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ORIGINAL SCIENTIFIC REPORT

European Society for Clinical Nutrition and Metabolism (ESPEN) Malnutrition Criteria for Predicting Major Complications After Hepatectomy and Pancreatectomy

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Abstract

Background Recently, diagnostic criteria for malnutrition have been proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN). This study aimed to investigate the utility of the ESPEN malnutrition criteria as a predictor for major complications following hepatectomy and pancreatectomy.

Methods Data were reviewed from 176 consecutive patients who underwent hepatectomy (n = 103) or pancreatectomy (n = 73) between November 2017 and December 2019. Patients were divided into two groups according to the ESPEN malnutrition criteria using a prospectively collected database. The clinical data and the surgical outcomes of patients in the malnourished and normal groups were retrospectively analyzed.

Results Thirty-five (20%) patients were diagnosed with malnourishment according to ESPEN criteria. The malnourished group had a significantly low preoperative albumin concentration (p = 0.001). After hepatectomy, major complications (Clavien grade ≥ 3a) occurred significantly more frequently in the malnourished group than in the normal group (p = 0.013). Multivariate analysis indicated that operative duration ≥ 300 min (hazard ratio: 22.47, 95% CI: 2.17 to 232.73, p = 0.009) and malnourishment (hazard ratio: 14.56, 95% CI: 2.58 to 82.17, p = 0.002) were independently associated with major complications after hepatectomy. On the other hand, malnutrition was not associated with major complications after pancreatectomy.

Conclusions The ESPEN malnutrition criteria are a valuable predictor for major complications following hepatectomy.

Introduction

Surgical resection is a standard treatment for hepatopancreatobiliary (HPB) malignancies [1–4]. Although hepatectomy and pancreatectomy have become safe surgeries with low mortality rates due to improvements in surgical techniques and perioperative management, postoperative morbidity rates remain high [5, 6]. Postoperative complications are risk factors for prolonged hospital stays and increased costs of care in surgical patients [7, 8]. Therefore, minimizing postoperative complications can potentially reduce medical costs and improve patient quality of life.

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Malnutrition is a well-known risk factor for postoperative complications after abdominal surgery [9, 10]. However, for HPB surgery, the data on the influence of malnutrition are limited by retrospective study designs and insufficient sample sizes. Another issue is that it is difficult to determine which criteria of malnutrition to adopt because numerous different clinical scores have been developed to detect malnutrition [11–13]. Therefore, identifying criteria that are practical and easy to use for assessing malnutritional status in HPB surgery is necessary.

Recently, diagnostic criteria for malnutrition have been proposed by the European Society for Clinical Nutrition and Metabolism (ESPEN), and these criteria have been validated by some studies [14–16]. However, the value of the ESPEN malnutrition criteria as a predictor for postoperative complications after HPB surgery is unclear. This study aimed to investigate the utility of the ESPEN malnutrition criteria as a predictor for major complications following hepatectomy and pancreatectomy.

Patients and methods

Between November 2017 and December 2019, 176 consecutive patients who underwent hepatectomy (n = 103) or pancreatectomy (n = 73) at our institution were enrolled in the study. Patients were divided into two groups according to the ESPEN malnutrition criteria using a prospectively collected database (Fig. 1). The clinical data and the surgical outcomes of patients in the malnourished and normal groups were retrospectively analyzed. Major hepatectomy was defined as the resection of three or more Couinaud's segments. All patients provided signed informed consent before undergoing therapy. This study was approved by the Institutional Review Board of our institution (No. 2019-136) and was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The new ESPEN diagnostic criteria for malnutrition

Multidisciplinary nutrition support teams provided nutritional assessment, as well as nutritional screening, as part of standard medical care in our hospital [17, 18]. The diagnosis of malnutrition was made by nutritional support teams based on the 2015 ESPEN criteria [14]. ESPEN - defined malnutrition is diagnosed in two steps. The first step is screening patients at risk of malnutrition using a validated nutritional screening tool. In the present study, we applied the Nutritional Assessment-Short Form as the screening tool. Consequently, screened patients were assessed if they satisfied at least one of the following criteria: (i) BMI <18.5 kg/m^2; (ii) unintentional weight loss > 5% over the past 3–6 months combined with BMI <20 kg/m^2 if age <70 years or <22.0 kg/m^2 if age ≥70 years; and (iii) unintentional weight loss combined with fat-free mass index <15.0 kg/m^2 for women or <17.0 kg/m^2 for men. The fat-free mass index was calculated by dividing the patient's estimated fat-free mass by the patient's height in meters squared (m^2) [19, 20]. The fat-free mass was obtained using the following formula that

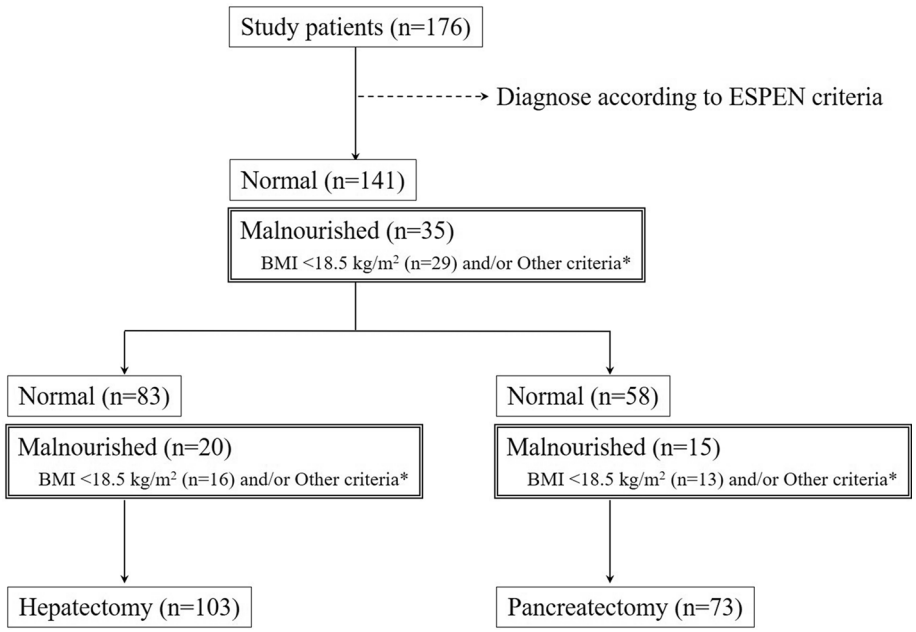

Fig. 1 Patient malnutrition assessment flow chart. *unintentional weight loss >5% over the past 3–6 months combined with BMI <20 kg/m^2 if age <70 years or <22.0 kg/m^2 if age ≥70 years and/or unintentional weight loss combined with fat-free mass index <15.0 kg/m^2 for women or <17.0 kg/m^2 for men

Table 1 Patient characteristics

	ESPEN criteria		*P*
	Normal (n = 141)	Malnourished (n = 35)	
Age (year)	69 (31–89)	72 (35–85)	0.204
Sex (male/female)	96/45	13/22	0.002
BMI (kg/m^2)	23.2 (18.7–40.8)	17.8 (15.4–21.2)	< 0.001
Albumin (g/dL)	3.8 (1.7–5.0)	3.4 (2.4–4.1)	0.001
ASA status (I/II/III)	57/78/6	17/14/4	0.120
Comorbidity			
Cardiovascular disease	25 (18%)	6 (17%)	1.000
Cerebrovascular disease	7 (5%)	3 (9%)	0.419
Pulmonary disease	11 (8%)	3 (9%)	1.000
Chronic kidney disease	10 (7%)	2 (6%)	1.000
Diabetes mellitus	31 (22%)	6 (17%)	0.646
Surgery			0.851
Hepatectomy	83 (59%)	20 (57%)	
Pancreatectomy	58 (41%)	15 (43%)	

Expressed as *N* (%) or median (range)

ESPEN European Society for Clinical Nutrition and Metabolism; *BMI* Body mass index; *ASA* American Society of Anesthesiologists

includes the estimated 24-h urine creatinine excretion rate (eCER): fat-free mass = 13.0 + 0.03 × eCER; eCER (mg/day) = 879.89 + 12.51 × weight (kg) − 6.19 × age (− 379.42 for female patients).

Postoperative complications

Postoperative complications were assessed according to the Clavien–Dindo classification system, and complications of grade 3a or worse were defined as major [21]. Any complications that developed within 90 days after the operation were included. No patients were lost to follow-up. Postoperative pancreatic fistula (≥ grade B) and bile leakage were defined according to the definitions of an international study group (i.e., ISGPF or ISGLS) [22, 23].

Outcome measurements

The first outcome measurement was performed by comparing the variables of patient demographic and clinical data as well as postoperative parameters between the malnourished and normal groups. The second outcome measurement was performed by analyzing the risk factors affecting the postoperative major complications in patients who underwent hepatectomy or pancreatectomy.

Statistical analysis

The continuous data are expressed as the medians (ranges). The statistical analyses were performed using chi square tests, Mann–Whitney *U* tests, or Fisher's exact probability tests as appropriate. The variables identified as potentially significant by univariate analysis (p value < 0.10) were selected for multivariate analysis with a logistic regression model to identify the independent predictors of postoperative major complications. All *P* values were 2-sided, and $P < 0.05$ was considered to indicate a statistically significant difference. All statistical calculations were performed using the IBM SPSS Statistics 21 software package (IBM Japan Inc., Tokyo, Japan).

Results

The patient characteristics related to hepatectomy and pancreatectomy are shown in Table 1. Thirty-five (20%) patients were diagnosed as malnourished according to the ESPEN criteria. The malnourished group had a significantly lower preoperative albumin concentration than the normal group (p = 0.001). The median age, ASA status, and incidence of comorbidities did not differ between the two groups. The incidence of chemotherapy prior to hepatectomy was 19% in the normal group and 25% in the malnourished group (p = 0.549). The incidence of chemotherapy prior to pancreatectomy was 9% in the

Table 2 Surgical outcome after hepatectomy

	ESPEN criteria		*P*
	Normal (n = 83)	Malnourished (n = 20)	
Major hepatectomy (≥ 3 segments*)	14 (17%)	9 (45%)	0.014
Multiple sites hepatectomy	15 (18%)	3 (15%)	1.000
Laparoscopic hepatectomy	29 (35%)	3 (15%)	0.109
Operative duration (min)	295 (123–877)	247.5 (113–569)	0.379
Total blood loss (mL)	224 (5–2856)	265.5 (1–2734)	0.802
Disease			0.340
Hepatocellular carcinoma	43 (52%)	8 (40%)	
Metastatic liver cancer	29 (35%)	6 (30%)	
Bile duct cancer	6 (7%)	3 (15%)	
Others	5 (6%)	3 (15%)	
Morbidity (overall)	18 (22%)	8 (40%)	0.149
Intraabdominal abscess	6 (7%)	2 (10%)	0.651
Bile leakage	4 (5%)	2 (10%)	0.330
Wound infection	3 (4%)	0	1.000
Refractory ascites	2 (2%)	0	1.000
Pleural effusion[a]	1 (1%)	1 (5%)	0.352
Liver failure	0	0	-
Other	4 (5%)	4 (20%)	0.044
Morbidity (≥ Clavien grade 3a)	4 (5%)	5 (25%)	0.013
Mortality	0	1 (5%)	0.194

Expressed as *N* (%) or median (range)

ESPEN European Society for Clinical Nutrition and Metabolism

*Couinaud's segments

[a]Required thoracentesis

normal group and 0% in the malnourished group (p = 0.576).

Table 2 shows the surgical outcomes after hepatectomy: 51 patients had hepatocellular carcinoma (HCC), 35 patients had metastatic liver cancer, 9 patients had bile duct cancer, and 8 patients had other diseases. Hepatectomy at multiple sites, use of a laparoscopic approach, operative duration, total blood loss volume, disease type, and overall morbidity did not differ between the two groups. A list of the observed morbidities is shown in Table 2, and the details of other morbidities are as follows: delayed gastric emptying (n = 1 in the normal group; n = 2 in the malnourished group), portal vein thrombosis (n = 1 in the normal group), anastomotic leakage of the colon after simultaneous colectomy (n = 1 in the normal group), pneumonia (n = 1 in the normal group), septicemia (n = 1 in the malnourished group), and cerebral infarction (n = 1 in the malnourished group). Although the mortality rate was not significantly different between the two groups, one patient in the malnourished group who underwent minor hepatectomy (i.e., left lateral sectionectomy) for HCC died from cerebral infarction postoperatively. There were significant differences between the two groups in the major hepatectomy rate (17% in the normal group vs. 45% in the malnourished group) and the major postoperative complication rate (5% in the normal group vs. 25% in the malnourished group). Among the nine malnourished patients who underwent major hepatectomy, three patients (33%) had major complications.

Table 3 shows the surgical outcomes after pancreatectomy: 41 patients had pancreatic cancer, 9 patients had bile duct cancer, and 23 patients had other diseases. Type of pancreatectomy, use of a laparoscopic approach, operative duration, total blood loss volume, disease type, pancreatic texture, and morbidity did not differ between the two groups. A list of observed morbidities is shown in Table 3, and the details of other morbidities are as follows: ascites (n = 3 in the normal group; n = 2 in the malnourished group), pneumonia (n = 2 in the normal group; n = 1 in the malnourished group), cholangitis (n = 1 in the normal group; n = 1 in the malnourished group), pleural effusion requiring thoracentesis (n = 1 in the malnourished group),

Table 3 Surgical outcome after pancreatectomy

	ESPEN criteria		*P*
	Normal (n = 58)	Malnourished (n = 15)	
Type of pancreatectomy			0.633
Pancreatoduodenectomy	31 (53%)	10 (67%)	
Distal pancreatectomy	23 (40%)	4 (27%)	
Total pancreatectomy	4 (7%)	1 (7%)	
Laparoscopic pancreatectomy	6 (10%)	2 (13%)	0.664
Operative duration (min)	353 (157–668)	343 (190–448)	0.633
Total blood loss (mL)	302 (10–4250)	200 (3–1234)	0.170
Disease			0.756
Pancreatic cancer	32 (55%)	9 (60%)	
Bile duct cancer	8 (14%)	1 (7%)	
Others	18 (31%)	5 (33%)	
Pancreatic texture			0.229
Soft	39 (67%)	7 (47%)	
Hard	19 (33%)	8 (53%)	
Morbidity (overall)	35 (60%)	10 (67%)	0.770
Pancreatic fistula (≥ grade B)	24 (41%)	3 (20%)	0.147
Bile leakage	2 (3%)	0	1.000
Intraabdominal abscess	7 (12%)	2 (13%)	0.664
Intraabdominal bleeding	3 (5%)	0	1.000
Delayed gastric emptying	1 (2%)	2 (13%)	0.105
Septicemia	0	2 (13%)	0.040
Other	6 (10%)	6 (40%)	0.013
Morbidity (≥ Clavien grade 3a)	24 (41%)	3 (20%)	0.147
Mortality	0	0	-

Expressed as *N* (%) or median (range)

ESPEN European Society for Clinical Nutrition and Metabolism

and portal vein thrombosis (n = 1 in the malnourished group). The in-hospital and 90-day postoperative mortality rates were zero in both groups.

The multivariate analysis indicated that operative duration ≥ 300 min (hazard ratio: 22.47, 95% CI: 2.17 to 232.73, p = 0.009) and malnourishment (hazard ratio: 14.56, 95% CI: 2.58 to 82.17, p = 0.002) were independently associated with major complications after hepatectomy (Table 4). On the other hand, malnutrition was not associated with major complications after pancreatectomy (Table 5). The multivariate analysis indicated that soft pancreas (hazard ratio: 4.50, 95% CI: 1.25 to 16.19, p = 0.021) and total blood loss ≥ 400 mL (hazard ratio: 4.91, 95% CI: 1.57 to 15.34, p = 0.006) were independently associated with major complications after pancreatectomy.

Discussion

This is the first nutritional study in the literature to note the new ESPEN malnutrition criteria in patients who underwent HPB surgery. In this study, 20% of all patients were diagnosed as malnourished according to the ESPEN criteria. The most interesting finding of this study was the difference between the results of the two surgeries (i.e., hepatectomy and pancreatectomy). Malnourishment was independently associated with major complications after hepatectomy. On the other hand, malnutrition was not associated with major complications after pancreatectomy.

In 2015, ESPEN presented new consensus criteria for the diagnosis of malnutrition with the aim of reaching uniformity between countries and/or studies [14]. According to a previous study on the prevalence of malnutrition diagnosed by the new ESPEN criteria, 0.5% of healthy

Table 4 Uni- and multivariate predictors of major complications after hepatectomy

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
> 5 (years) (*n* = 34)	2.46	0.32–19.0	0.390			
<75 (years) (*n* = 69)	1					
Sex						
Female (*n* = 31)	1.32	0.17–10.01	0.788			
Male (*n* = 72)	1					
Albumin						
<3.0 (g/dL) (*n* = 5)	1.20	0.02–78.52	0.755			
>3.0 (g/dL) (*n* = 98)	1					
Diabetes mellitus						
Present (*n* = 22)	0.39	0.03–4.96	0.470			
Absent (*n* = 81)	1					
ASA status						
III (*n* = 9)	1.23	0.04–40.47	0.907			
I/II (*n* = 94)	1					
Extent of hepatectomy						
Major (*n* = 23)	1.38	0.18–10.39	0.755			
Minor (*n* = 80)	1					
Operative duration						
>300 (min) (*n* = 48)	16.59	1.01–271.67	0.049	22.47	2.17–232.73	0.009
< 300 (min) (*n* = 55)	1			1		
Total blood loss						
>400 (mL) (*n* = 27)	3.60	0.58–22.23	0.169			
<400 (mL) (*n* = 76)	1					
ESPEN criteria						
Malnourished (*n* = 20)	10.39	0.98–109.90	0.052	14.56	2.58–82.17	0.002
Normal (*n* = 83)	1			1		

ASA American Society of Anesthesiologists; *ESPEN* European Society for Clinical Nutrition and Metabolism

elderly individuals and 6% of geriatric outpatients were identified as malnourished [24]. These values are very low compared with those of the present study, which indicates that patients with HPB disease might have a higher prevalence of malnutrition than the healthy and geriatric populations. Similarly, in a recent study of geriatric gastrointestinal cancer, 20% of the patients were classified as malnourished according to the new ESPEN criteria [16]. In another report, 16.9% of the patients admitted with a proximal femoral fracture were diagnosed as malnourished by the new ESPEN criteria [25]. Therefore, it should be noted that the number of patients requiring surgery that have malnutrition is higher than expected.

Hepatectomy is one of the common procedures in HPB surgery that can lead to postoperative complications. Patients with HCC have underlying chronic liver disease, and patients with metastatic liver cancer may have a history of chemotherapy prior to hepatectomy; thus, these patients are at risk of developing postoperative complications. Preoperative nutritional status is one of the key factors for the success of a hepatectomy. Currently, various nutritional assessment tools are widely used for patients with HPB disease. Schiesser et al. [26] reported that 27.3% of the patients who underwent elective hepatobiliary surgery were malnourished, as determined by the Nutrition Risk Screening 2002 (NRS 2002) score. The Patient-Generated Subjective Global Assessment (PG-SGA) score is another nutritional assessment method [27, 28]. Huang et al. [29] showed that 33.4% of the patients who underwent hepatectomy for HCC were malnourished by using the PG-SGA, and malnourishment was associated with more postoperative complications than a healthy nutritional status. Therefore, the authors concluded that the PG-SGA is an effective tool for predicting postoperative

Table 5 Uni- and multivariate predictors of major complications after pancreatectomy

Variable	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
>75 (years) (*n* = 17)	1.39	0.30–6.42	0.675			
<75 (years) (*n* = 56)	1					
Sex						
Female (*n* = 36)	0.48	0.14–1.62	0.236			
Male (*n* = 37)	1					
Albumin						
<3.0 (g/dL) (*n* = 10)	4.97	0.80–31.02	0.086	3.80	0.79–18.40	0.097
>3.0 (g/dL) (*n* = 63)	1			1		
Diabetes mellitus						
Present (*n* = 15)	0.73	0.18–2.92	0.661			
Absent (*n* = 58)	1					
Preoperative chemotherapy						
Present (*n* = 5)	1.54	0.17–14.21	0.703			
Absent (*n* = 68)	1					
Pancreatic texture						
Soft (*n* = 46)	4.71	1.12–19.77	0.034	4.50	1.25–16.19	0.021
Hard (*n* = 27)	1			1		
Operative duration						
>300 (min) (*n* = 52)	0.48	0.12–1.99	0.313			
<300 (min) (*n* = 21)	1					
Total blood loss						
>400 (mL) (*n* = 29)	4.76	1.20–18.91	0.027	4.91	1.57–15.34	0.006
<400 (mL) (*n* = 44)	1			1		
ESPEN criteria						
Malnourished (*n* = 15)	0.55	0.10–2.97	0.487			
Normal (*n* = 58)	1					

ESPEN European Society for Clinical Nutrition and Metabolism

complications in patients with HCC following hepatectomy. However, the PG-SGA is a questionnaire completed by the individual, and thus the nutritional status can be underestimated or overestimated. In addition, the NRS 2002 or PG-SGA are just nutritional screening tools, not diagnostic tools. Conversely, the new ESPEN criteria are diagnostic criteria for malnutrition that are simple and practical to use.

When comparing the short-term results of hepatectomy and pancreatectomy, although the mortality rates are generally similar, pancreatectomy has a higher complication rate [5, 6]. Pancreatectomy is a highly invasive procedure with an inherent risk of complications. Postoperative pancreatic fistula (POPF) was the most common complication and subsequently triggered other infectious complications. Many studies have described risk factors for POPF and reported that pancreatic texture and duct size were significant factors [30, 31]. In our series of patients receiving pancreatectomy, the POPF rate was as high as 37% in the total patients, and POPF was responsible for 50% of the overall morbidity. Taking this into consideration, nutritional status may be only a secondary factor in patients who undergo pancreatectomy. The beneficial effect of nutrition may not be sufficient to overcome these major factors affecting the outcome of pancreatectomy.

Many studies have addressed different screening tools and their ability to identify malnourished patients and patients who are at nutritional risk. In contrast, only a few studies have compared different screening tools to investigate their correlation and reliability [11]. Probst et al. [12] reported a prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatectomy. They concluded that none of the nutritional assessment scores that assessed malnutrition were relevant to

complications after pancreatectomy and that these scores may thus be abandoned. McKenna et al. [13] investigated the optimal definition of malnutrition before major oncologic resection for 6 cancer types (i.e., colorectal, gastric, esophageal, liver, lung, and pancreatic cancer). They concluded that postoperative risk due to malnutrition varies based on both the definition of malnutrition used and the specific cancer type. Even in our study, a clinically relevant definition of malnutrition for patients undergoing pancreatectomy remains to be established.

This study has some limitations that need to be addressed. First, this was a retrospectively designed study, and a propensity score matching analysis was not possible because the number of patients, who were identified with the new malnutrition criteria at a single center, was too small. Second, there were no comparisons of different diagnostic criteria for malnutrition to investigate their correlation and reliability. Biochemical nutritional marker analysis is sometimes performed to evaluate the immune-nutritional status, but this is sometimes unreliable and should only be used as a subsidiary tool to supplement nutrition risk screening assessment. In the future, multicenter large-series studies evaluating the clinical impact of malnutrition criteria, including the ESPEN malnutrition criteria after HPB surgery, will compensate for the limitations of this study.

In conclusion, our study indicates that the ESPEN malnutrition criteria are a valuable predictor for major complications following hepatectomy. Routine preoperative assessment of the ESPEN malnutrition criteria could help manage meticulous follow-up after hepatectomy.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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Informed consent All patients provided signed informed consent before undergoing therapy.

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