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Prognostic Significance of GLIM-Defined Malnutrition in Patients With Resectable Pancreatic Adenocarcinoma Following Upfront Surgery

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ABSTRACT

Aim: Regarding the resectability of pancreatic adenocarcinoma (PDAC), not only anatomical factors but also biological and conditional factors have come to be considered. This study examined the impact of the Global Leadership Initiative on Malnutrition (GLIM) criteria on prognosis after resection of anatomically resectable PDAC.

Methods: The medical records of consecutive patients who underwent resection for resectable PDAC between January 1, 2014, and December 31, 2022, were retrospectively reviewed. Patients were classified as normal, moderately, or severely malnourished according to the GLIM criteria.

Results: In total, 194 patients were included in the analysis. According to the GLIM criteria, 61 (31.4%), 49 (25.2%), and 84 (42.3%) patients were normal, moderately, and severely malnourished, respectively. Patients with malnutrition had shorter overall, recurrence-free, and disease-specific survival (OS, RFS, and DSS) than normal patients (OS, normal vs. moderate, $p=0.015$; normal vs. severe, $p<0.001$; RFS, normal vs. moderate $p=0.012$, normal vs. severe, $p<0.001$; DSS, normal vs. moderate, $p=0.023$; normal vs. severe, $p<0.001$). In multivariate analysis regarding OS using all factors, moderate or severe malnutrition according to the GLIM criteria ($p=0.007$), performance status ($p=0.086$), preoperative diabetes ($p=0.017$), tumor diameter ≥ 3 cm ($p=0.002$), lymph node metastasis ($p<0.001$), and postoperative adjuvant therapy ($p=0.027$) were independent prognostic factors. In multivariate analysis using preoperative factors, malnutrition according to the GLIM criteria remained a significant prognostic factor ($p=0.003$).

Conclusion: The GLIM criteria are effective prognostic predictors in patients with resectable PDAC undergoing upfront surgery. Preoperative nutritional assessment using these criteria may contribute to determining treatment plans for resectable PDAC.

1 | Introduction

Pancreatic adenocarcinoma (PDAC) is the seventh leading cause of cancer-related deaths worldwide and is predicted to become the second leading cause of cancer-related deaths in the United States by 2030 [1, 2]. With a 5-year survival rate of 10%, it has the lowest survival rate among all solid tumors [1]. Treatment of PDAC is based on the classification of resectability according to the presence or absence of distant metastasis and its relationship with important blood vessels [3]. Although resection followed by adjuvant chemotherapy is recommended as the only curative method for resectable PDAC, the prognosis remains unsatisfactory [4]. Although some reports have demonstrated the usefulness of neoadjuvant therapy for resectable PDAC, the results vary among studies, and the appropriate targets and treatment methods remain controversial [5, 6]. It has been reported that the pre-treatment nutritional condition of patients, such as sarcopenia, malnutrition, and inflammatory markers, affects the prognosis of pancreatic cancer after resection [7–12]. Recent proposals suggest that even if a patient has anatomically resectable pancreatic cancer, those in poor condition should be treated as borderline resectable, and neoadjuvant therapy should be considered [13]. However, no solid standard indicators of patient condition have been established to date. The Global Leadership Initiative on Malnutrition (GLIM) criteria were the first international consensus diagnostic criteria for malnutrition proposed in 2018, which used phenotypic and etiological criteria to determine malnutrition and its severity [14]. The GLIM criteria have been reported to correlate with prognosis in various cancers; however, reports on their impact on the prognosis of resected PDAC are scarce [15–19]. The purpose of this study was to investigate the relationship between preoperative nutritional assessment based on GLIM criteria and the prognosis of patients who underwent upfront resection for a diagnosis of resectable PDAC.

2 | Methods

2.1 | Ethics Statement

This study was approved by the Institutional Review Board of Kobe University Graduate School of Medicine (B240241). This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

2.2 | Patients

The medical records of consecutive patients who underwent initial pancreatic resection at Kobe University Hospital between January 1, 2014, and December 31, 2022, were retrospectively reviewed. The inclusion criteria were patients with resectable PDAC according to the National Comprehensive Cancer Network (NCCN) guidelines, who underwent upfront pancreatectomy with curative intent [3]. Patients whose final pathology was other than PDAC, unresectable PDAC, borderline resectable PDAC, or who received neoadjuvant therapy were excluded.

2.3 | Preoperative Management

In principle, all patients with PDAC underwent multi-detector row computed tomography (CT), endoscopic ultrasound, and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic and fluorodeoxyglucose positron emission tomography, unless special circumstances prevented testing from being performed. Resectability was assessed according to the most recent version of the NCCN guidelines. Kobe University Hospital introduced neoadjuvant chemotherapy for resectable PDAC in late 2022; however, before that, neoadjuvant treatment was only performed as part of clinical studies. As this study only included cases that underwent upfront surgery, no neoadjuvant treatment was administered in any of the cases analyzed. In principle, if the most recent cross-sectional image was obtained more than 1 month before the scheduled surgery date, a repeat CT scan was performed. Preoperative biliary drainage procedures such as endoscopic biliary drainage were performed as needed. Although explicit criteria for performance status, cardiac function, or respiratory function were not established, patients were deemed ineligible for surgery if the preoperative anesthesiology assessment determined they were unable to tolerate the procedure or if their likelihood of returning home postoperatively was low. Patients with a performance status of 0–2 were considered for surgery; however, among those with a PS of 2, only individuals assessed as capable of tolerating the planned surgical procedure—taking into account its invasiveness—were included. No specific nutritional intervention or rehabilitation was performed before pancreatic resection during the study period.

2.4 | Nutritional Assessment According to the GLIM Criteria

The GLIM criteria consider phenotypic and etiological criteria to determine malnutrition and its severity [14]. These criteria stipulate that at least one of the following conditions should be met for the diagnosis of nutritional disorders: phenotypic criteria (unintentional weight loss, low body mass index [BMI], and muscle weakness) and epidemiological criteria (reduced food intake and causative disease of nutritional disorders). As this study focused on patients with PDAC requiring resection, all patients met the epidemiological criteria. All patients were administered a standardized questionnaire at their initial consultation to determine the presence or absence of weight loss within 6 months. In addition, medical records were reviewed to assess changes in body weight over time. The BMI used for the GLIM criteria in this study was calculated based on the body weight at the time of admission immediately prior to surgery. Muscle weakness was evaluated by calculating the skeletal muscle index at the third lumbar vertebral level (L3-SMI cm^2/mm^2) using preoperative CT images taken immediately before surgery (within 2 months).

The severity grades of the GLIM criteria used in this study are presented in Table 1. In the final determination of malnutrition according to the GLIM criteria, patients were assigned to the most severe category applicable among the indicators of weight loss, BMI, and L3-SMI. The cut-off values for BMI and L3-SMI were based on previous reports that evaluated the GLIM criteria in patients with cholangiocarcinoma and hepatocellular carcinoma [17, 18]. Patients who did not meet the criteria for malnutrition were included in the control group.

2.5 | Surgical Procedure

Pancreatectomy with standard lymph node dissection was performed for resectable PDAC. Pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy were performed based on the tumor location and extent. Intraoperative frozen sections of the transection margins of the pancreatic parenchyma were also examined in all cases; if positive, parenchyma

TABLE 1 | Reference values of phenotypic criteria of GLIM criteria used in this study.

	Weight loss	Low BMI	Reduced muscle mass
Moderate malnutrition	5%–10% within 6 months	$< 18.5\,kg/m^2$ ($<$ 70 y.o.) $< 20\,kg/m^2$ ($\geq$ 70 y.o.)	L3-SMI $< 45.0\,cm^2/m^2$ (male) L3-SMI $< 34.0\,cm^2/m^2$ (female)
Severe malnutrition	$>$ 10% within 6 months	$< 17.0\,kg/m^2$ ($<$ 70 y.o.) $< 17.8\,kg/m^2$ ($\geq$ 70 y.o.)	L3-SMI $< 37.9\,cm^2/m^2$ (male) L3-SMI $< 28.6\,cm^2/m^2$ (female)

Abbreviations: BMI, body mass index; GLIM, Global Leadership Initiative on Malnutrition; L3-SMI, skeletal muscle index of third lumbar level.

resection was extended when deemed feasible. In principle, peritoneal washing cytology and abdominal para-aortic lymph node sampling were routinely performed. However, because positivity in either was not an exclusion criterion for surgical indication during the study period, the specimens were submitted as permanent specimens and evaluated after surgery.

2.6 | Postoperative Management

During the study period, post-pancreatectomy management was performed according to a standardized protocol at Kobe University Hospital. In all pancreatic resection procedures, drinking water was initiated on postoperative day (POD) 1, and oral intake of solid foods was initiated on POD 4 after confirming the return of intestinal peristalsis. Amylase and bilirubin concentrations in the abdominal drain fluid were measured on PODs 1, 3, 4, and 5. If no pancreatic fistula or bile leakage was present, the drain was removed on POD 4; otherwise, the drain was not removed and was replaced as necessary. Routine contrast-enhanced CT was performed on POD 7 to exclude pseudoaneurysms and intraperitoneal abscesses. Antibiotics were administered when signs of infection were observed. Patients were discharged when signs of infection, such as blood test results and fever, improved; the drain was completely removed; and sufficient oral intake was achieved. The Clavien–Dindo classification was used to assess overall postoperative complications [20]. The diagnosis and grading of postoperative pancreatic fistula, post-pancreatectomy hemorrhage, and delayed gastric emptying were made according to the International Study Group definitions [21–23].

2.7 | Postoperative Follow-Up

The patients were followed up at the Kobe University Hospital outpatient clinic. As postoperative surveillance, physical examinations, tumor marker measurements, and CT scans were performed every 3 months for the first 2 years. From the third year onward, physical examinations and tumor marker measurements were continued every 3 months, whereas CT scans were performed every 6 months. Postoperative adjuvant chemotherapy with tegafur/gimeracil/oteracil (S-1) was started once postoperative inflammation improved and oral intake was resumed, unless special circumstances prevented administration or the patient refused the treatment. Diagnosis of recurrence was mainly performed by imaging diagnosis, with changes in tumor markers considered as auxiliary indicators. When regular CT scans and tumor marker measurements were not sufficient to confirm recurrence, EOB-MRI and/or FDG-PET were added.

2.8 | Statistical Analysis

Patient demographics, preoperative examinations, perioperative outcomes, pathological results, and follow-up information were compared according to the GLIM criteria. Fisher's exact probability test was used for categorical variables, whereas the Mann–Whitney *U* test was used for continuous variables. Postoperative overall survival (OS), recurrence-free survival (RFS), and disease-free survival (DSS) were evaluated using Kaplan–Meier curves, with significance assessed using the log-rank test. In the analysis of OS, death from any cause was considered an event. In the analysis of RFS, all recurrences and all deaths, including non-cancer-related deaths, were considered events. In the analysis of DSS, death due to pancreatic cancer was treated as the event, whereas deaths from other causes and survival at the time of final follow-up were treated as censored. To determine the prognostic value of the GLIM criteria, univariate and multivariate analyses of prognostic factors for OS, including various nutritional indicators (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], Glasgow prognostic score [GPS], modified GPS [mGPS], prognostic nutritional index [PNI], and controlling nutritional status [CONUT] score) were performed using the Cox proportional hazards model. The cut-off points for various nutritional indicators were set based on previous studies [7–12]. In addition to the multivariate analysis including all factors (Model 1), a multivariate analysis including only preoperative factors (Model 2) was performed to verify whether the GLIM criteria contribute to determining the treatment plan for resectable PDAC. Furthermore, univariate and multivariate (logistic regression model) analyses were conducted to identify predictors of early recurrence within 1 year after surgery. Cases censored due to the absence of recurrence within 1 year postoperatively were excluded from this analysis. Variables with $p < 0.10$ in univariate analysis were incorporated into the multivariate analysis. The level of statistical significance was set at $p < 0.05$ in all analyses. All statistical analyses were performed using the JMP 12 software (SAS Institute Japan, Tokyo).

3 | Results

3.1 | Patient Characteristics

Of the 730 patients reviewed, 194 were included in the analysis. The patient flowchart is shown in Figure 1. Table 2 shows the characteristics of the study participants. Eighty-two female and 112 male participants with a median age of 72 years (range: 30–89 years) were enrolled in the study. Among them, 117 (60.3%), 68 (35.1%), and nine (4.6%) underwent pancreatoduodenectomy,

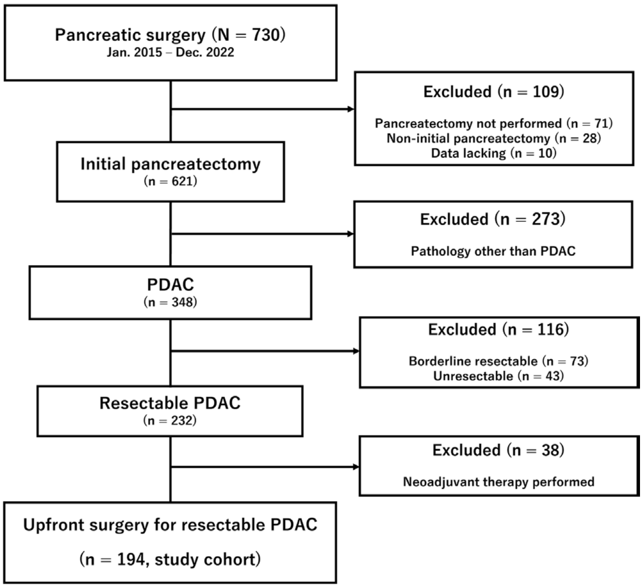

FIGURE 1 | Patient flowchart.

distal pancreatectomy, and total pancreatectomy, respectively. No perioperative mortality occurred within 30 days of surgery. In the pathological diagnosis, 20 R1 cases were identified. There were 10 cases of tumor exposure on the peripancreatic dissection surface, 6 cases of high-grade PanIN at the pancreatic resection margin, and 4 cases of positive invasive cancer at the pancreatic resection margin. The final diagnosis was stage 4 in 16 cases. Among them, para-aortic lymph node metastasis was identified in 14 cases. In the remaining two cases, tumor cells separate from the main tumor were found on the surface of the pancreas in the pathological specimens, and the tumor was diagnosed as peritoneal dissemination after surgery.

3.2 | Nutritional Assessment According to the GLIM Criteria

According to the GLIM criteria, 61 (31.4%), 49 (25.3%), and 84 (43.3%) patients were normal or moderately or severely malnourished, respectively. Besides factors included in the GLIM criteria, patients with malnutrition were significantly older (normal, 68 years [range: 30–83 years] vs. moderate, 73 years [range: 42–86 years] vs. severe, 74 years [range: 42–89 years], $p = 0.004$), and less likely to receive adjuvant chemotherapy compared with normal patients (normal, 78.7% vs. moderate, 65.3% vs. severe, 56.0%, $p = 0.015$). Other patient backgrounds, including tumor-related factors, did not differ significantly among the groups (Table 3).

3.3 | Impact of Malnutrition on Prognosis After Resection

After a median follow-up of 29.0 months (range: 1.5–113.7 months), 127 (65.5%) patients had tumor recurrence, and 127 (65.5%) patients died. Figure 2 shows the results of the Kaplan–Meier analyses of OS, RFS, and DSS according to the GLIM criteria. Patients with moderate and severe malnutrition had significantly shorter OS, RFS, and DSS compared with normal patients (OS, normal vs. moderate, $p = 0.015$; normal vs. severe, $p < 0.001$; RFS, normal vs. moderate $p = 0.012$, normal vs. severe, $p < 0.001$; DSS, normal vs. moderate, $p = 0.023$; normal vs. severe, $p < 0.001$). The median survival times of the normal, moderate, and severe malnutrition groups were 62.2, 33.0, and 21.6 months, respectively. The 1-year OS rates were 90.2% (normal), 85.7% (moderate), and 67.9% (severe), respectively (normal vs. moderate: $p = 0.480$, normal vs. severe: $p = 0.002$). The 1-year RFS rates were 78.7% (normal), 67.4% (moderate), and 45.2% (severe), respectively (normal vs.

TABLE 2 | Patient characteristics.

	Total ($N = 194$)
Age, years, median (range)	72 (30–89)
Sex, *n* (%)	
Male	112 (57.7)
Female	82 (42.3)
Body mass index (kg/m^2)	21.7 (14.6–32.3)
Performance status, *n* (%)[a]	
0, 1	182 (93.8)
2	12 (6.2)
Preoperative diabetes, *n* (%)	
Present	89 (45.9)
Absent	105 (54.1)
CA19-9, U/mL, median (range)	90 (1–5978)
CEA, U/mL, median (range)	2.9 (0.4–73.9)
Operation method, *n* (%)	
PD	117 (60.3)
DP	68 (35.1)
TP	9 (4.6)
Portal vein resection, *n* (%)	45 (23.2%)
Tumor size, cm, median (range)	2.6 (0.1–6.5)
Lymph node metastasis, *n* (%)	122 (62.9)
UICC stage, *n* (%)	
1a	35 (18.0)
1b	32 (16.5)
2a	2 (1.0)
2b	79 (40.7)
3	30 (15.5)
4	16 (8.2)
R0 resection, *n* (%)	174 (89.7)
Adjuvant chemotherapy, *n* (%)	127 (65.4)
Follow-up period, months, median (range)	29 (1.5–113.7)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DP, distal pancreatectomy; PD, pancreatoduodenectomy; TP, total pancreatectomy; UICC, Union for International Cancer Control.
[a]According to the ECOG (eastern cooperative oncology group) definition.

TABLE 3 | Patient characteristics according to GLIM criteria.

	Normal (n = 61)	Moderate malnutrition (n = 49)	Severe malnutrition (n = 84)	p
Age, years, median (range)	68 (30–83)	73 (42–86)	74 (42–89)	0.004*
Sex, n (%)				
Male	31 (50.8)	28 (57.1)	53 (63.1)	0.334
Female	30 (49.2)	21 (42.9)	31 (36.9)	
Body mass index, < 70 y.o., (kg/m^2)	23.3 (19.7–32.3)	21.1 (17.6–27.1)	18.9 (14.6–25.0)	< 0.001*
Body mass index, ≥ 70 y.o., (kg/m^2)	23.9 (21.2–28.5)	21.6 (18.1–26.8)	19.9 (14.6–31.1)	< 0.001*
Unintentional body weight loss, n (%)				
< 5%	61 (100)	41 (83.7)	56 (66.7)	< 0.001*
≤ 5%, < 10%	0	8 (16.3)	5 (6.0)	
≥ 10%	0	0	23 (27.4)	
L3-SMI, male, cm^2/cm^2	48.2 (45.0–61.4)	40.3 (38.2–47.1)	33.3 (26.6–57.1)	< 0.001*
L3-SMI, female, cm^2/cm^2	37.9 (34.1–55.1)	31.0 (28.9–34.6)	27.4 (19.1–37.3)	< 0.001*
Performance status, n (%)[a]				
0, 1	59 (96.7)	45 (91.8)	78 (92.9))	0.474
2	2 (3.3)	4 (8.2)	6 (7.1)	
Preoperative diabetes, n (%)				
Absent	39 (63.9)	28 (57.1)	38 (45.2)	0.073
Present	22 (36.1)	21 (42.9)	46 (54.8)	
CA19-9, U/mL, median (range)	44 (1–1782)	118 (1–3651)	131.5 (1–5978)	0.195
CEA, U/mL, median (range)	2.6 (0.5–11.9)	3.4 (0.4–20.6)	2.9 (0.6–73.9)	0.441
Operation method, n (%)				
PD	34 (55.7)	31 (63.3)	52 (61.9)	0.482
DP	25 (41.0)	17 (34.7)	26 (31.0)	
TP	2 (3.3)	1 (2.0)	6 (7.1)	
Portal vein resection, n (%)	18 (29.5)	6 (12.2)	21 (25.0)	0.073
POPF, grade B/C, n (%)[b]	15 (24.2)	8 (15.4)	9 (10.1)	0.069
DGE, all grade, n (%)[b]	12 (19.4)	9 (17.3)	10 (11.2)	0.346
Clavien-Dindo ≥ Grade 3, n (%)	3 (4.8)	5 (9.6)	12 (13.5)	0.190
Tumor size, cm, median (range)	2.5 (0.2–6.0)	3.0 (0.12–6.5)	2.7 (0.9–6.2)	0.175
Lymph node metastasis, n (%)	38 (62.3)	29 (59.2)	55 (65.5)	0.764
UICC stage, n (%)				
1a	13 (21.3)	8 (16.3)	14 (16.7)	0.739
1b	9 (14.8)	9 (18.4)	14 (16.7)	
2a	0 (0)	1 (2.0)	1 (1.2)	
2b	28 (45.9)	19 (38.8)	32 (38.1)	
3	5 (8.2)	9 (18.4)	16 (19.1)	
4	6 (9.8)	3 (6.1)	7 (8.3)	

(Continues)

TABLE 3 | (Continued)

	Normal ($n=61$)	Moderate malnutrition ($n=49$)	Severe malnutrition ($n=84$)	p
R0 resection, n (%)	58 (95.1)	41 (83.7)	75 (89.3)	0.135
Adjuvant chemotherapy, n (%)	48 (78.7)	32 (65.3)	47 (56.0)	0.015*

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DGE, delayed gastric emptying; DP, distal pancreatectomy; GLIM, Global Leadership Initiative on Malnutrition; L3-SMI, skeletal muscle index of third lumbar level; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; UICC, Union for International Cancer Control.
[a]According to the ECOG (eastern cooperative oncology group) definition.
[b]According to the ISGPS (International Study Group of Pancreatic Surgery) definition.
*Statistically significant ($p<0.05$).

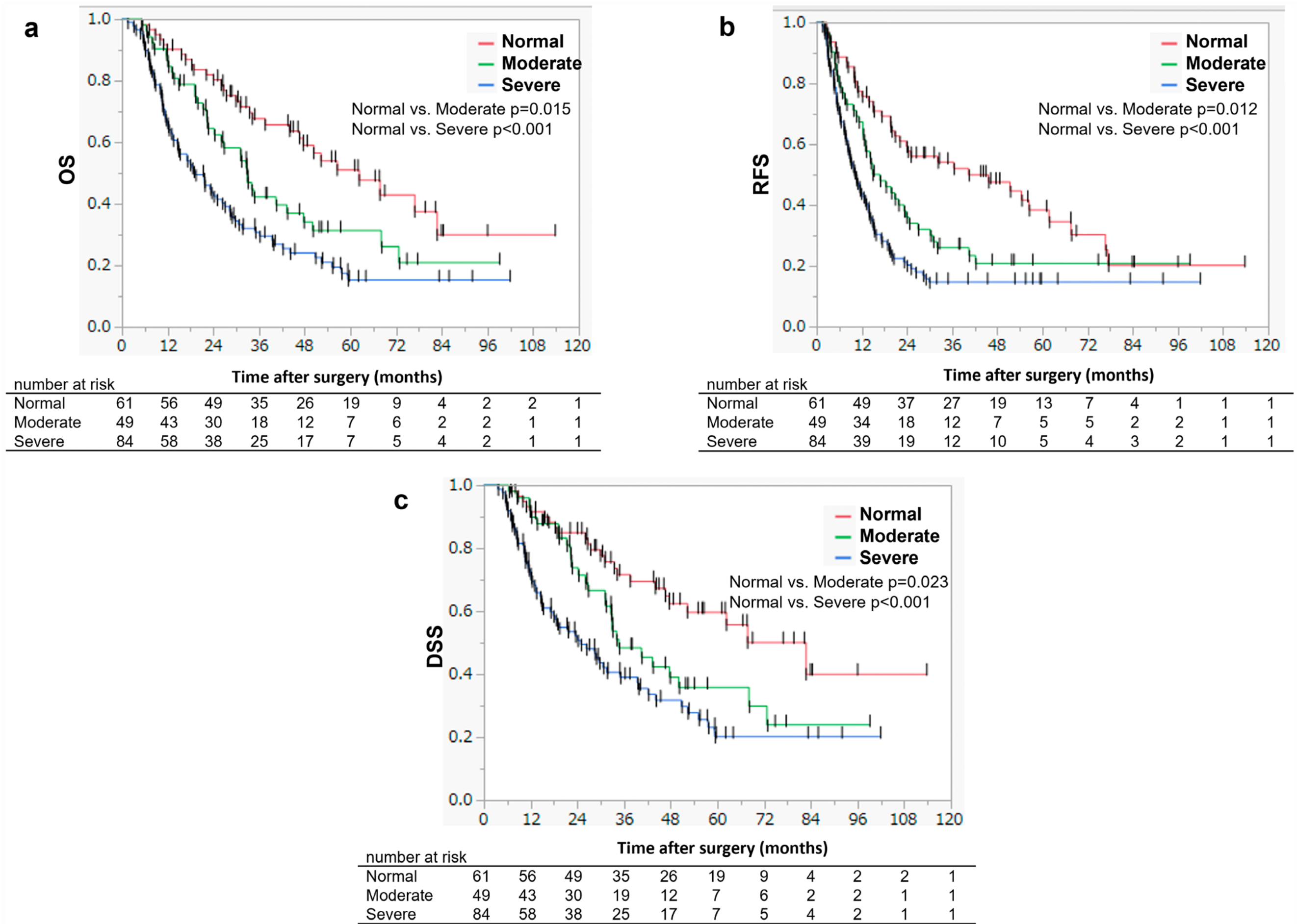

FIGURE 2 | (a) Kaplan–Meier curves of overall survival after surgery stratified by GLIM criteria. Normal vs. moderate, $p=0.015$; normal vs. severe, $p<0.001$ (Log-rank test). (b) Kaplan–Meier curves of recurrence-free survival after surgery stratified by GLIM criteria. Normal vs. moderate $p=0.012$, normal vs. severe, $p<0.001$ (Log-rank test). (c) Kaplan–Meier curves of disease-specific survival after surgery stratified by GLIM criteria. Normal vs. moderate $p=0.023$, normal vs. severe, $p<0.001$ (Log-rank test).

moderate: $p=0.182$, normal vs. severe: $p<0.001$). As with OS and RFS, patients with moderate to severe malnutrition according to the GLIM criteria had significantly worse DSS compared to normal patients (normal vs. moderate, $p=0.023$; normal vs. severe, $p<0.001$). Table 4 shows the results of the univariate and multivariate analyses of OS. In the univariate analysis, malnutrition according to the GLIM criteria ($p<0.001$), performance status ≥2 ($p<0.001$), preoperative diabetes ($p=0.002$), NLR ≥5 ($p=0.011$), PNI <45 ($p<0.001$), GPS 1,2 ($p=0.002$), CONUT ≥3 ($p=0.021$), postoperative pancreatic fistula grade B/C ($p=0.039$), tumor diameter ≥3 cm ($p<0.001$), lymph node metastasis ($p<0.001$), R0 resection ($p<0.001$), postoperative adjuvant therapy ($p=0.005$) were significant prognostic factors.

In the multivariate analysis regarding OS using all factors, moderate or severe malnutrition according to the GLIM criteria ($p=0.007$), performance status ($p=0.086$), preoperative diabetes ($p=0.017$), tumor diameter ≥3 cm ($p=0.002$), lymph node metastasis ($p<0.001$), and postoperative adjuvant therapy ($p=0.027$) were independent prognostic factors. In the multivariate analysis regarding OS using only preoperative factors, moderate or severe malnutrition according to the GLIM criteria

TABLE 4 | Cox-regression model for predictors of overall survival.

	Univariate	Univariate	Multivariate (Model 1)	Multivariate (Model 1)	Multivariate (Model 2)	Multivariate (Model 2)
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years ≥ 70	1.11 (0.78–1.58)	0.572				
Sex, male	1.09 (0.77–1.56)	0.631				
Performance status, 2[a]	5.95 (2.81–11.4)	< 0.001*	2.18 (0.89–4.98)	0.086*	4.22 (1.89–8.68)	< 0.001*
Preoperative diabetes	1.76 (1.24–2.50)	0.002*	1.60 (1.09–2.35)	0.017*	1.59 (1.10–2.30)	0.014*
GLIM moderate/severe	2.30 (1.54–3.55)	< 0.001*	1.81 (1.17–2.88)	0.007*	1.89 (1.24–2.95)	0.003*
NLR ≥ 5	2.39 (1.24–4.18)	0.011*	2.08 (0.97–4.16)	0.060	2.07 (0.99–4.01)	0.052
PLR ≥ 150	1.12 (0.79–1.59)	0.525				
LMR ≥ 3	0.74 (0.50–1.13)	0.159				
PNI < 45	1.97 (1.39–2.80)	< 0.001	1.30 (0.82–2.06)	0.263	1.33 (0.85–2.05)	0.215
GPS 1,2	2.08 (1.32–3.16)	0.002*	1.23 (0.69–2.14)	0.475	1.23 (0.69–2.16)	0.473
mGPS 1,2	1.35 (0.88–2.04)	0.165				
CONUT ≥ 3	1.55 (1.07–2.21)	0.021*	0.85 (0.51–1.41)	0.548	0.89 (0.54–1.43)	0.634
CA19-9 ≥ 37 U/mL	1.41 (0.96–2.09)	0.077	1.00 (0.67–1.53)	0.994	1.08 (0.72–1.65)	0.704
CA19-9 ≥ 500 U/mL	1.09 (0.68–1.67)	0.714				
CEA ≥ 5 U/mL	1.11 (0.70–1.71)	0.644				
Operation method						
PD (vs. DP)	1.02 (0.71–1.49)	0.244				
TP (vs. DP)	2.09 (0.86–4.37)					
Portal vein resection	1.13 (0.74–1.68)	0.556				
POPF grade B/C[b]	0.58 (0.32–0.97)	0.039*	0.81 (0.44–1.41)	0.478		
DGE, all grade	0.85 (0.50–1.36)	0.513				
Clavien-Dindo ≥ Grade 3	1.57 (0.88–2.61)	0.123				
Tumor size ≥ 3 cm	1.93 (1.36–2.74)	< 0.001*	1.87 (1.27–2.75)	0.002*	1.98 (1.37–2.86)	< 0.001*
Lymph node metastasis	2.14 (1.46–3.22)	< 0.001*	2.50 (1.64–3.89)	< 0.001*		
R0 resection	0.37 (0.23–0.63)	< 0.001*	0.63 (0.37–1.13)	0.118		
UICC M1	1.46 (0.82–2.43)	0.190				
Adjuvant chemotherapy	0.59 (0.41–0.85)	0.005*	0.59 (0.38–0.94)	0.027*		

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CONUT, controlling nutritional status; DGE, delayed gastric emptying; DP, distal pancreatectomy; GLIM, Global Leadership Initiative on Malnutrition; GPS, Glasgow prognostic score; L3-SMI, skeletal muscle index of third lumbar level; mGPS, modified GPS; NLR, neutrophil-lymphocyte ratio; PD, pancreaticoduodenectomy; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; POPF, postoperative pancreatic fistula; UICC, Union for International Cancer Control.
[a]According to the ECOG (eastern cooperative oncology group) definition.
[b]According to the ISGPS (International Study Group of Pancreatic Surgery) definition.
*Statistically significant ($p < 0.05$).

($p = 0.003$), performance status ($p < 0.001$), preoperative diabetes ($p = 0.014$), and tumor diameter ≥ 3 cm ($p < 0.001$) remained independent prognostic factors.

3.4 | Impact of Malnutrition on Early Recurrence Within 1 Year After Resection

In the analysis regarding early recurrence (within 1 year after resection), follow-up censored cases without recurrence within 1 year ($n = 10$) were excluded. Early recurrence was observed in 65 patients. In the univariate analysis, malnutrition based on the GLIM criteria ($p = 0.002$), preoperative diabetes ($p = 0.048$), NLR ≥ 5 ($p = 0.046$), PNI < 45 ($p = 0.027$), GPS 1 or 2 ($p = 0.002$), tumor diameter ≥ 3 cm ($p < 0.001$), lymph node metastasis ($p = 0.031$), R0 resection ($p = 0.019$), and postoperative adjuvant therapy ($p = 0.044$) were significantly associated with early recurrence within 1 year postoperatively (Table 5). In the multivariate analysis, malnutrition according to the GLIM criteria ($p = 0.047$) and tumor diameter ≥ 3 cm ($p = 0.017$) remained

TABLE 5 | Logistic regression model for predictors of early recurrence (within 1 year).

	Univariate	Univariate	Multivariate	Multivariate
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Age, years ≥ 70	1.23 (0.67–2.32)	0.500		
Sex, male	0.99 (0.53–1.83)	0.962		
Performance status ≥ 2[a]	3.22 (0.76–16.1)	0.110		
Preoperative diabetes	1.85 (1.01–3.43)	0.048*	1.71 (0.85–3.47)	0.129
GLIM moderate/severe	2.99 (1.48–6.39)	0.002*	2.22 (1.01–5.11)	0.047*
NLR ≥ 5	3.20 (1.02–11.0)	0.046*	3.54 (0.94–14.4)	0.062
PLR ≥ 150	1.03 (0.56–1.90)	0.927		
LMR ≥ 3	1.03 (0.51–2.14)	0.945		
PNI < 45	2.02 (1.09–3.78)	0.027*	1.20 (0.52–2.88)	0.673
GPS 1,2	3.86 (1.67–9.34)	0.002*	2.50 (0.87–7.52)	0.090
mGPS 1,2	2.13 (1.00–4.55)	0.051		
CONUT ≥ 3	1.66 (0.87–3.18)	0.127		
CA19-9 ≥ 37 U/mL	1.80 (0.93–3.61)	0.083	1.35 (0.63–2.97)	0.438
CA19-9 ≥ 500 U/mL	1.44 (0.66–3.10)	0.351		
CEA ≥ 5 U/mL	0.91 (0.40–1.98)	0.807		
Operation method				
PD (vs. DP)	1.37 (0.71–2.68)	0.440		
TP (vs. DP)	2.32 (0.50–10.8)			
Portal vein resection	1.99 (1.00–3.99)	0.052	1.64 (0.72–3.74)	0.238
POPF grade B/C[b]	0.69 (0.27–1.63	0.410		
DGE, all grade	0.65 (0.26–1.52)	0.334		
Clavien-Dindo ≥ Grade 3	1.71 (0.61–4.72)	0.297		
Tumor size ≥ 3 cm	2.89 (1.56–5.44)	< 0.001*	2.44 (1.18–5.15)	0.017*
Lymph node metastasis	2.03 (1.07–3.96)	0.031*	1.68 (0.78–3.69)	0.185
R0 resection	0.31 (0.11–0.82)	0.019*	0.64 (0.20–1.99)	0.437
UICC M1	1.72 (0.61–4.72)	0.297		
Adjuvant chemotherapy	0.51 (0.27–0.98)	0.044*	0.58 (0.26–1.27)	0.170

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CONUT, controlling nutritional status; DGE, delayed gastric emptying; DP, distal pancreatectomy; GLIM, Global Leadership Initiative on Malnutrition; GPS, Glasgow prognostic score; L3-SMI, skeletal muscle index of third lumbar level; mGPS, modified GPS; NLR, neutrophil-lymphocyte ratio; PD, pancreaticoduodenectomy; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; POPF, postoperative pancreatic fistula; UICC, Union for International Cancer Control.
[a]According to the ECOG (eastern cooperative oncology group) definition.
[b]According to the ISGPS (International Study Group of Pancreatic Surgery) definition.
*Statistically significant ($p < 0.05$).

significant (Table 5). Variables with a p-value < 0.10 in the univariate analysis were included in the multivariate model; however, due to the strong correlation between GPS and mGPS, only GPS, which showed greater significance, was included.

4 | Discussion

In the present study, patients with resectable PDAC showed a high incidence of malnutrition (69.5%). The GLIM criteria were independent prognostic factors after upfront resection of anatomically resectable PDAC. Moreover, malnutrition diagnosed by the GLIM criteria was identified as an independent risk factor for early recurrence. Postoperative OS, RFS, and DSS were well-stratified according to malnutrition severity, further demonstrating the usefulness of the GLIM criteria for predicting prognosis. To our knowledge, this is the first report to examine the correlation between the GLIM criteria and the prognosis of resectable PDAC after upfront surgery. The lack of correlation between the GLIM criteria and tumor size, tumor markers, and the presence of metastasis suggested that the criteria reflected the patient's general condition rather than tumor factors. The introduction of postoperative adjuvant chemotherapy was limited in patients with malnutrition, potentially due to the reduced tolerability of treatment owing to their preoperative general condition and delayed postoperative recovery.

In a similar study, Lee et al. [19] reported that the GLIM criteria were prognostic factors for pancreatic head cancer after resection. They reported a lower incidence of malnutrition compared with the present study (32.9%), even though the participants were Asian. Considering that this incidence was lower than that in patients with hepatocellular carcinoma (56%) and bile duct cancer (78.9%) who were evaluated for nutritional status using the same method as in the present study, differences in the assessment method of the GLIM criteria may have led to discordant findings [17, 18]. In the present study, skeletal muscle mass loss, one of the assessment indicators of the GLIM criteria, was diagnosed using L3-SMI. However, other studies, such as that by Lee et al. [19], did not mention the method used to assess skeletal muscle mass loss. In addition, the age group in the study by Lee et al. was approximately 10 years younger than that in the present study, and the performance status was limited to 0 or 1, which may have contributed to the difference in the malnutrition incidence compared with our study. Additionally, Lee et al. included all patients with cancer of the pancreatic head who underwent resection during the study period, with no restrictions on resectability status or neoadjuvant therapy, whereas the present study included only participants with "anatomically" resectable PDAC undergoing upfront surgery. The strength of the present study is that it may help inform the development of treatment plans for resectable PDAC in clinical practice.

In the last decade, some reports have demonstrated the superiority of neoadjuvant therapy over upfront surgery for resectable PDAC. However, the results vary among studies, and the appropriate targets and treatment methods remain controversial [5, 6]. Neoadjuvant therapy carries a risk of tumor progression if ineffective, and some researchers suggest that the indication for neoadjuvant therapy for resectable PDAC should be selected based on the risk of recurrence [24, 25]. In the Japanese guidelines, neoadjuvant chemotherapy with gemcitabine + S-1 is recommended for resectable PDAC based on the results of a randomized controlled trial (Prep02/JSAP05) for resectable and borderline resectable PDAC [26]. Unfortunately, however, the results of this study have not yet been published in the literature, and detailed analysis is not possible. In the NCCN guidelines, immediate surgery is permitted for the patients with resectable PDAC if no high-risk features (equivocal or indeterminate imaging findings, markedly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain) are present, whereas the initiation of neoadjuvant therapy is recommended if high-risk features are present [3]. Concurrently, an international consensus on borderline resectability in 2017 proposed that PDAC should be evaluated not only from an anatomical perspective but also from biological and conditional perspectives. Biological evaluation was based on serum carbohydrate antigen 19-9 levels or regional lymph node metastasis, as predicted by cross-sectional imaging. Patient condition is evaluated using the Eastern Cooperative Oncology Group performance status [13]. The need for treatment strategies to consider not only anatomical but also biological and conditional factors is now widely recognized. The aforementioned international consensus included performance status as a condition factor among the criteria for determining resectability [13]. In fact, performance status was an independent prognostic factor in the present study. However, although various nutritional indicators have been reported to be prognostic factors for PDAC, the consensus has not included nutritional indicators. GPS, mGPS, PNI, and CONUT have been used as nutritional assessment tools in patients with PDAC undergoing resection, and their correlation with patient prognosis has been reported [7–12]. However, the appropriate method for evaluating patient nutritional condition remains controversial. The GLIM criteria, the first international consensus diagnostic criteria for malnutrition, were proposed in 2018; however, few reports have applied this relatively new nutritional assessment tool for resectable PDAC. In the present study, we compared the prognostic predictive ability of the GLIM criteria with those of other nutritional assessment tools and found that the GLIM criteria are the best indicators. Definitive verification was not possible because of the limited sample size in the present study. Further research is needed to determine which indicator is most useful for the preoperative evaluation of the nutritional condition of patients with PDAC. As more data accumulate on malnutrition assessments, including the GLIM criteria, treatment policies for resectable PDAC may become clearer.

This study has some limitations. As a retrospective study, potential biases could not be excluded. In the present study, the assessment of weight loss was based solely on the questionnaire for patients without medical records from more than 6 months prior to surgery. Therefore, there is a possibility that unrecognized weight loss may have been missed in patients who were unaware of their weight changes or did not have a routine habit of weighing themselves. The study participants were patients with resectable PDAC who underwent upfront surgery. Although no clear evidence exists to recommend neoadjuvant therapy for resectable PDAC, many high-volume centers have begun to administer this treatment in this patient population. Further verification is required to determine whether the results of the present study are applicable to patients receiving neoadjuvant therapy. The cutoff values for NLR, PLR, LMR, and PNI used in this study were based on several previous large-scale studies. However, no universally accepted cutoff values have been established for these immunological and nutritional indicators. Therefore, caution is warranted when interpreting the results, given the variability in cutoff values used across studies. Additionally, the multivariate analysis of early recurrence included a relatively large number of variables in relation to the number of events; therefore, the results should be interpreted with caution.

In conclusion, the GLIM criteria are effective prognostic predictors for patients with resectable PDAC undergoing upfront surgery. Therefore, preoperative nutritional assessment using the GLIM criteria may contribute to developing treatment plans for patients with resectable PDAC.

Author Contributions

Takuya Mizumoto: conceptualization, methodology, data curation, software, investigation, writing – original draft, writing – review and editing, visualization. **Yoshihide Nanno:** conceptualization, supervision, writing – review and editing, data curation. **Jun Ishida:** conceptualization, data curation. **Dongha Lee:** conceptualization, data curation. **Kenji Fukushima:** supervision, conceptualization. **Shohei Komatsu:** conceptualization, supervision. **Hiroaki Yanagimoto:** supervision, conceptualization. **Sadaki Asari:** conceptualization, supervision. **Masahiro Kido:** conceptualization, supervision. **Takumi Fukumoto:** conceptualization, supervision.

Ethics Statement

This study was approved by the Institutional Review Board of Kobe University Graduate School of Medicine (B240241). This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments.

Consent

In accordance with ethical committee regulations, the authors disclosed study information in a disclosure document as an opt-out, which served as a substitute for informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

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