

Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy

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ABSTRACT

Background. The impact of prehabilitation on physical fitness and postoperative course after hepato-pancreato-biliary (HPB) surgeries for malignancy is unknown. The current study aimed to investigate the effect of preoperative exercise and nutritional therapies on nutritional status, physical fitness, and postoperative outcomes of patients undergoing an invasive HPB surgery for malignancy.

Methods. Patients who underwent open abdominal surgeries for HPB malignancies (major hepatectomy, pancreatoduodenectomy, or hepato-pancreatoduodenectomy) between 2016 and 2017 were subjected to prehabilitation. Patients before the introduction of prehabilitation were included as historical control subjects for 1:1 propensity score-matching (no-prehabilitation group). The preoperative nutritional status and postoperative course were compared between the two groups.

Results. The prehabilitation group consisted of 76 patients scheduled to undergo HPB surgeries for malignancy. An identical number of patients were selected as the no-prehabilitation group after propensity score-matching. During

the waiting period, serum albumin levels were significantly deteriorated in the no-prehabilitation group, whereas this index did not deteriorate or even improved in the prehabilitation group. By performing prehabilitation, a 6-min walk distance and total muscle/fat ratio were significantly increased during the waiting period. Although the overall incidence of postoperative complications did not differ between the two groups, the postoperative hospital stay was shorter in the prehabilitation group than in the no-prehabilitation group (median, 23 vs 30 days; $p = 0.045$). **Conclusion.** The introduction of prehabilitation prevented nutritional deterioration, improved physical fitness before surgery, and shortened the postoperative hospital stay for the patients undergoing HPB surgeries for malignancy.

Because of advancements in perioperative patient management and surgical technology, surgery for gastrointestinal malignancy has become a relatively safe procedure with better postoperative outcomes. However, surgery for hepato-pancreato-biliary (HPB) malignancies still is an invasive and complicated procedure with high postoperative morbidity and mortality rates.^{1,2}

Poor preoperative physical fitness has been shown to increase the risk and incidence of postoperative complications^{3–5} and mortality.^{6,7} Previous studies by the authors reported that preoperative poor skeletal muscle mass⁸ and poor functional exercise capacity⁹ were associated not only with a higher rate of postoperative morbidity and mortality but also with worse long-term survival for patients undergoing surgery for HPB malignancies. These results clearly

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indicate the importance of increasing skeletal muscle mass and improving physical fitness before HPB surgeries for malignancies.

In recent years, much focus has been placed on the importance of “prehabilitation,” an optimization of physical fitness before surgery, with the intent of improving postoperative outcomes.^{10,11} Previous reviews indicated that preoperative physical exercise and nutritional interventions for patients undergoing elective colorectal resection for cancer is feasible, safe, and efficacious.^{12–15} However, the impact of preoperative physical exercise on physical fitness, postoperative complications, and hospital stay after highly invasive HPB surgeries for malignancy is unknown. Moreover, the benefit of nutritional intervention combined with physical exercise has not been well evaluated.

Accordingly, this study aimed to investigate the effect of preoperative exercise and nutritional therapies on physical fitness, nutritional status, postoperative complications, and hospital stay during the waiting period for patients undergoing a highly invasive HPB surgery for malignancy.

METHODS

Participants

Patients who underwent highly invasive open abdominal surgeries for HPB malignancies between July 2016 and October 2017 at Nagoya University Hospital were subjected to preoperative exercise and nutritional therapies (prehabilitation group). In this study, only highly invasive surgeries such as major hepatectomy with at least 3 Couinaud segments, pancreatoduodenectomy, and hepato-pancreatoduodenectomy were included in the study.

The exclusion criteria ruled out patients who underwent preoperative chemotherapy or chemoradiotherapy, those unable to do physical training, those with metabolic dysfunction for amino acids, those with severe complications (e.g., heart disease, pulmonary disease, renal disease, hepatic disease), those with a severe mental dysfunction, and those with a severe cognitive disorder.

A backward consecutive series of patients who underwent highly invasive surgeries for HPB malignancies before the clinical trial (without preoperative exercise and nutritional therapies between June 2014 and November 2015) were enrolled as historical control subjects (no-prehabilitation group). This study was approved by the Ethics Committee of Nagoya University Hospital (approval no. 2015-0515) and registered in the University Hospital Medical Information Network (<http://www.umin.ac.jp>; registration number ID 000020780). Written informed

consent for participation was obtained from each patient before enrollment.

Data Collection

Demographic data including age, sex, height, body weight, body mass index, diagnosis, cancer stage, presence of preoperative cholangitis, presence of preoperative biliary drainage, and other comorbidities were recorded. The Charlson comorbidity index was used for uniform scoring of the comorbid conditions.¹⁶ The waiting period for surgery was determined as the term between the date of hospitalization for examination of cancer (first hospitalization) and the date of re-hospitalization for surgery (second hospitalization). Intraoperative data such as operative procedure, operation time, intraoperative blood loss, and use of allogeneic blood transfusion also were recorded.

The severity of postoperative complications was classified using the Clavien-Dindo classification system.^{17,18} A major complication was defined as a complication with a Clavien grade of 3 or higher. Postoperative infectious complications included intraabdominal abscess, bacteremia, cholangitis, surgical-site infection, and pneumonia. Liver failure and bile leakage were defined according to the definition of the International Study Group of Liver Surgery.^{19,20} Postoperative pancreatic fistula was defined according to the definition of the International Study Group of Pancreatic Fistula.^{21,22}

The discharge criteria were constant throughout the study period. Discharge from the hospital was allowed when patients were afebrile without any drainage tube and with stable oral intake.

Measurement of Physical Fitness

In the prehabilitation group, physical fitness was assessed at both the first and second hospitalizations. The evaluated physical fitness indexes included a 6-min walk distance (6MWD) according to the guidelines of the American Thoracic Society,²³ isometric knee extensor muscle strength measured by a hand-held dynamometer (Mutus F-100; Anima Co., Tokyo, Japan), grip strength measured by a digital dynamometer (Grip-D; Takei Co., Niigata, Japan), and the 10-m usual walking speed test. Total skeletal muscle mass and fat mass also were measured using a bioelectric impedance analysis system (In Body 720; Biospace, Tokyo, Japan) at both the first and second hospitalizations.

Measurement of Nutritional Status

In both the no-prehabilitation and prehabilitation groups, the data on body weight, body mass index, serum

albumin, and prognostic nutritional index (PNI) were collected both at both the first and second hospitalizations. As an indicator of nutritional status, PNI was assessed using the following equation as described previously:²⁴

$$\text{PNI} = 10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count in the peripheral blood (/mm}^3\text{)}.$$

Prehabilitation Program

The patients were supervised by physical therapists (H.N., T.I., M.N., and Y.M.) at the first hospitalization and asked to record their exercise as well as their nutritional therapy history during the waiting period.

Preoperative Exercise Therapy

The exercise therapy comprised 60 min of home-based, unsupervised exercise once a day at least 3 times per week. Moderate aerobic exercise and resistance training were combined. In the aerobic exercise, the patients were asked to walk for at least 30 min with an exercise intensity of 3–4 according to the modified Borg Scale score.²⁵ For the resistance exercises, the patients were asked to do at least two sets of 10 squats, 10 calf raises, 10 sit ups, 10 bridge ups, and 10 upper-limb movements with an appropriate weight.

Preoperative Nutritional Therapy

The patients were asked to take a leucine-rich essential amino acid supplement (Amino L40; AJINOMOTO, Tokyo, Japan) (Table S1) within 30 min after the start and end of exercise therapy.

Statistical Analysis

The data for continuous variables were expressed as median (interquartile range [IQR]). Differences between the two groups were analyzed using Chi square or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. The data at the first hospitalization and those at the second hospitalization were compared using the non-parametric Wilcoxon rank-sum test. For comparison of multiple groups, one-way analysis of variance (ANOVA) with a post hoc test (Dunnnett test) was used. The correlation between the two variables was determined by Spearman's rank correlation coefficient.

Using multivariate logistic regression analysis, propensity scores were estimated for the patients included in the prehabilitation and no-prehabilitation groups. The following seven preoperative variables were used in the model: gender, age, body mass index, waiting period before

surgery, surgical procedure, serum albumin, and lymphocyte count at the hospitalization for examination. Subsequently, a one-to-one match between the two groups was performed by the nearest neighbor-matching method within 0.05 standard deviations. Subsequently, the demographic data, preoperative nutritional status, incidence of postoperative complications, and hospital stay were compared between the no-prehabilitation and prehabilitation groups.

All analyses were conducted using SPSS version 24 (SPSS Inc., Tokyo, Japan). All *p* values lower than 0.05 were considered statistically significant.

RESULTS

Participants

The prehabilitation group consisted of 108 patients scheduled to undergo either major hepatectomy (resection of at least 3 Couinaud segments), pancreatoduodenectomy, or hepato-pancreatoduodenectomy (Fig. S1). Of these patients, 19 declined to participate, 10 did not record their history of exercise and nutritional therapies, 2 did not undergo tumor resection due to unresectable local invasion or distant metastasis, and 1 finally had benign disease diagnosed by pathologic examination. Thus, 76 patients finally were analyzed as the prehabilitation group. As historical control subjects, a backward consecutive series of 142 patients who underwent highly invasive surgeries for HPB malignancies without prehabilitation was selected (no-prehabilitation group). After one-to-one propensity score matching, 76 patients in each group finally were analyzed.

Baseline Characteristics

Gender, age, height, body weight, body mass index, diagnosis, cancer stage, Charlson comorbidity index, incidence of preoperative cholangitis, and preoperative biliary drainage did not differ significantly between the two groups (Table 1). The median waiting period before surgery (i.e., the interval between the first and second hospitalizations) was 28 days in the no-prehabilitation group and 32 days in the prehabilitation group (*p* = 0.755).

Intra- and Postoperative Characteristics

The proportion of surgical procedures did not differ between the two groups (Table 2). Among the patients who underwent major hepatectomy, 37 (80%) of 46 patients in the no-prehabilitation group and 35 (85%) of 41 patients in the prehabilitation group underwent combined extrahepatic

TABLE 1 Baseline characteristics of the patients in the no-prehabilitation and prehabilitation groups

	No-prehabilitation (<i>n</i> = 76) <i>n</i> (%)	Prehabilitation (<i>n</i> = 76) <i>n</i> (%)	<i>p</i> Value
Male gender	53 (70)	51 (67)	0.727
Median age: years (IQR)	69 (60–75)	69 (65–76)	0.310
Median height: cm (IQR)	165 (157–168)	163 (156–170)	0.603
Median body weight: kg (IQR)	58.1 (49.8–65.4)	56.1 (50.3–64.5)	0.743
Median BMI: kg/m ² (IQR)	21.4 (19.6–23.7)	22.2 (20.4–23.7)	0.395
Diagnosis			0.868
Biliary tract cancer	55 (72)	56 (74)	
Pancreatic cancer	15 (20)	14 (18)	
Hepatocellular carcinoma	3 (4)	4 (5)	
Other malignancies	3 (4)	2 (3)	
Cancer stage (0/1/2/3/4)	1/15/19/14/27	2/7/35/22/10	0.296
Comorbidities			
Hypertension	21 (28)	29 (38)	
Diabetes mellitus	11 (14)	9 (12)	
Dyslipidemia	5 (7)	11 (14)	
Chronic kidney disease	5 (7)	1 (1)	
Heart disease	3 (4)	3 (4)	
Respiratory disease	6 (8)	0 (0)	
Nervous disease	4 (5)	3 (4)	
Charlson Comorbidity Index (0/≥ 1)	44/32	41/35	0.624
Preoperative cholangitis	11 (14)	16 (21)	0.289
Preoperative biliary drainage	57 (75)	55 (72)	0.713
Median waiting period: days (IQR)	28 (20–46)	32 (19–50)	0.755

IQR interquartile range, *BMI* body mass index

bile duct resection for biliary malignancies. Intraoperative variables including operation time, blood loss, and rate of allogeneic blood transfusion also did not differ between the two groups.

No patients died within 90 days after surgery in either of the two groups. Although the overall morbidity rate, as indicated by a Clavien-Dindo grade of 3 or higher, did not differ between the two groups ($p = 0.329$), the incidence of clinically significant bile leakage (grade \geq B) was significantly lower in the prehabilitation group than in the no-prehabilitation group (25% vs 11%; $p = 0.020$). Additionally, the postoperative hospital stay in the prehabilitation group was significantly shorter than in the no-prehabilitation group (median, 23 days vs 30 days; $p = 0.045$) (Table 2).

Nutritional Status

During the waiting period (median, 28 days), the indexes for nutritional status (body weight, body mass index, and serum albumin) all were significantly deteriorated in the no-prehabilitation group (Table 3). However,

the levels of serum albumin did not deteriorate or even increased during the waiting period (median, 32 days) in the prehabilitation group. The level of PNI tended to decrease in the no-prehabilitation group ($p = 0.056$). In sharp contrast, the level of PNI improved significantly during the waiting period in the prehabilitation group (median, 43.8 to 45.0; $p = 0.045$).

Impact of the Waiting Period on Nutritional Status

Changes in the body weight, serum albumin, and PNI were compared between the no-prehabilitation and prehabilitation groups according to the length of the waiting period before surgery (< 3 weeks, 3–6 weeks, and > 6 weeks). In the no-prehabilitation group, the decrease in body weight was greater depending on the length of the waiting period before surgery. The decrement in body weight of the patients who waited more than 6 weeks was significantly greater than that of the patients who waited less than 3 weeks ($p = 0.047$, Dunnett test) (Fig. 1a). However, this change was attenuated in the prehabilitation group. Although serum albumin level and

TABLE 2 Intra- and postoperative characteristics of the patients in the no- prehabilitation and prehabilitation groups

	No-prehabilitation (n = 76) n (%)	Prehabilitation (n = 76) n (%)	p Value ^a
Intraoperative characteristics			
Surgical procedure			0.444
Hepatectomy	46 (61)	41 (54)	
Pancreaticoduodenectomy	24 (32)	25 (33)	
Hepato-pancreatoduodenectomy	6 (8)	10 (13)	
Median operation time: min (IQR)	541 (407–639)	478 (388–585)	0.085
Median blood loss: ml (IQR)	936 (645–1426)	837 (596–1384)	0.740
Allogeneic blood transfusion	17 (22)	26 (34)	0.105
Postoperative characteristics			
90-Day mortality	0 (0)	0 (0)	1.000
Overall morbidity (Clavien-Dindo grade \geq 3)	38 (50)	32 (42)	0.329
Infectious complication	25 (33)	19 (25)	0.283
Intraabdominal abscess	14 (18)	11 (14)	0.512
Bacteremia	6 (8)	5 (7)	0.754
Cholangitis	8 (11)	8 (11)	1.000
Surgical-site infection	3 (4)	2 (3)	0.649
Pneumonia	1 (1)	1 (1)	1.000
Bile leakage grade \geq B	19 (25)	8 (11)	0.020
Pancreatic fistula grade \geq B	12 (16)	13 (17)	0.827
Liver failure grade \geq B	1 (1)	4 (5)	0.367
Delayed gastric emptying grade \geq B	6 (8)	7 (9)	0.772
Median postoperative hospital stay: days (IQR)	30 (21–40)	23 (16–34)	0.045

IQR interquartile range

^ap Values lower than 0.05 are indicated in bold

TABLE 3 Nutritional status of the patients in the no-prehabilitation and prehabilitation groups

	No-prehabilitation		P Value ^a	Prehabilitation		P Value ^a
	Hospitalization for examination (1st hospitalization) Median (IQR)	Re-hospitalization for surgery (2nd hospitalization) Median (IQR)		Hospitalization for examination (1st hospitalization) Median (IQR)	Re-hospitalization for surgery (2nd hospitalization) Median (IQR)	
Body weight (kg)	58.1 (49.8–65.4)	57.7 (48.5–63.9)	< 0.001	56.1 (50.3–64.5)	55.0 (50.4–64.3)	0.025
BMI (kg/m ²)	21.4 (19.9–23.7)	21.1 (19.6–23.0)	< 0.001	22.2 (20.3–23.7)	21.7 (20.0–23.6)	0.029
Serum albumin (g/dl)	4.0 (3.6–4.3)	3.7 (3.3–4.2)	0.002	3.7 (3.4–4.1)	3.8 (3.5–4.1)	0.103
PNI	45.5 (42.1–50.4)	44.0 (41.0–49.0)	0.056	43.8 (40.1–48.5)	45.0 (42.0–49.0)	0.045

BMI body mass index, PNI prognostic nutritional index

^ap Values lower than 0.05 are indicated in bold

*PNI was calculated by the following formula: $10 \times \text{serum albumin value [g/dl]} + 0.005 \times \text{total lymphocyte count in the peripheral blood [}/\text{mm}^3]$

PNI decreased during the waiting period in the no-prehabilitation group, these indexes of nutritional status did not deteriorate or even improved in the prehabilitation group (Fig. 1b, c).

Alteration of Physical Fitness in the Prehabilitation Group

For the patients with prehabilitation, the 6MWD at the second hospital stay was significantly longer than at the first hospital stay for both the males and females (Table 4).

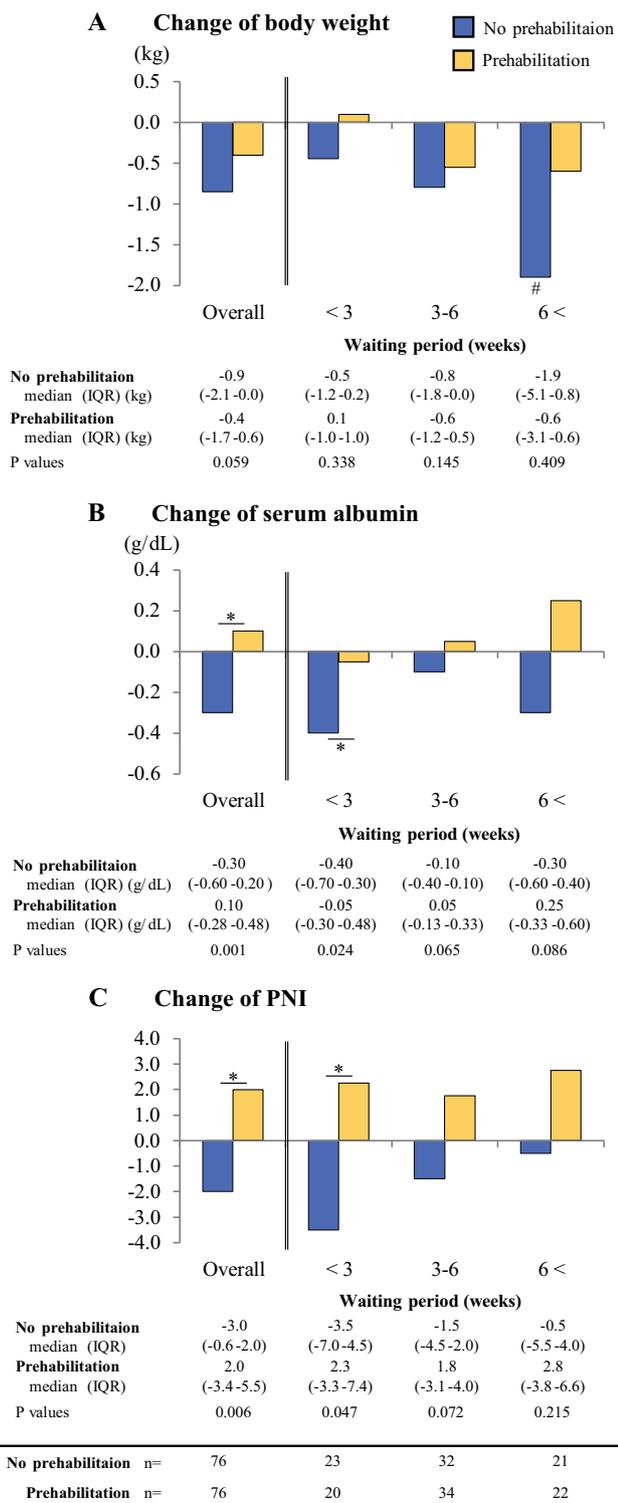


FIG. 1 Changes in preoperative nutritional status. Changes in **a** body weight, **b** serum albumin (Alb) level, and **c** prognostic nutritional index (PNI) depending on the preoperative waiting period (< 3 weeks, 3–6 weeks, and > 6 weeks). The no-prehabilitation group is represented by the hatched bar and the prehabilitation group by the gray bar. *No-prehabilitation group vs prehabilitation group ($p < 0.05$). # $p < 0.05$ vs the group of patients who waited less than 3 weeks before surgery. IQR, interquartile range

Although the difference was not statistically significant, total skeletal muscle mass measured at the second hospital stay was greater than at the first hospital stay for both the males and females. In contrast, the total fat mass for both the males and females at second hospital stay was significantly less than at the first hospital stay. Consequently, the muscle/fat ratio at the second hospital stay was significantly better than at the first hospital stay for both the males and females. Interestingly, the levels of serum albumin and the 6MWD showed a significant positive correlation in the prehabilitation group (Fig. S2).

DISCUSSION

Some evidence has indicated the impact of skeletal muscle mass and functional exercise capacity on the short- and long-term postoperative outcomes for patients undergoing major surgeries for gastrointestinal malignancies.^{26–28} The current authors previously showed that poor skeletal muscle mass and impaired functional exercise capacity have a negative impact on the incidence of postoperative complications, as well as on long-term survival after surgery for HPB malignancies.^{8,9}

Based on these observations, it was highly recommended that patients improve their skeletal muscle mass and functional exercise capacity before surgery. Therefore, a clinical trial for prehabilitation was started in 2016 with the intention of improving postoperative outcomes after highly invasive HPB surgeries. As was expected, the introduction of prehabilitation efficiently prevented nutritional status deterioration in malignant patients, enhanced physical fitness before surgery, and reduced the postoperative hospital stay after surgery. As additional findings, the incidence of clinically significant bile leakage was reduced and the postoperative hospital stay was shortened in the prehabilitation group compared with the no-prehabilitation group, although the exact causation of these findings was not proved in this study.

At the authors’ institution, a high-volume center for HPB malignancies, patients generally have to wait for 3–7 weeks (median, ~ 1 month) before surgery. Many patients with gastrointestinal malignancies tend to lose appetite and do not actively exercise before surgery because of various symptoms accompanying malignant disease. These negative facts may lead to a loss of skeletal muscle mass, muscle strength, functional exercise capacity, and nutritional status during the waiting period. The longer the waiting period, the greater the loss of skeletal muscle mass and nutrition. The analysis of the patients in the no-prehabilitation group (before the introduction of prehabilitation) clearly demonstrated that the loss of body weight was greater depending on the length of the preoperative

TABLE 4 Physical fitness of patients who received prehabilitation

	Hospitalization for examination (1st hospitalization) Median (IQR)	Re-hospitalization for surgery (2nd hospitalization) Median (IQR)	<i>p</i> Value ^a
6-Min walk distance (m)			
Overall	530 (470–571)	554 (499–620)	< 0.001
Male	552 (494–591)	567 (518–640)	< 0.001
Female	489 (432–544)	520 (426–570)	0.001
Knee extension strength (kgf/kg)			
Overall	0.47 (0.38–0.56)	0.48 (0.40–0.57)	0.798
Male	0.50 (0.38–0.59)	0.49 (0.43–0.58)	0.933
Female	0.43 (0.37–0.49)	0.42 (0.34–0.54)	0.627
Grip strength (kg)			
Overall	30.2 (22.4–35.7)	30.5 (23.4–35.1)	0.519
Male	34.1 (29.8–37.1)	33.7 (30.5–36.8)	0.344
Female	21.0 (18.8–23.6)	21.4 (18.4–23.9)	0.786
10-m usual walking speed (m/s)			
Overall	0.96 (0.77–1.26)	0.95 (0.74–1.32)	0.733
Male	0.91 (0.73–1.26)	0.85 (0.72–1.31)	0.633
Female	1.01 (0.89–1.32)	1.04 (0.79–1.34)	0.879
Total skeletal muscle mass (kg/m ²) ^b			
Overall	8.97 (7.91–9.73)	9.10 (8.08–9.90)	0.081
Male	9.53 (8.83–10.1)	9.60 (9.02–10.2)	0.169
Female	7.89 (7.60–8.52)	7.91 (7.53–8.31)	0.201
Total fat mass (kg/m ²) ^b			
Overall	5.32 (3.86–6.71)	5.04 (3.64–6.37)	< 0.001
Male	5.05 (3.50–6.16)	4.53 (3.03–5.65)	< 0.001
Female	6.45 (5.11–8.26)	6.37 (4.74–8.05)	0.009
Muscle/fat ratio			
Overall	1.75 (1.26–2.27)	1.83 (1.39–2.50)	< 0.001
Male	1.89 (1.57–2.81)	2.13 (1.75–2.93)	< 0.001
Female	1.22 (0.94–1.59)	1.24 (1.00–1.69)	0.028

^a*p* Values lower than 0.05 are indicated in bold

^bTotal skeletal muscle mass and fat mass were measured by a bioelectrical impedance analysis system

waiting period. In sharp contrast to the no-prehabilitation group, the loss of body weight was minimized and the serum albumin levels and PNI were even improved during the waiting period in the prehabilitation group. Moreover, in the prehabilitation group, the level of serum albumin showed a positive correlation with the level of 6MWD. These results clearly indicated a benefit of prehabilitation (a combination of exercise and nutritional therapy) in improving nutritional status and enhancing physical fitness for patients undergoing HPB surgeries for malignancy.

The difference in median postoperative hospital stay between the no-prehabilitation and prehabilitation groups was 7 days (median, 30 vs 23 days). A shortening of hospital stay through the introduction of prehabilitation not only reduced the medical cost, but also increased the

sickbed turnover rate. In this study, all the patients performed exercise by themselves at home during the waiting period, and no outpatient care was needed. Moreover, the amino acid supplement used for nutritional therapy was purchased at the patients' own cost. Thus, the introduction of prehabilitation may provide positive economic effects without additional medical cost burdens on the hospital.

Previous reports have indicated that the combination of exercise and intake of amino acid supplement (especially leucine-rich supplement) effectively improved the physical fitness of Japanese elderly women with sarcopenia.²⁹ Therefore, in the current study, the patients were instructed to take a leucine-rich essential amino acid supplement (Amino L40) before and after the exercise. As was expected, a combination of exercise and amino acid

supplement was found to increase the serum albumin, 6MWD, total skeletal muscle mass, and muscle/fat mass ratio after prehabilitation.

Barberan-Garcia et al.³⁰ previously reported that patients who performed prehabilitation before elective major abdominal surgery had enhanced aerobic capacity and reduced postoperative complications. However, their study assessed only 6MWD and did not objectively assess nutritional status and physical fitness (e.g., muscle strength, walking speed, body composition). In contrast, the current study clearly demonstrated the beneficial effect of prehabilitation on nutritional status, total skeletal muscle mass, total fat mass, and physical fitness. To the authors' knowledge, this is the first report to show clearly the benefit of prehabilitation on the preoperative condition of patients with gastrointestinal malignancy.

The incidences of major postoperative complications and infectious complications did not differ significantly between the two groups. Surgeries for HPB malignancy generally are highly invasive, with a high incidence of postoperative complications. The incidence of postoperative complications may be affected by various factors including background comorbidities, cancer stage, and operative complexity. In fact, the Charlson comorbidity index, the operation time, and intraoperative blood loss had a significant impact on the incidence of major complications classified as Clavien-Dindo grade 3 or higher (data not shown). The beneficial effect of prehabilitation may not be sufficient to overcome these major factors affecting the outcomes of surgery. Nevertheless, the shorter hospital stay in the prehabilitation group may indicate faster recovery from postoperative complications after highly invasive HPB surgery.

The current study had several limitations. First, the study was not a randomized controlled trial but compared the data of patients before and after the introduction of prehabilitation. Ideally, the exact effects of prehabilitation should be elucidated through a randomized controlled trial. However, in reality, a randomized controlled trial was difficult to perform because most of the patients eligible for enrollment desired to perform prehabilitation when the investigators explained this study. Therefore, the method of comparing the patients with historical control subjects using propensity score-matching was selected.

Second, there was variability among the patients during the waiting period. Because the number of surgeries that can be performed at a single institution is limited, it was unrealistic to set a uniform waiting period for all the patients. Additionally, this study did not include patients who underwent neoadjuvant chemotherapy or chemoradiotherapy for HPB malignancies. These patients generally

have a long waiting period before surgery. The impact of prehabilitation on these patients should be elucidated in a future study.

Third, the intensity of home-based exercise may potentially have differed among the patients because they were unsupervised at home. Exercise self-efficacy has been shown to predict adherence outcomes of home-based exercise in breast cancer survivors.³¹ The impact of self-efficacy on the outcome of prehabilitation should be elucidated in a future study.

In conclusion, the current study demonstrated that our prehabilitation program was associated with improved physical fitness and preservation of nutritional status compared with appropriately matched patients who did not receive this therapy before HPB surgery for malignancy. Although the exact causative mechanism has not been elucidated, the postoperative hospital stay was shorter in the prehabilitation group than in the no-prehabilitation group. Thus, the introduction of prehabilitation has the potential to reduce the total perioperative medical costs for this type of surgery.

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