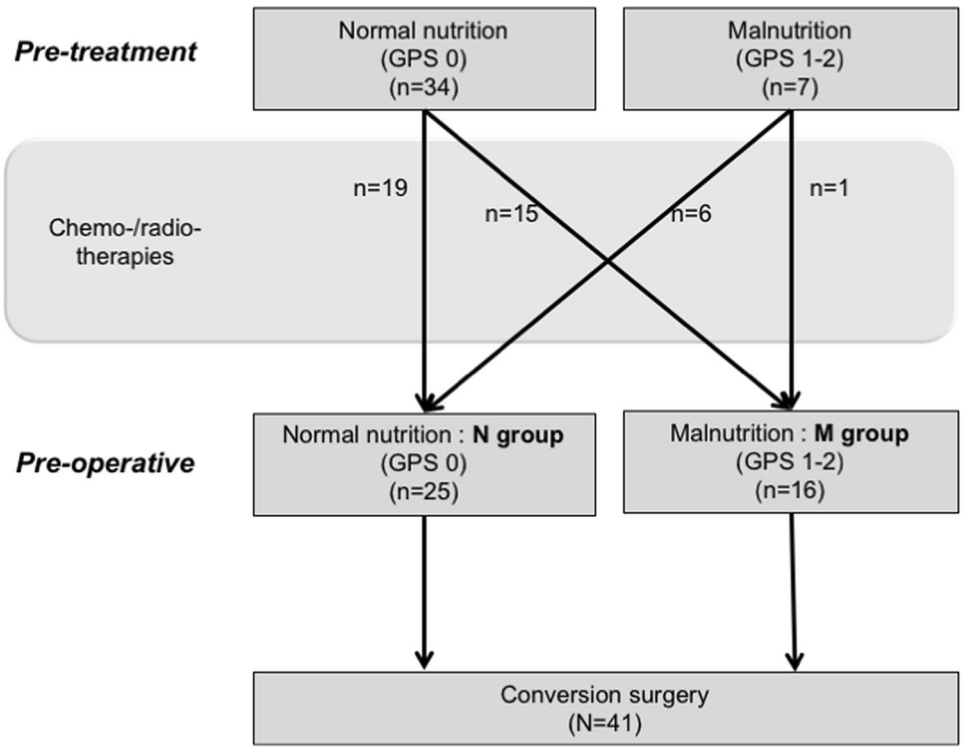

Fig. 1 Flowchart of the patient selection. A total of 41 patients who received multimodality therapies and subsequent conversion surgery (CS) for initially unresectable pancreatic adenocarcinoma (UR-PA) were divided into two groups according to their preoperative Glasgow prognostic score (GPS). The N group consisted of 25 patients with a favorable nutrition status (GPS 0), and the M group consisted of the remaining 16 patients with malnutrition status (GPS 1–2). Among the 34 patients exhibiting a better nutrition status (GPS 0) before preoperative treatment, 19 maintained a favorable nutrition status during the preoperative period, but the remaining 15 deteriorated into a malnutrition status after that period

patients received systemic chemotherapy alone (as more than two regimens in 2), 25 patients received chemoradiotherapy, and 12 received induction chemotherapy [26, 27]. Chemoradiotherapy was administered at a total radiation dose of 45–50 Gy with a daily fraction of 2–2.4 Gy, five times per week. The targeted fields included the primary pancreatic tumor, the surrounding arteries, and the retroperitoneal soft tissue. Preoperative treatment responses were evaluated using RECIST a few weeks after the last dose. In this cohort, pancreaticoduodenectomy ($n=21$), distal pancreatectomy with celiac axis resection ($n=15$), or total pancreatectomy ($n=5$) with extended lymph node dissections was performed. The pathological findings were evaluated based on the 8th TNM classification by the Union for International Cancer Control (UICC) and Evan's classification [28]. According to previously reported evidence, adjuvant gemcitabine or S1 therapy was administered routinely during the postoperative period [29–31].

Inflammation-based nutrition assessment

Systemic inflammation-based nutritional states before and after the preoperative treatment were evaluated by well-known scoring systems using nutritional and immunological factors; namely, the GPS, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic nutritional index (PNI) based on Alb and lymphocyte count, and the controlling nutritional status (CONUT) [20, 32–35]. Blood samples were collected within a few days before chemo-/radiotherapy induction or surgery. No clinical evidence of infection or other inflammatory conditions was documented at the time of blood sampling. The GPS was defined as follows: a normal Alb level $\geqq 3.5$ g/dl and a CRP $\leqq 1.0$ mg/dl was scored as 0, a low Alb < 3.5 g/dl and a high CRP > 1.0 mg/dl was scored as 2, and only a low Alb < 3.5 g/dl or a high CRP > 1.0 mg/dl was scored as 1. The PNI was calculated as $(10 \times \text{Alb}) + (0.005 \times \text{lymphocyte count})$ and a PNI < 40 indicated malnutrition. The CONUT scores were defined as follows: Alb $\geqq 3.5$ g/dl, 3.0–3.49 g/dl, 2.5–2.99 g/dl, and < 2.5 g/dl scored 0, 2, 4 and 6, respectively; total cholesterol $\geqq 180$ mg/dl, 140–179 mg/dl, 100–139 mg/dl, and < 100 mg/dl scored 0, 1, 2 and 3, respectively; a lymphocyte count $\geqq 1600$ /μl, 1200–1599/μl, 800–1199/μl, and < 800/μl scored 0, 1, 2 and 3, respectively. The CONUT score was calculated as the summation of all scores, and $\geqq 5$ indicated malnutrition. NLR and PLR were calculated by dividing the neutrophil count by the lymphocyte count and the platelet count by lymphocyte count, respectively. NLR $\geqq 3.77$ or PLR $\geqq 228.9$ indicated malnutrition.

Statistical analysis

The X^2 test was used to compare categorical variables and the Mann–Whitney U test was used to evaluate continuous variables. Survival curves were estimated by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate analyses were performed using the Cox multivariate proportional hazard regression model

Table 1 Descriptive statistics for the total cohort as stratified by the preoperative nutritional status

	Total cohort	Preoperative nutritional status		*p* value
		N group (GPS 0)	M group (GPS 1–2)	
Number	41	25	16	
Gender (*n*)				
Male	27 (65.9)	17 (68.0)	10 (62.5)	
Female	14 (34.1)	8 (32.0)	6 (37.5)	0.717
Age (year)				
Median (range)	65 (41–79)	64 (52–74)	69 (41–79)	0.239
Pre-treatment CA19-9 value (U/ml)				
Median (range)	238.0 (0.6–87,100.0)	222.1(5.4–11,341.0)	283.7 (0.6–87,100.0)	0.748
Preoperative CA19-9 value (U/ml)				
Median (range)	45.0 (0.6–37,370.0)	38.6 (6.2–4430.0)	71.1 (0.6–37,370.0)	0.423
Post-surgical CA19-9 value (U/ml)				
Median (range)	19.4 (1.9–4543.0)	18.4 (1.9–4543.0)	48.7 (9.8–2188.0)	0.236
NCCN resectability, *n* (%)				
UR-LA	30 (73.2)	17 (68.0)	13 (81.2)	
UR-M	11 (26.8)	8 (32.0)	3 (18.8)	0.350
Biliary drainage, *n* (%)				
Yes	12 (29.3)	9 (36)	3 (18.8)	
No	29 (70.7)	16 (64)	13 (81.2)	0.236
Preoperative therapy, *n* (%)				
Systemic chemotherapy	16 (39.0)	9 (36.0)	7 (43.8)	
Chemoradiotherapy	25 (61.0)	16 (64.0)	9 (56.2)	0.620
Duration of preoperative therapy (day)				
Median (range)	178.0 (60–846)	178 (60–449)	178 (70–846)	0.631
RECIST, *n* (%)				
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	
Partial response	15 (36.6)	10 (40.0)	5 (31.2)	
Stable disease	25 (61.0)	15 (60.0)	10 (62.5)	
Progressive disease	1 (2.4)	0 (0.0)	1 (6.3)	0.411
Pancreatectomy procedure, *n* (%)				
Pancreaticoduodenectomy	21 (51.2)	14 (56.0)	7 (43.7)	
DP-CAR	15 (36.6)	8 (32.0)	7 (43.7)	
Total pancreatectomy	5 (12.2)	3 (12.0)	2 (12.6)	0.720
Evans's grade, *n* (%)				
I	3 (7.3)	2 (8.0)	1 (6.3)	
IIA	26 (63.4)	16 (64.0)	10 (62.5)	
IIB	7 (17.1)	5 (20.0)	2 (12.5)	
III	5 (12.2)	2 (8.0)	3 (18.7)	0.732
T classification (UICC), *n* (%)				
1	7 (17.1)	3 (12.0)	4 (25.0)	
2	22 (53.7)	14 (56.0)	8 (50.0)	
3	9 (21.9)	5 (20.0)	4 (25.0)	
4	3 (7.3)	3 (12.0)	0 (0)	0.382
N classification (UICC), *n* (%)				
0	20 (48.8)	14 (56.0)	6 (37.4)	
1	10 (24.4)	5 (20.0)	5 (31.3)	
2	11 (26.8)	6 (24.0)	5 (31.3)	0.501
Residual tumor, *n* (%)				

Table 1 (continued)

	Total cohort	Preoperative nutritional status		*p* value
		N group (GPS 0)	M group (GPS 1–2)	
R0	32 (78.0)	23 (92.0)	9 (56.2)	
R1	9 (22.0)	2 (8.0)	7 (43.8)	0.007
Adjuvant therapy, *n* (%)				
Yes	32 (78.0)	23 (92.0)	9 (56.2)	
No	9 (22.0)	2 (8.0)	7 (43.8)	0.007

GPS Glasgow Prognostic Score, *CA19-9* carbohydrate antigen 19–9, *NCCN* National Comprehensive Cancer Network, RECIST response evaluation criteria in solid tumors, *UR-LA* locally advanced disease of unresectable cancer, *DP-CAR* distal pancreatectomy with celiac axis resection, *UICC* Union for International Cancer Control

in a stepwise manner. The pre-treatment CA19-9 value and duration of neoadjuvant therapy were categorized as partitioned by the median values (300 U/ml) and day (140 days), respectively. The hazard ratio (HR) and 95% confidential interval (CI) were calculated in each category. All statistical analyses were performed with JMP Pro 14.2.0 (SAS Institute Inc., Cary, NC) and GraphPad Prism (San Diego, CA), and $p < 0.05$ was considered significant.

Results

Baseline characteristics

The subjects comprised 27 men and 14 women, with a median age of 65 years (Table 1). The 41 patients were divided into two groups based on the preoperative GPS (Fig. 1): 25 with normal nutritional status (GPS 0, N group) and 16 with malnutrition (GPS 1–2, M group) (Table 1). Of the original 34 patients with normal nutrition status (GPS 0) before treatment, 19 maintained favorable nutrition during the preoperative period, but 15 suffered deterioration of their nutritional status during the preoperative period. The nutritional status of six of the seven patients with malnutrition (GPS 1–2) before treatment improved (GPS 0) during the preoperative period (Supplemental Table 2).

Clinicopathological factors associated with preoperative malnutrition

Preoperative nutrition status is not associated with the perioperative CA19-9 value, duration of preoperative therapy, or NCCN resectability, UR-LA, or UR-M (Table 1). The presence of biliary drainage and combined radiotherapy were not significantly related to preoperative malnutrition. No significant difference was found in Evan's classification, UICC classification, RECIST, or surgical procedure between the groups. The malnutrition status before CS was significantly related to a macroscopically positive margin (R1) and absence of adjuvant chemotherapy ($p = 0.007$ and 0.007, respectively).

Survival analysis stratified by nutritional status before CS

Among the 41 patients undergoing multimodality therapy and subsequent CS for initially UR-PA, the median OS (mOS) and disease-free survival (mDFS) were 26.4 and 8.3 months, respectively. According to the survival analysis stratified by the preoperative nutrition status, the M group had significantly poorer survival after CS, than the N group (mOS 9.6 vs 40.7 m: $p = 0.001$, mDFS 6.2 vs 21.4 m: $p = 0.026$) (Fig. 2).

Subgroup survival analysis according to nutritional status during preoperative therapy

According to the subgroup analysis stratified by alteration in nutritional status during the preoperative period, 19 patients whose nutritional status was maintained (GPS 0) had a significantly better prognosis after CS than 15 patients whose nutrition status deteriorated to GPS 1–2 during the preoperative period (Normal- > Normal vs. Normal- > Malnutrition: mOS 40.7 vs 9.7 m, p = 0.003; mDFS 16.3 vs 6.2 m, $p = 0.018$) (Fig. 3). The nutritional status of six of the seven patients with initially confirmed malnutrition (GPS 1–2) improved to GPS 0 during preoperative treatment, and their prognoses were similar to those with GPS 0 preoperatively (Malnutrition- > Normal: mOS 36.5 m, mDFS 31.0 m). This preoperative nutrition alteration was not associated significantly with preoperative treatment efficacy based on a decreased preoperative CA19-9 value or pathological evaluation by Evan's classification (Supplemental Table 2).

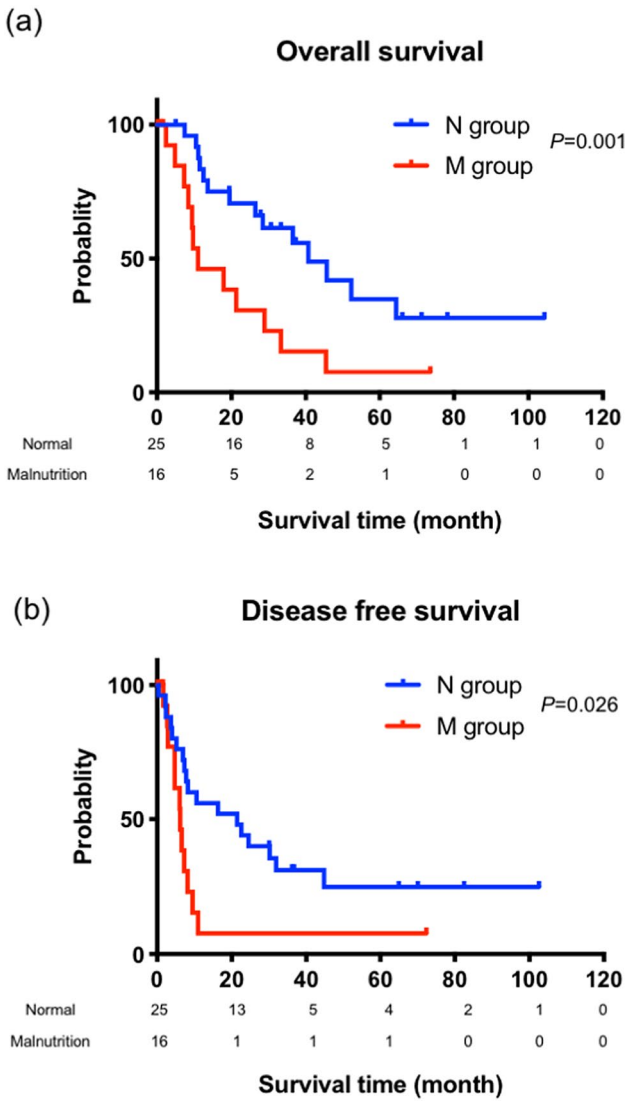

Fig. 2 Survival analysis stratified by the preoperative nutrition status. Patients in the M group had significantly poorer overall survival (OS) and disease-free survival (DFS) than those in the N group (median OS 9.6 vs 40.7 m: $p=0.001$, median DFS 6.2 vs 21.4 m: $p=0.026$)

Survival analysis using other nutritional scoring systems

Figure 4 shows the survival analysis stratified by a nutritional assessment using the well-known scoring systems, PNI, CONUT, NLR, and PLR. Among these scoring systems, a significant survival difference was observed in the CONUT assessment. Patients with a low CONUT score, indicative of normal nutrition, had significantly longer OS than those with a high CONUT score ($p=0.004$).

Uni- and multivariate analyses using the Cox Proportional Hazards Model

Table 2 shows the results of the univariate analysis conducted to clarify which clinicopathological factors influenced the postoperative OS of the 41 patients. A preoperative CA19-9 value ≥ 37 U/ml ($p=0.007$), pathological lymph node metastases ($p=0.005$), and microscopically residual tumor (R1) ($p=0.018$) were significantly associated with shorter OS. The multivariate analysis identified the following as significant independent predictors of poor prognosis: preoperative CA19-9 value ≥ 37 U/ml (HR4.089, 95%CI 1.367–12.225, $p=0.012$), pathological lymph node metastases (HR 2.314, 95%CI 1.015–5.275, $p=0.046$), and elevation to GPS 1–2 (M group) (HR3.437, 95%CI 1.116–10.589, $p=0.032$).

Discussion

The NCCN guidelines [25] recommend surgical resection for UR-PA as a second-line option only for patients with good performance status and for whom systemic chemo-/radiotherapies have had favorable efficacy. However, few reports have discussed the prognostic implications for patients with UR-PA. In the current study, the GPS was considered the most reliable indicator of the systemic inflammation-based nutritional status of UR-PA patients undergoing long-term chemo-/radiotherapy with the intention of CS. Those with an elevated GPS preoperatively had a significantly worse prognosis and the GPS was an independent predictor of prognosis for patients undergoing CS following preoperative treatment for initially UR-PA.

A decrease in the serum CA19-9 level or a positive standard uptake value of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) after preoperative treatment are considered optimal indicators of treatment efficacy [36–40]. Most surgeons focus on CA19-9 alterations or radiological findings when deciding on the optimal timing for surgical resection; however, GPS alteration in the preoperative period should also be considered because the long-term administration of systemic chemotherapy frequently causes malnutrition. In this study, 44% (15/34) of patients with a good nutritional status became malnourished after preoperative treatment, and 94% (15/16) of those with malnutrition suffered early recurrence within 12 months after CS. With regard to patient selection for CS among those who received long-term chemo-/radiotherapy, the GPS is a useful tool to estimate postoperative survival and define the optimal timing of CS.

The GPS, which was proposed by McMillan et al. in 2003 [20], reflects both nutritional and systemic-inflammatory status based on the serum CRP and Alb values.

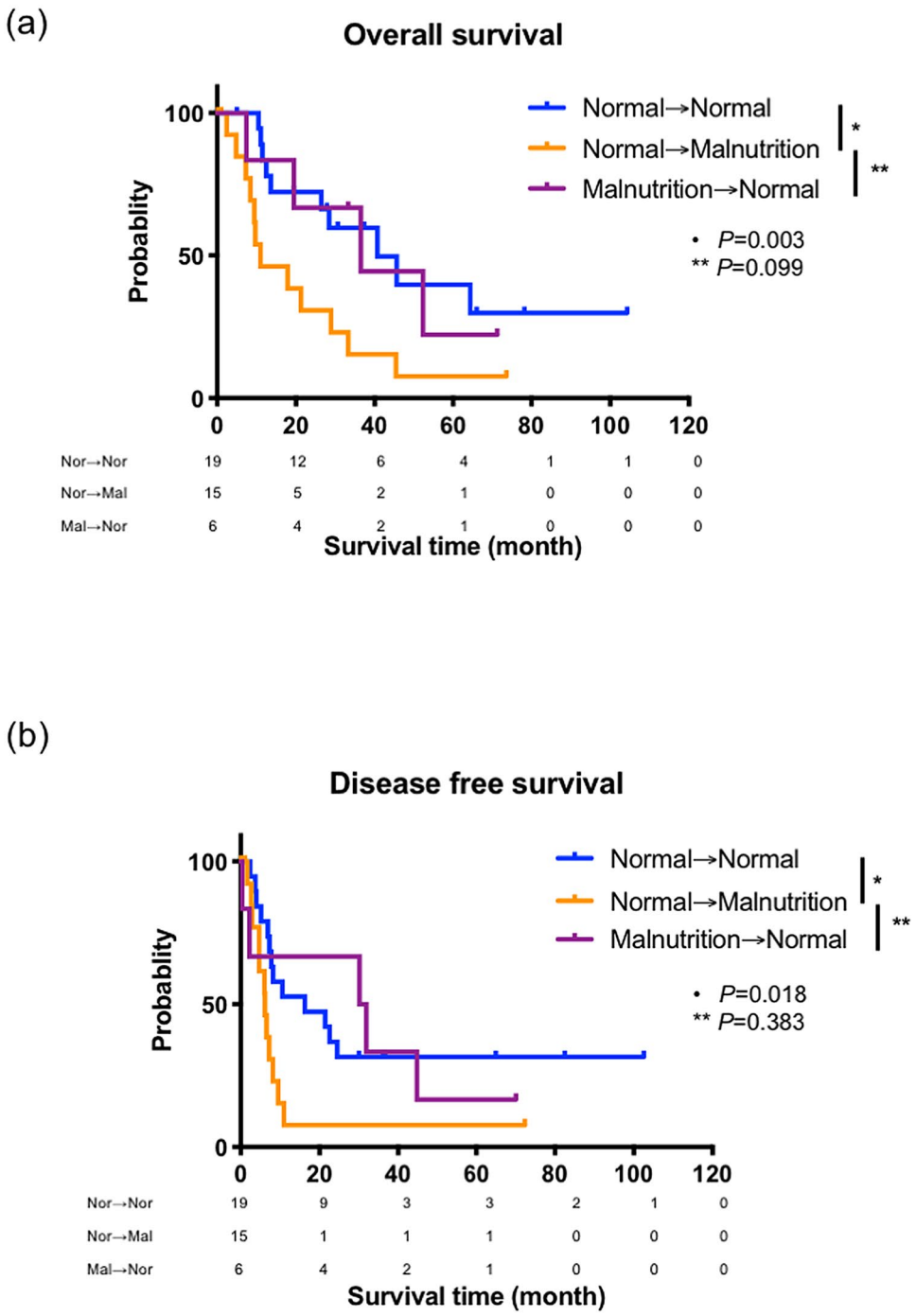

Fig. 3 Subgroup survival analysis stratified by preoperative nutrition alteration. Patients maintaining a normal nutritional status during the preoperative period (GPS 0) had a significantly better prognosis than those whose nutritional status deteriorated from GPS 0 to GPS 1–2 (median OS 40.7 vs 9.7 m, $p=0.003$; median DFS 16.3 vs 6.2 m, $p=0.018$). Patients whose nutritional status improved from GPS 1–2 to GPS 0 had a better prognosis, similar to that of those with a favorable nutritional status during that time (median OS 36.5 m, median DFS 31.0 m)

This scoring system can distinguish different stages of cachexia [41] and has been advocated as a good predictor of prognosis for patients undergoing surgical resection or systemic chemo-/radiotherapy for esophageal cancer and potentially resectable PA [21–23]. CRP is one of the acute phase proteins produced by upregulated interleukin (IL)-6. Pro-inflammatory cytokines (IL-1, IL-6, tumor necrosis alpha (TNF)-α, and interferon (IFN)-γ) are activated and released through a tumor-mediated pathway in the regional tumor area and induce the host-derived systemic-inflammatory response in patients with cancer. These circulating cytokines cause metabolic changes to a hypercatabolism state and muscle degradation, finally resulting in malnutrition [15]. These cytokines also induce the formation of microenvironments in distant organs, which are conducive to the adhesion and outgrowth of cancer cells, and are termed "pre-metastatic niches" [42]. In short, elevated systemic inflammation directly enhances cancer

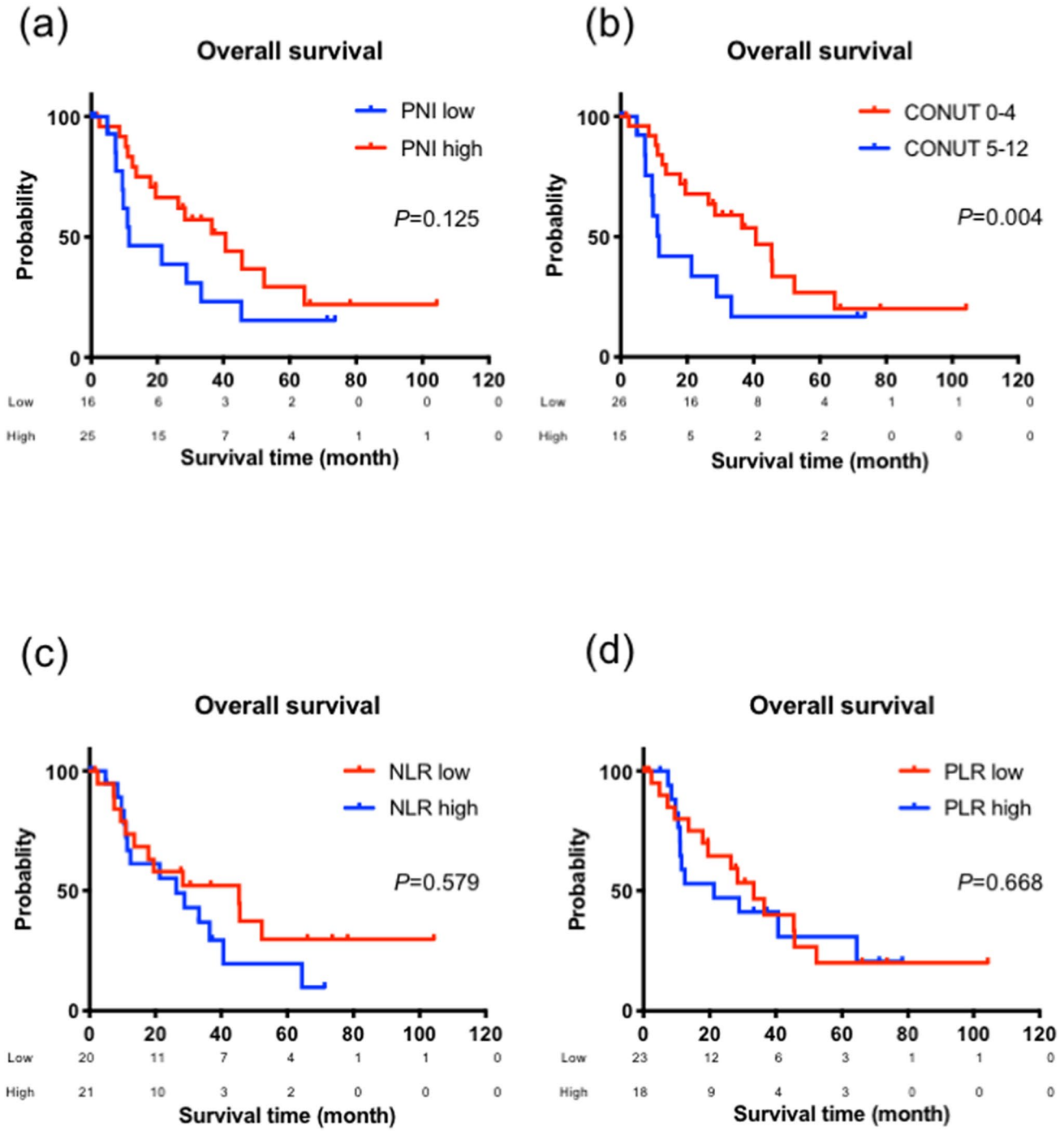

Fig. 4 Survival analysis according to other nutritional scoring systems: PNI, CONUT, NLR, and PLR. In the assessment using the CONUT score, patients with preoperative malnutrition status showed significantly poorer survival than those with a normal nutritional status ($p=0.004$). The other assessments by PNI, NLR or PLR revealed no survival differences

cell metastases in other lesions and promotes the systemic progression of cancer disease.

Interestingly, the patients in this study, whose nutritional status recovered (from GPS 1–2 to GPS 0) during their preoperative therapy exhibited as favorable a prognosis as those who maintained a normal nutrition status (GPS 0) (Fig. 3). Those patients might have received nutrition intervention influencing systemic inflammation preoperatively, but they did not necessarily show favorable treatment efficacy in pathological findings or CA19-9 alteration (Supplemental Table 2). In short, systemic inflammation did not correspond to therapeutic efficacy proven by a conventional biomarker

Table 2 Uni- and multivariate analyses of the predictive factors in patients undergoing conversion surgery for initially unresectable pancreatic adenocarcinoma (UR-PA)

	Univariate			Multivariate	
	Median survival (95%CI)	Hazard ratio (95%CI)	*p* value	Hazard ratio (95%CI)	*p* value
Gender					
Male	28.9 (11.1–45.4)				
Female	13.1 (2.4–64.4)	1.086 (0.470–2.508))	0.847		
Pre-treatment CA19-9 value					
< 300 U/ml	40.7 (11.5–64.4)				
≧ 300 U/ml	13.1 (4.8–28.4)	1.601 (0.735–3.487)	0.236		
Preoperative CA19-9 value					
< 37 U/ml	52.3 (17.9-)				
≧ 37 U/ml	11.3 (7.3–28.4)	3.151 (1.362–7.291)	0.007	4.089 (1.367–12.225)	0.012
Preoperative therapy					
Chemotherapy	17.9 (4.8–33.3)				
Chemo-radiotherapy	28.9 (10.5–52.3)	0.668 (0.303–1.475)	0.318		
NCCN resectability					
UR-M	28.4 (7.4–)				
UR-LA	21.3 (10.5–40.7)	0.981 (0.410–2.344)	0.965		
RESICT					
CR/PR	26.4 (8.4-)				
SD/PD	24.0 (11.0–40.7)	1.349 (0.584–3.118)	0.483		
Duration of preoperative therapy					
< 140 days	20.0 (7.3–40.7)				
> 140 days	26.4 (12.5–52.3)	0.871 (0.401–1.892)	0.728		
Operative procedure					
DP-CAR or TP	21.3 (7.3–40.7)				
PD	26.4 (11.1–45.6)	1.275 (0.577–2.816)	0.548		
UICC T					
1, 2	45.4 (1.0-)				
3, 4	19.5 (11.0–36.5)	1.379 (0.473–4.023)	0.556		
UICC N					
0	45.4 (21.3-)				
1, 2	11.1 (7.3–19.5)	3.139 (1.407–7.005)	0.005	2.314 (1.015–5.275)	0.046
Residual tumor					
R0	28.4 (12.5–45.6)				
R1	9.7 (0.2–33.3)	3.053 (1.211–7.698)	0.018	1.477 (0.379–5.755)	0.574
GPS assessment					
N group	40.7 (19.5–64.4)				
M group	9.6 (2.4–21.3)	2.865 (1.314–6.250)	0.001	3.437 (1.116–10.589)	0.032
Adjuvant therapy					
Yes	28.4 (12.5–45.6)				
No	4.8 (0.2–64.4)	1.191 (0.440–3.226)	0.730		

UP-PA unresectable pancreatic adenocarcinoma, CA19-9 carbohydrate antigen 19–9, NCCN National Comprehensive Cancer Network, RECIST response evaluation criteria in solid tumors, DP-CAR distal pancreatectomy with celiac axis resection, TP total pancreatectomy, PD pancreaticoduodenectomy, UICC Union for International Cancer Control, GPS Glasgow Prognostic Score

or pathological findings. Therefore, a novel intervention targeting systemic inflammatory status potentially extends postoperative survival, especially for patients with preoperative malnutrition [43]. A novel molecular-targeting drug, such as anti-IL-6 or TNF-b antibody, was evaluated recently in a clinical trial for patients with cancer-induced cachexia [44]. In another trial, the oral nutritional supplementation of eicosapentaenoic acid or L-carnitine showed positive effects

in patients with systemic-inflammation [45]. A combination therapy of these agents with conventional chemo-/radiotherapy might provide survival benefit from CS for patients with an elevated GPS.

This study also indicated that an elevated GPS is significantly associated with the absence of adjuvant therapy. A preoperative elevated GPS is associated with a high risk of postoperative complications and might impair activities of daily living [46]. Those systemic conditions lack tolerance to systemic chemotherapy, which would negatively affect overall survival after CS. There are various inflammation-based nutritional scoring systems based on nutritional, inflammatory and immunological factors; however, which system is the most useful and beneficial for patients with PA is still being debated. In this study, the CONUT score was found to be a significant prognostic factor in the univariate analysis, but the survival difference was not significant, compared with that in the GPS analysis. In essence, Kanda et al. found that a low preoperative PNI is an independent risk factor for perioperative complications and a significant predictor of poor survival for patients with pancreatic or gastric cancer [47, 48]. Previous studies also found that a high CONUT score can predict poor prognosis in patients with esophageal and colorectal cancer [49, 50]. However, the PNI and CONUT do not include the CRP value. Accurate assessment of systemic inflammatory status is indispensable to evaluate cachectic status in patients with PA. Prior to our study, Ikuta et al. presented supportive data indicating the prognostic importance of the preoperative modified GPS in patients with UR-PA undergoing CS [19].

This study had several limitations. First, the results were based on retrospective data from a single-center study, including confounding factors and selection bias. For the purpose of this study, the cohort consisted only of patients who underwent CS after a favorable response to non-surgical treatments; therefore, this cohort did not represent all UR-PA patients. To evaluate the utility of GPS in all UR-PA patients, patients who receive chemo-/radiotherapy without any surgical treatment should be included. Second, the number of patients was small, although it would be difficult to collect a large number of patients prospectively, who undergo successful CS for initially UR-PA. Third, the nutritional support during preoperative treatment did not follow a strict protocol; therefore, this bias potentially influenced the preoperative inflammation-based nutrition status and survival difference. Fourth, the indication was not strictly controlled because of the retrospective nature of the study. Fifth, the heterogeneity of the chemotherapeutic agents and regimens of preoperative therapy can influence the survival of patients with UR-PA.

In conclusion, an elevated GPS before surgery was a significant indicator of poor survival and an independent factor of a worse prognosis in patients with UR-PA who underwent multimodality treatment and subsequent CS. A novel therapy targeting the systemic inflammatory-based nutritional status could emphasize the benefit of CS for patients with an elevated GPS.

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Declarations

Conflict of interest We have no conflicts of interest to declare regarding this research.

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