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Preoperative frailty as a predictive factor for postoperative complications in patients with pancreatic cancer

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ABSTRACT

Frailty is considered one of the most important indicators of a patient's general condition. However, only a few studies have investigated the association between preoperative frailty and postoperative complications in pancreatic cancer. Therefore, this study aimed to examine this association in patients with pancreatic cancer. We retrospectively reviewed 52 consecutive patients who underwent pancreatectomy for pancreatic cancer between July 2019 and March 2021. Patients were classified into two groups according to the presence of postoperative complications. Their characteristics and clinical parameters, including physical function, were analyzed. Patients with postoperative complications had a higher prevalence of frailty (58.8% vs 14.3%, $p = 0.003$) and a shorter 6-min walk distance (380 m vs 436 m, $p = 0.020$) than those without postoperative complications. Logistic regression analysis identified preoperative frailty as the only independent risk factor for complications after pancreatectomy ($p = 0.002$). Preoperative frailty is associated with postoperative complications of pancreatectomy. Since preoperative frailty can be easily evaluated, it is a useful predictor of postoperative complications after pancreatectomy.

Keywords: pancreatic cancer, postoperative complication, frailty

Abbreviations:
PC: pancreatic cancer
CFS: Clinical Frailty Scale
NAC: neoadjuvant chemotherapy
Alb: serum albumin
6MWD: 6-min walk distance

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INTRODUCTION

Improvements in the survival rate of patients with pancreatic cancer (PC) have been reported due to advancements in chemotherapy and surgical techniques.[1] Pancreatectomy is a highly invasive procedure and has a high incidence rate of postoperative complications, such as pancreatic fistula and subsequent intra-abdominal abscess, ranging from 18% to 60%.[2] Therefore, it requires prolonged hospitalization. Cardiopulmonary function and lower limb muscle strength have been reported to significantly decrease 3 months after pancreatectomy.[3] Thus, careful attention should be paid to postoperative complications and physical conditions during the perioperative period.

Frailty is defined as a clinical syndrome of progressive decline in physical and mental functioning, regardless of comorbidities,[4] and it is a particularly important issue in an aging society. Frailty is a good predictor of postoperative complications after hepatectomy[5] and a possible prognostic factor.[6] Therefore, in providing perioperative physical therapy, frailty is considered one of the most important indicators to understand the patient's general condition, such as physical function and exercise tolerance.

Although several studies have investigated the association between preoperative frailty and postoperative complications, only a few have focused exclusively on PC.[7-9] Moreover, they focused on relatively severe postoperative complications.[8,9] Therefore, this study aimed to investigate whether preoperative frailty is a useful predictor of all postoperative complications, with an exclusive focus on patients with PC.

MATERIALS AND METHODS

Patients

In this retrospective study, patient data were obtained from their medical records. Of the 69 consecutive patients who underwent pancreatectomy at our hospital between July 2019 and March 2021, 52 with PC were included in this study after excluding 17 patients with diseases other than PC and data loss (Fig. 1). According to the Declaration of Helsinki, an opt-out procedure was conducted on our website, and the outline of the study was open to the public so that patients could have the opportunity to refuse to be included in the study. This study was approved by the Institutional Review Board of Kitakyushu Municipal Medical Center (approval number: 202105011).

Measurement of frailty

The Clinical Frailty Scale (CFS) was used to evaluate frailty.[10] The CFS assesses the health status of the patient over the past 2 weeks. It includes the following four characteristics of the patient: movement, functioning, thinking, and emotions. Each level is scored by comparing a picture with a description.[11] The CFS is a combination of clinical judgment and objective measurement, with grades ranging from 1 (very fit) to 9 (terminally ill).[12] In this study, a CFS grade ≥ 4 was used to define frailty.[5] The use of the CFS was determined by two experienced physical therapists (MO and SK).

Postoperative complications

The Clavien–Dindo (CD) classification, which is categorized into five levels according to the degree of treatment, was used to assess the postoperative complications in this study.[13] Grade II or higher level was indicated a complication.[14]

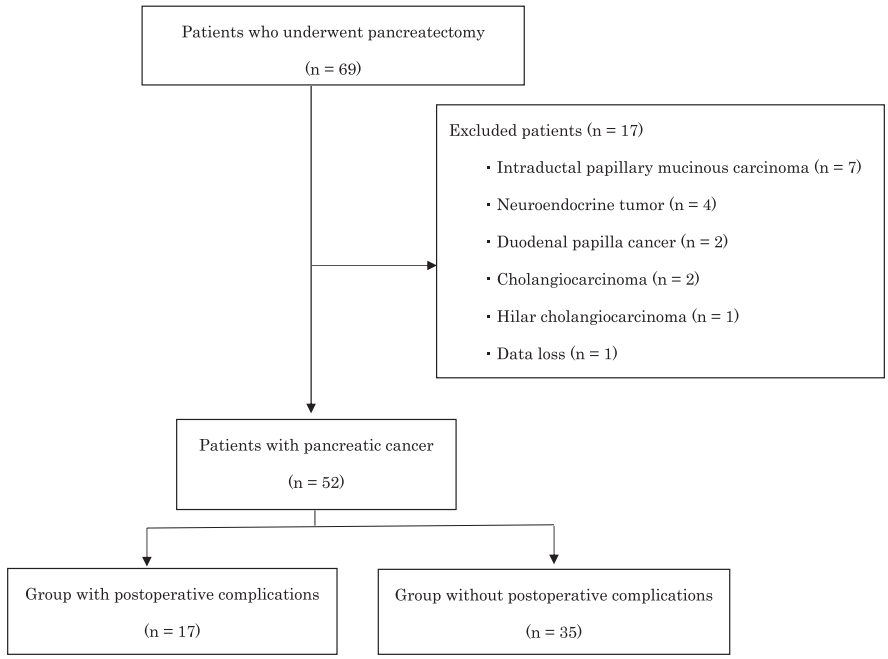

Fig. 1 Patient flow diagram
Sixty-nine patients underwent pancreatectomy during the study period. Among them, 52 patients who underwent pancreatectomy for pancreatic cancer were enrolled after excluding 17 patients with other diseases. Finally, the characteristics and clinical parameters of patients with (n = 17) and without (n = 35) postoperative complications were analyzed.

Measurement items

The variables were as follows: age, sex, body mass index (BMI), Brinkman index score, cancer stage,[15] preoperative neoadjuvant chemotherapy (NAC), Geriatric Nutritional Risk Index score, length of hospital stay after surgery, and Charlson Comorbidity Index (CCI) score. Further, CCI score was classified as 0 (low), 1–2 (medium), 3–4 (high), and ≥ 5 (very high).[16] Respiratory function variables included vital capacity (VC), predicted VC (%VC), forced expiratory volume in 1 s (FEV1.0), and predicted FEV1.0 (%FEV1.0). Surgical factors included operative time, total fluid volume, and blood loss volume. Preoperative blood data included hemoglobin, serum total protein, and serum albumin (Alb) levels. Preoperative physical function was assessed by measuring the 6-min walk distance (6MWD), grip strength, and knee extensor strength. The 6MWD was measured under maximal effort according to the American Thoracic Society.[17] Knee extension muscle strength was assessed using a handheld dynamometer (Anima Co, Ltd, μTas F-1). It was measured with the patient in the sitting position and the knee positioned at approximately 90° flexion. The dynamometer force pad was placed just proximal to the ankle joint and used to measure the force produced during quadriceps muscle contraction. Grip strength was measured twice on each side using a digital grip strength meter (Takei Scientific Instruments Co, Ltd, Grip D) in the standing position, and the maximum value was adopted. Since muscle strength varies with body size, the measurement results were divided by body weight to normalize body size.[18]

Physical therapy program

Coughing and breathing exercises, training for upper and lower limb muscle strength, and ergometry were performed for preoperative physical therapy from the day of admission to the day before surgery for all patients in this study. Early mobilization and exercise therapy were started on the day after surgery until the day before discharge.

Statistical analyses

Data are presented as median (interquartile range), regardless of normality. Patients were classified into two groups: those with and without postoperative complications. For continuous variables, the unpaired t-test for normality and Mann–Whitney U test for non-normality were used. For categorical variables, the chi-squared test was used. Logistic regression analysis was performed to identify whether preoperative frailty was a useful predictor of postoperative complications.

The dependent variable was the presence or absence of postoperative complications, and the independent variable was preoperative frailty. Age, 6MWD, and Alb level were selected as adjustment variables based on previous studies.[14,19-21] To compare postoperative survival in patients with and without preoperative frailty, survival curves were obtained using the Kaplan–Meier method, and log-rank tests were performed to determine differences between the two groups. All statistical analyses were performed using EZR on commander version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

RESULTS

Patients' basic characteristics

Table 1 shows the basic characteristics of the 52 patients. There were 26 men and 26 women, with a median age of 72 (interquartile range, 69–76) years. Among the 52 patients, 39 (75 %) received NAC. Pancreatoduodenectomy (PD) and distal pancreatectomy (DP) were performed in 29 (55.8 %) and 23 (44.2 %) patients, respectively.

Postoperative complications

Descriptions of postoperative complications are shown in Table 2. Postoperative complications were observed in 17 (32.7%) patients, including 14 with pancreatic fistula (six with pancreatic fistula only [CD classification, III a for all], three with abscess [II, III a, and III b], two with hemorrhage [II and III b], one with atelectasis [II], one with wound infection [II], one with bile leakage [III a], one with a pulmonary embolus [II], one with atelectasis [II], and one with respiratory failure [IV a]).

Comparison of factors between groups with and without postoperative complications

The results of the comparison between groups with and without postoperative complications are shown in Table 3. The prevalence of preoperative frailty was significantly higher (58.8 % vs 14.3 %, $p = 0.003$) and 6MWD was significantly lower (380 m vs 436 m, $p = 0.022$) in the group with postoperative complications than in the group without postoperative complications. Regarding surgical procedure, there was no significant difference in complication rates between PD and DP (35.3% vs 65.7%, $p = 0.073$). Respiratory function, surgical information, blood data, and NAC results did not show any significant difference between the two groups. As expected, the length of hospital stay was significantly longer in the group with postoperative complications than in the group without postoperative complications (31 days vs 20 days, $p < 0.001$).

Table 1 Preoperative characteristics of the study patients

Age, years	72 (69–76)
Male/female, n (%)	26/26 (50/50)
BMI (kg/m^2)	22.2 (21.3–24.2)
Procedure, PD/DP (%)	29 (55.8)/23 (44.2)
Stage, n (%)	
0	2 (3.8)
IA	4 (7.7)
IB	0 (0)
II A	20 (38.4)
II B	24 (46.1)
III	1 (1.9)
IV	1 (1.9)
NAC (%)	39 (75)
Comorbidities, n (%)	
Diabetes	30 (57.7)
Respiratory disease	9 (17.3)
Heart disease	9 (17.3)

Values are reported as the median (interquartile range) or number of patients (percentage).
BMI: body mass index
PD: pancreatoduodenectomy
DP: distal pancreatectomy
NAC: neoadjuvant chemotherapy

Table 2 Postoperative complications observed in 17 patients after pancreatectomy

Pancreatic fistula	14 (82)	
Pancreatic fistula only		6 (35)
+ Intra-abdominal abscess		3 (18)
+ Intra-abdominal hemorrhage		2 (12)
+ Bile leakage		1 (6)
+ Atelectasis		1 (6)
+ Wound infection		1 (6)
Pulmonary embolus	1 (6)	
Atelectasis	1 (6)	
Respiratory failure	1 (6)	

Data are presented as n (%).

Table 3 Comparison of factors between groups with and without postoperative complications

Variables	With complications (n=17)	Without complications (n=35)	*p*-value
Age (years)	73 (71–77)	72 (66–75)	0.132
Male/female, n (%)	10/7 (59/41)	16/19 (46/54)	0.555
BMI (kg/m^2)	21.9 (20.7–24.0)	23.7 (21.8–24.7)	0.140
Frailty, n (%)	10 (58.8)	5 (14.3)	0.003
Brinkman index	535 (0–925)	204 (0–735)	0.247
GNRI	96.5 (91.7–102.5)	94.1 (91–100.5)	0.788
Cancer stage, n (%)			0.950
0	2 (12)	0 (0)	
IA	0 (0)	4 (11)	
IB	0 (0)	0 (0)	
IIA	6 (35)	14 (40)	
IIB	8 (47)	16 (46)	
III	1 (6)	0 (0)	
IV	0 (0)	1 (3)	
CCI, n (%)			0.540
Low	6 (35)	9 (26)	
Medium	8 (47)	22 (63)	
High	3 (18)	4 (11)	
NAC, n (%)	12 (70.6)	27 (77.1)	0.506
LOS (day)	31 (28–49)	20 (18–24)	<0.01
Surgical procedure, PD / DP, n (%)	6 (35.3) / 11 (64.7)	23 (65.7) / 12 (34.3)	0.073
Operative time (min)	306 (235–382)	371 (312–462)	0.106
Infusion volume (mL)	3220 (2380–3620)	3255 (2653–5005)	0.233
Blood loss (mL)	460 (280–745)	370 (207–647.5)	0.470
6MWD (m)	380 (345–435)	436 (408–483)	0.022
Grip strength (%)	21.5 (12.3–40.5)	32.5 (14.5–48.1)	0.155
KES (%)	37.2 (24.0–54.8)	44.2 (32.6–51.0)	0.135
VC (L)	2.69 (2.19–3.12)	2.81 (2.52–3.17)	0.308
%VC (%)	101.1 (94.2–110.4)	111.4 (94.7–117.2)	0.201
FEV1 (L)	1.90 (1.71–2.45)	2.11 (1.77–2.37)	0.441
FEV1% (%)	75.3 (66.3–78.6)	76.9 (67.9–80.9)	0.565
Hb (g/dL)	10.9 (10.6–12.5)	11.7 (11–12.3)	0.490
TP (g/dL)	6.3 (6.0–6.9)	6.2 (5.9–6.6)	0.532
Alb (g/dL)	3.4 (3.1–3.6)	3.6 (3.3–3.9)	0.074

Values are reported as the median (interquartile range) or number of patients (percentage).
BMI: body mass index
GNRI: Geriatric Nutritional Risk Index
CCI: Charlson Comorbidity Index
NAC: neoadjuvant chemotherapy
LOS: length of hospital stay
6MWD: 6-min walk distance
KES: knee extension strength
VC: vital capacity
%VC: percent vital capacity
FEV1: forced expiratory volume in 1 s
FEV1%: percent forced expiratory volume in 1 s
Hb: hemoglobin
TP: serum total protein
Alb: serum albumin

Association between postoperative complications and preoperative frailty

The results of the multivariate analysis are shown in Table 4. Preoperative frailty was used as an independent variable, and age, 6MWD, and Alb level were used as adjustment variables. Therefore, preoperative frailty was an independent risk factor for postoperative complications ($p = 0.031$), with an odds ratio of 5.950 (95% confidence interval, 1.18–30.00).

Table 4 Factors associated with postoperative complications

	Odds ratio	95% CI	*p*-value
Frailty	5.950	1.18–30.00	0.031
Age (year)	1.070	0.96–1.19	0.237
6MWD (m)	0.997	0.99–1.01	0.572
Alb (g/dL)	0.410	0.08–2.25	0.304

6MWD: 6-min walk distance
Alb: serum albumin
CI: confidence interval

Comparison of postoperative survival in patients with and without frailty

The Kaplan–Meier curves comparing the postoperative survival of patients with PC with and without frailty showed a significant difference ($p < 0.05$) between the groups (Fig. 2).

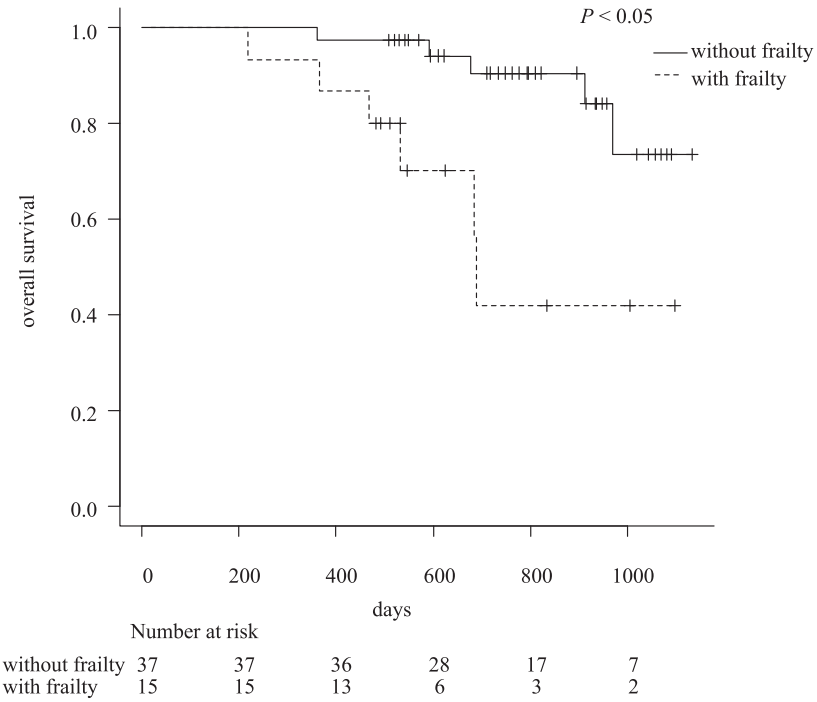

Fig. 2 Kaplan–Meier curves comparing the survival of patients with and without frailty
Patients without frailty had a significantly more favorable prognosis than those with frailty ($p < 0.05$).

DISCUSSION

In this study, we investigated whether preoperative frailty is associated with postoperative complications in patients with PC. Our study found that preoperative frailty was an independent predictive factor for the occurrence of postoperative complications.

High frailty levels before PD for PC are predictors of postoperative complications and mortality.[7] Our study showed similar results for both PD and DP; therefore, the presence of preoperative frailty is an important predictor of pancreatectomy. It remains unclear why preoperative frailty leads to an increased incidence of postoperative complications; however, in general, frailty is characterized by a heterogeneous combination of decreased mobility, weakness, reduced muscle mass, and poor nutritional status.[22] These factors are hypothesized to decrease the physiological reserve and increase vulnerability to acute stress[7]; thus, frailty may contribute to the development of complications.

Recently, NAC has become a standard treatment for PC because it leads to a higher R0 resection rate and a lower positive lymph node rate than upfront surgery.[23] NAC did not significantly increase postoperative complications in this study; however, NAC may further reduce the physical function and activity of patients.[24] Preoperative physical function has been correlated with postoperative complications, length of hospital stay, and prognosis.[25] Several studies have reported that preoperative exercise intervention improves postoperative outcomes in surgical patients,[26,27] and preoperative exercise capacity has been reported to predict postoperative physiological reserve by loading the whole-body oxygen delivery system.[28] These reports suggest that preventing preoperative physical frailty may reduce the incidence of postoperative complications. Therefore, a combination of NAC and preoperative exercise therapy may be a useful treatment strategy for PC.

Another important predictive factor for postoperative complications is exercise tolerance, as measured using 6MWD. Several studies have reported that 6MWD is a useful predictive factor for postoperative complications in various cancers.[14,19,20] Further, 6MWD is associated with maximum oxygen uptake[29] and may correlate with loss of muscle mass and tissue fragility; therefore, it may contribute to increased postoperative complications. Cardiopulmonary exercise tests are usually performed to objectively evaluate general exercise tolerance; however, it may be difficult to perform this evaluation in all hospitals or facilities. This study showed that a shorter 6MWD tended to increase postoperative complications, although this was not an independent factor. This may be due to the small sample size, compared with those of other reports. Further studies with larger sample sizes are required to clarify this issue.

A previous study showed that poor nutritional status with low Alb level (< 3.5 g/dL) or low BMI (< 18.5 kg/m^2) before surgery for pancreatic head cancer was a predictor of postoperative complications.[21] In our study, the group with postoperative complications showed insignificantly lower Alb levels than the group without postoperative complications (3.42 g/dL vs 3.64 g/dL, $p = 0.074$) (Table 3). The association between preoperative malnutrition and worse postoperative outcomes has not yet been elucidated. However, considering the fragility of tissues, susceptibility to infection, and the possibility of vessel wall fragility,[21] preoperative nutritional status might be an important factor. Therefore, the association between exercise tolerance and nutritional status should be investigated in the future.

We used the CFS to evaluate frailty because of the ease and efficacy of using this judgment tool. Other methods used to assess frailty take a longer time to evaluate, such as the modified Frailty Index[7] and Edmonton Frail Scale.[30] Further studies are required to clarify the most useful preoperative assessment for frailty.

Postoperative complications were defined as CD classification II or higher. In contrast, a

previous study that focused on PC defined it as CD classification III or higher.[9,19] However, CD classification II or higher, which requires medical treatment, such as antimicrobial agents, should be considered a postoperative complication because it may affect the length of the hospital stay.

Finally, the prognosis of patients with frailty was worse than of that of those without frailty in this study, as reported in a previous study.[31] As mentioned above, preventing frailty with exercise therapy may contribute to short-term outcomes and prognosis in the era of NAC for PC.

Our study has some limitations. First, this was a retrospective study conducted at a single center involving a small number of patients. Second, the optimal tool for measuring frailty may differ in each study.[6] A prospective study with a larger number of patients is required to determine the association between frailty and postoperative complications.

CONCLUSIONS

Frailty assessed using CFS is a useful predictor of postoperative complications in patients with PC.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

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