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Original Article

Outcomes of an outpatient home-based prehabilitation program before pancreaticoduodenectomy: A retrospective cohort study

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Backgrounds/Aims: Prehabilitation aims for preoperative optimisation to reduce postoperative complications. However, there is a paucity of data on its use in patients undergoing pancreaticoduodenectomy (PD). Thus, this study aims to evaluate the outcomes of a home-based outpatient prehabilitation program (PP) versus no-PP in patients undergoing PD.
Methods: This retrospective cohort study compared patients who underwent PP versus no-PP before elective PD from January 2016 to December 2020. Inclusion criteria for PP were < 65 years or 65–74 years with FRAIL score < 3. No-PP included dietician, case manager and anesthesia review. PP included additional physiotherapy sessions, caregiver training and interim phone consultation. Univariate and multivariate analysis were used to evaluate length of stay (LOS), morbidity, 30-day readmission, and 90-day mortality.
Results: Seventy-one patients (PP: n = 50 [70.4%]; no-PP: n = 21 [29.6%]) were included in this study. Median age was 65 years (interquartile range [IQR]: 58–72 years). Majority (n = 58 [81.7%]) of patients underwent open surgery. Ductal adenocarcinoma was the most common histology (49.3%). Patient demographics were comparable between both groups. Overall median LOS was 11.0 days (IQR: 8.0–17.0 days). Compared to no-PP, PP was not independently associated with reduced intra-abdominal collections (odds ratio [OR]: 0.43; 95% confidence interval [CI]: 0.03–6.11, $p = 0.532$), major morbidity (OR: 1.31; 95% CI: 0.09–19.47; $p = 0.845$) or 30-day readmission (OR: 3.16; 95% CI: 0.26–38.27; $p = 0.365$). There was one (1.4%) 30-day mortality.
Conclusions: Our outpatient PP with unsupervised exercise regimes did not improve postoperative outcomes following elective PD.

Key Words: Enhanced recovery after surgery; Pancreaticoduodenectomy; Preoperative exercise; Preoperative care; Pancreatic neoplasms

INTRODUCTION

Pancreatic cancer has a poor prognosis, with an estimated 5-year overall survival rate of 30% after curative resection and an estimated 5-year overall survival time of less than six months for untreated metastatic disease [1]. Surgery is recommended for survival gains. However, only 20% to 30% of patients are amenable to surgical resection because of an insidious course of the disease and late presentation [2]. Pancreaticoduodenectomy (PD) is one of the most technically challenging surgeries, with postoperative mortality rates of approximately 5% and postoperative morbidity rates ranging from 20% to 50% [3,4]. Clinical outcomes are not only influenced by surgical expertise and technical finesse, but also related to patient frailty, sarcopenia, malnutrition resulting from pancreatic neoplasm and its sequelae such as jaundice, loss of appetite and vomiting [5]. Cooper et al. [6] have reported age- and cancer-related skeletal muscle mass loss in pancreas cancer patients. This is aggravated in patients subjected to neoadjuvant chemotherapy protocols. Sarcopenia is an independent predictor of complications following pancreatectomy [7].

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The Enhanced Recovery After Surgery (ERAS) protocol was first introduced in 2005 [8]. ERAS initiatives incorporated perioperative strategies to improve clinical outcomes. One component of ERAS is an emphasis on postoperative mobilization. This provides minimal opportunity to enhance the preoperative functional state of a patient. Preoperative exercise programs may effectively prevent or restore the loss of skeletal muscle mass, thus improving clinical outcomes [9]. In addition, there is emerging evidence that prehabilitation initiatives may improve biochemical indices and surgical outcomes in pancreas cancer patients. A 1 : 1 propensity score-matched study by Nakajima et al. [10] on 152 patients comparing preoperative exercise and nutritional therapy for patients undergoing hepato-pancreato-biliary (HPB) surgeries for malignancy (prehabilitation vs. historical cohorts, n = 76 per arm) demonstrated improvement in serum albumin, prognostic nutritional index, and decreased length of hospitalization stay (p = 0.045) with prehabilitation. In a small study including 20 PD patients per group, Ausania et al. [11] have reported that the incidence of delayed gastric emptying (DGE) is decreased in the prehabilitation group. However, a recent systematic review by Bundred et al. [12] in 2020 including 193 patients from six studies on patients who underwent prehabilitation before surgery for pancreatic cancer demonstrated equivocal gains. Such differences could be due to inclusion of distal pancreatectomy patients. Due to the paucity of data, more evidence is required. Thus, we evaluated the impact of the prehabilitation initiative in patients undergoing PD. The aim of our study was to compare peri-operative outcomes in patients undergoing PD who underwent outpatient prehabilitation program (PP) versus no-PP.

MATERIALS AND METHODS

This retrospective cohort study compared patients undergoing elective PD who received PP versus no-PP. No-PP was defined as standard hospital protocol for patients undergoing elective surgery. Our institution initiated the ERAS protocol in the colorectal surgery department in 2016. Since 2018, the ERAS protocol has been expanded to HPB surgical services. Prehabilitation was carried out in addition to implementation of the ERAS protocol. The HPB unit has implemented both patient-led outpatient and inpatient supervised prehabilitation initiatives (Fig. 1). We used the FRAIL questionnaire, a simple validated screening tool for identifying frail patients at risk of developing disability and decline in health functioning and mortality, to screen patients for eligibility for PP (Appendix 1) [13]. PP was defined as our outpatient home-based PP. All patients with 1) age of 65–74 years with FRAIL score < 3 or 2) age < 65 years were recommended for PP (Fig. 1). Exclusion criteria were: (1) patients ≥ 75 years old or (2) frail patients (defined as age 65–74 years old with FRAIL score ≥ 3). Patients who fit the exclusion criteria of the PP were recommended to enrol in our inpatient supervised PP (Recovery of Surgery in the Elderly [ROSE] programme; Appendix 2) instead due to increased comorbidities [14]. However, for this group of patients who declined inpatient prehabilitation, the outpatient home-based PP was offered. The no-PP group consisted of patients who declined to participate in our ROSE program (inpatient) or outpatient PP. Patients who lacked mental capacity to consent were also excluded from the study. This study was approved by our local institutional review board for ethical compliance (approval number: 2022/00358). Data were prospectively collected through our standing pancreas surgery registry (reference number: 2018/00049).

Participation in PP was voluntary. Patients were made aware that participation was subject to local resources and logistics. For example, if a jaundice patient could undergo PD without the need for biliary decompression, early surgery with standard ERAS protocol was the preferred approach. All patients who could not undergo expeditious surgery (for any reason) were enrolled into the outpatient PP. Patients started the PP together with their routine preoperative evaluation before the elective

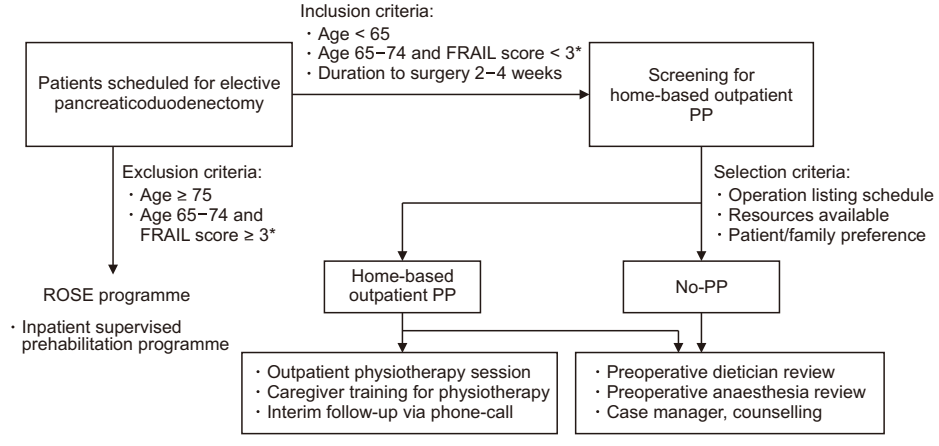

Fig. 1. Study protocol for participation recruitment and conduct of the entire study. PP, prehabilitation program; ROSE, Recovery of Surgery in the Elderly; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight.

surgery. The duration of PP spanned over a minimum of 2 weeks and a maximum of 4 weeks before surgery. Surgery was not delayed for the PP. Additional costs borne by the PP were known to patients enrolled in the outpatient PP. They were bundled along with the inpatient surgery billing, which was claimable from the patients' government-maintained medical account savings. All patients undergoing pancreatic surgery at our HPB unit were enrolled into a prospective standing database approved by the institutional review board. This was a clinical audit for which de-identified data were provided by the coordinator to the clinical team. No attempts were made to link data to patient identifiers, share data files through non-secure electronic platforms or access patient records by any study team members. This study was conducted following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for retrospective cohort studies [15].

No-prehabilitation program (standard hospital protocol)

Patients in the no-PP group were enrolled with ongoing ERAS protocol. Patients were preoperatively assessed by (1) a dietician for nutritional screening, assessment, and optimization, (2) an anaesthetist for fitness for surgery and medical optimization, and (3) a case manager for preoperative counselling and patient and caregiver education. Dieticians conducted nutritional assessments using appropriate history and clinical examination, anthropometric measurements, and laboratory data. Daily nutritional goals were set through nutrition education (e.g., food guide pyramid) and counselling. All patients were prescribed Oral IMPACT (Nestlé, Vevey, Switzerland) three times a day for five days before surgery. Oral IMPACT is an arginine-, RNA-, and omega-3 fatty acid supplement demonstrated to be able to reduce postoperative morbidity and length of stay (LOS) after PD [16]. Carbohydrate loading was also performed for all patients as part of the ERAS protocol. In our hospital, case managers with a minimum qualification of diploma are integral members of multidisciplinary teams. They look into the community aspect of clinical care, provide psychological support, and liaise with medical social workers for post-discharge care needs of patients. Case managers upscale the mental readiness of patients and family members for surgery through discussions and education related to postoperative care (e.g., urinary catheter, use of the pain-control device and early mobilization). In addition, they explore social setup and initiate discussions related to discharge planning. Choice of PD vs. pylorus-preserving PD (PPPD) was based on surgeons' discretion in view of comparable overall morbidity and mortality [17]. Postoperatively, all patients were prescribed pancreatic enzyme replacement therapy. Octreotide was given selectively by most consultants. It was routinely given by one consultant.

Outpatient home-based prehabilitation program

For our outpatient home-based PP, in addition to routine ERAS protocols, an outpatient one-hour physiotherapy session was arranged. Physiotherapists taught a fixed set of exercise regime as described: (1) deep breathing exercises facilitated by the incentive spirometer and a supported cough during this session to be done at least four times a day for a minimum of 10 breaths each time until the surgery date, (2) lower limb strengthening exercises, and (3) a walking program (30 minutes, five times per week). The walking program of 30 minutes for 5 times/week was chosen in line with the definition of "moderate-intensity exercise" set by the guidelines of the American College of Sports Medicine [18]. The next-of-kin were also engaged in monitoring and encouraging the patient to enhance compliance. The patient and next-of-kin were given targets to walk 30 minutes and do deep breathing exercises four times (× 10 each time) daily. A follow-up phone call was made by the case manager to check the progress and compliance and document targets achieved. In patients who did not achieve targets, next-of-kins were coached to assist patients to achieve targets. Tailoring was made to the prescribed physiotherapy regime based on the physiotherapist's assessment of the patient and at the physiotherapist's discretion.

Study variables and outcomes

Study variables included baseline patient demographics, perioperative details including surgical access, operating time, estimated blood loss (EBL), pancreatic texture, size of the pancreatic duct, involvement of portal vein-superior mesenteric vein (PV-SMV), and celiac axis-superior mesenteric artery (CA-SMA), histology and size of the tumor. PV-SMV involvement and CA-SMA involvement were defined as the presence of either abutment (tumor inseparable from the vessel for ≤ 180° circumference of the vessel) or encasement (tumor inseparable from the vessel for > 180° of the vessel).

Primary outcomes were LOS and any morbidity (defined as presence of any postoperative morbidity such as clinically relevant postoperative pancreatic fistula [POPF], intra-abdominal collection, DGE, ileus, surgical site infection, pneumonia or pleural effusion). Secondary outcomes included length of high dependency unit (HDU) stay, major morbidity (Clavien-Dindo ≥ Grade 3A complications), need for repeat surgery, 30-day readmission, and 90-day mortality [19]. POPF was defined as the presence of any clinically relevant POPF according to the 2016 updated International Study Group on Pancreatic Surgery [20]. Thirty-day readmission and 90-day mortality were defined as readmission within 30 days of discharge and mortality within 90 days from the surgery date, respectively.

Statistical analysis

Sample size calculation was performed for a parallel 2 : 1 (PP versus no-PP) group allocation feasibility study with α of 0.10 and power of 0.80 to reduce postoperative morbidity from

40% to 20%. A total of 71 patients were required. We chose an estimated reduction of 20% based on the simulated model by Dagorno et al. [21] to predict reduction in postoperative morbidity in patients undergoing HPB surgery. A sample size of 56 patients (28 patients per arm) was required for statistically significant reduction in LOS with α of 0.05 and power of 0.80 in the study by Dagorno et al [21]. All data extracted were tabulated into an excel sheet and transposed into IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) for statistical analysis. Categorical values are described as percentages. They were analyzed by the chi-squared test or Fisher exact test for expected cell count < 5. Continuous variables are expressed as median (interquartile range [IQR]). They were analyzed by the Mann–Whitney U test. Univariate analysis and multivariate analysis were performed using logistic regression. The following variables were used in our multivariate analysis in view of (1) confounding impact on postoperative outcomes as determined in prior studies: age, sex, American Society of Anesthesiologists (ASA) score, body mass index (BMI), albumin, tumor size, pancreas texture, size of the pancreatic duct [22-24], and (2) statistically significant differences between PP and no-PP: bilirubin, EBL and presence of nodal involvement. Although jaundice, abdominal pain, carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9) levels were statistically significantly different between study groups, they were not included in the multivariate analysis as these factors were not clinically significant in postoperative outcomes. A p-value of less than 0.05 was considered statistically significant.

Table 1. Baseline demographics and clinical profile of the study population in a PP vs. no-PP

Demographic	Study population			
	Overall (n = 71)	PP (n = 50)	No-PP (n = 21)	p-value
Age (yr)	65 (58–72)	66 (58.8–74)	63 (55–68.5)	0.169
Sex, male	38 (53.5)	26 (52.0)	12 (57.1)	0.692
Body mass index (kg/m^2)	22.3 (19.7–25.1)	22.3 (19.6–24.5)	22.3 (19.6–25.3)	0.811
Smoking	20 (28.2)	14 (28.0)	6 (28.6)	0.961
ASA score	2 (2–3)	2 (2–3)	2 (2–3)	0.381
ECOG performance status	0 (0–1)	0 (0–1)	0 (0–1)	0.174
Comorbidity				
Hypertension	45 (63.4)	32 (64.0)	13 (61.9)	0.867
Diabetes mellitus	29 (40.8)	21 (42.0)	8 (38.1)	0.760
Hyperlipidemia	38 (53.5)	27 (54.0)	11 (52.4)	0.901
Ischemic heart disease	6 (8.5)	4 (8.0)	2 (9.5)	0.833
Chronic renal impairment	2 (2.8)	1 (2.0)	1 (4.8)	0.521
COPD	1 (1.4)	1 (2.0)	0 (0)	0.514
CVA and/or TIA	4 (5.6)	2 (4.0)	2 (9.5)	0.357
Anticoagulation use	13 (18.3)	9 (18.0)	4 (19.0)	0.917
Immunocompromised	3 (4.2)	2 (4.0)	1 (4.8)	0.884
Clinical presentation				
Abdominal pain	25 (35.2)	13 (26.0)	12 (57.1)	0.012*
Vomiting	7 (9.9)	4 (8.0)	3 (14.3)	0.417
Jaundice	34 (47.9)	17 (34.0)	17 (81.0)	< 0.001*
Loss of weight	28 (39.4)	19 (38.0)	9 (42.9)	0.702
Laboratory investigations				
Haemoglobin (g/L)	12.4 (11.0–13.3)	12.3 (10.9–13.2)	12.9 (11.3–13.5)	0.344
Creatinine (μmol/L)	67 (54–82)	67 (52–80)	73 (58–89)	0.609
Albumin (g/L)	37 (34–40)	37 (32–40)	36 (34–39)	0.368
Bilirubin (μmol/L)	34 (12–112)	19 (11–51)	140 (67–194)	< 0.001*
CA 19-9 (U/mL)	58 (14–252)	49 (8–210)	131 (25–684)	0.046*
CEA (ng/mL)	0 (0–3)	0 (0–2)	1 (0–4)	0.082
Preoperative biliary decompression	28 (39.4)	20 (40.0)	8 (38.1)	0.881

Values are presented as median (interquartile range) or number (%).
ASA, American Society of Anesthesiologists; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ECOG, Eastern Cooperative Oncology Group; PP, prehabilitation program; TIA, Transient ischaemic attack.
*Statistically significant (p < 0.05).

RESULTS

A total of 71 patients (PP: n = 50, 70.4%; no-PP: n = 21, 29.6%) were included in this study. All recruited patients (n = 50) reported compliance to prescribed exercises. The overall median age was 65 years (IQR: 58–72 years) with approximately equal sex distribution (male: n = 38, 53.5%). The median ASA score was 2 (IQR: 2–3). Median CA 19-9 and CEA were 58 U/mL (IQR: 14–252 U/mL) and 0 ng/mL (IQR: 0–3 ng/mL), respectively. Twenty-eight (39.4%) patients underwent preoperative biliary decompression. Clinical profiles and demographics of patients who underwent PP were mostly comparable to those who underwent no-PP except for presence of abdominal pain (57.1% vs. 26.0%, $p = 0.012$), jaundice (81.0% vs. 34.0%, $p < 0.001$), preoperative bilirubin (median: 19 μmol/L vs. 140 μmol/L, $p < 0.001$) and CA 19-9 levels (median 49 U/mL vs. 131 U/mL, $p = 0.046$) (Table 1).

Seven patients underwent PPPD (PP: n = 2, non-PP: n = 5; $p = 0.011$). The most common histology was ductal adenocarcinoma (n = 35, 49.3%), followed by intraductal papillary mucinous neoplasm (n = 13, 18.3%). Perioperative details were mostly comparable between PP and no-PP (Table 2). However, EBL was significantly higher in the PP group than in the no-PP group (median: 400 mL, IQR: 300–513 mL vs. median: 250 mL, IQR: 200–275 mL, $p = 0.001$).

Overall median LOS was 11.0 days (IQR: 8.0–17.0 days). Majority of patients were admitted to HDU postoperatively (n = 70, 98.6%). Univariate analysis demonstrated comparable post-

Table 2. Intra-operative details of the study population

Intra-operative detail	Study population			
	Overall (n = 71)	PP (n = 50)	No-PP (n = 21)	*p*-value
Operating time (min)	495 (425–570)	493 (433–570)	500 (414–576)	0.980
Estimated blood loss (mL)	300 (200–500)	400 (300–513)	250 (200–275)	0.001*
Type of surgery				0.011*
Conventional pancreaticoduodenectomy	64 (90.1)	48 (96.0)	16 (76.2)	
Pylorus-preserving pancreaticoduodenectomy	7 (9.9)	2 (4.0)	5 (23.8)	
Surgical access				0.596
Laparoscopic	4 (5.6)	2 (4.0)	2 (9.5)	
Laparoscopic converted to open	9 (12.7)	7 (14.0)	2 (9.5)	
Open	58 (81.7)	41 (82.0)	17 (81.0)	
Venous resection	6 (8.5)	6 (12.0)	0 (0)	0.097
PV-SMV involvement (yes)	13 (18.3)	7 (14.0)	6 (28.6)	0.147
Abutment (≤ 180° circumference)	10 (14.1)	4 (8.0)	6 (28.6)	
Encased (> 180° circumference)	3 (4.2)	3 (6.0)	0 (0)	
CA-SMA involvement (yes)	4 (5.6)	2 (4.0)	2 (9.5)	0.357
Abutment (≤ 180° circumference)	3 (4.2)	1 (2.0)	2 (9.5)	
Encased (> 180° circumference)	1 (1.4)	1 (2.0)	0 (0)	
Pancreatic duct diameter (mm)	3 (2–5)	4 (2–5)	3 (2–4)	0.284
Pancreas texture				0.154
Soft	32 (45.1)	25 (50.0)	7 (33.3)	
Firm	25 (35.2)	18 (36.0)	7 (33.3)	
Hard	14 (19.7)	7 (14.0)	7 (33.3)	
Histology				0.180
Ductal adenocarcinoma	35 (49.3)	23 (46.0)	12 (57.1)	
Ampullary adenocarcinoma	5 (7.0)	4 (8.0)	1 (4.8)	
Intraductal papillary mucinous neoplasm	13 (18.3)	12 (24.0)	1 (4.8)	
Neuroendocrine tumour	3 (4.2)	2 (4.0)	1 (4.8)	
Cholangiocarcinoma	4 (5.6)	1 (2.0)	3 (14.3)	
Others	11 (15.5)	8 (16.0)	3 (14.3)	
Size of tumour (mm)	28 (21–34)	27 (20–31)	30 (25–35)	0.107
Lymph node involvement	31 (43.7)	18 (36.0)	13 (61.9)	0.045*
Octreotide given postoperatively	8 (11.3)	4 (8.0)	4 (19.0)	0.179

Values are presented as median (interquartile range) or number (%).
CA-SMA, celiac axis-superior mesenteric artery; PP, prehabilitation program; PV-SMV, portal vein-superior mesenteric vein.
*Statistically significant ($p < 0.05$).

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Table 3. Postoperative outcomes comparing outpatient PP vs. no-PP in patients who underwent pancreaticoduodenectomy delirium

Postoperative outcome	Study population			Univariate analysis		Multivariate analysis	
	Overall (n = 71)	PP (n = 50)	No-PP (n = 21)	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Admission into ICU[a)]	2 (2.8)	1 (2.0)	1 (4.8)	0.41 (0.02–6.85)	0.521	-	-
Admission into HDU[a)]	70 (98.6)	49 (98.0)	21 (100)	N/A	0.514	-	-
Length of HDU stay (day)	4.0 (3.0–5.0)	4.0 (3.0–5.5)	4.0 (2.5–4.0)	N/A	0.143	N/A	N/A
Length of hospitalisation stay (day)	11.0 (8.0–17.0)	12.5 (8.8–18.0)	10.0 (7.5–15.5)	N/A	0.138	N/A	N/A
Any morbidity	39 (54.9)	28 (56.0)	11 (52.4)	1.16 (0.42–3.22)	0.780	2.80 (0.38–20.88)	0.315
Clinically relevant POPF	15 (21.1)	12 (24.0)	3 (14.3)	1.90 (0.48–7.56)	0.360	1.57 (0.18–13.58)	0.682
Intra-abdominal collection/abscess	11 (15.5)	8 (16.0)	3 (14.3)	1.14 (0.27–4.81)	0.855	0.43 (0.03-6.11)	0.532
DGE[a)]	6 (8.5)	3 (6.0)	3 (14.3)	0.38 (0.07–2.08)	0.252	-	-
Ileus	6 (8.5)	4 (8.0)	2 (9.5)	0.83 (0.14–4.90)	0.833	2.31 (0.06–86.29)	0.650
SSSI[a)]	5 (7.0)	5 (10.0)	0 (0)	N/A	0.133	-	-
Pneumonia/pleural effusion[a)]	5 (7.0)	4 (8.0)	1 (4.8)	1.74 (0.18–16.56)	0.626	-	-
Chyle leak[a)]	2 (2.8)	1 (2.0)	1 (4.8)	0.41 (0.02–6.85)	0.521	-	-
Others[b)]	25 (35.2)	18 (36.0)	7 (33.3)	1.13 (0.38–3.30)	0.830	0.60 (0.07–5.16)	0.641
Major morbidity (Clavien-Dindo ≥ Grade 3A)	12 (16.9)	10 (20.0)	2 (9.5)	2.38 (0.47–11.92)	0.282	1.31 (0.09–19.47)	0.845
Reoperation[a)]	1 (1.4)	1 (2.0)	0 (0)	N/A	0.514	-	-
30-day readmission	17 (23.9)	14 (28.0)	3 (14.3)	2.33 (0.59–9.18)	0.217	3.16 (0.26–38.27)	0.365
30-day mortality[a)]	1 (1.4)	1 (2.0)	0 (0)	N/A	0.514	-	-
90-day mortality[a)]	1 (1.4)	1 (2.0)	0 (0)	N/A	0.514	-	-

Values are presented as number (%) or median (interquartile range).

CI, confidence interval; DGE, delayed gastric emptying; HDU, high dependency unit; ICU, intensive care unit; NGT, nasogastric tube; OR, odds ratio; POPF, postoperative pancreatic fistula; PP, prehabilitation program; SSSI, superficial surgical site infection.

[a)]Multivariate analysis was not performed for these variables as odds ratio was statistically incorrect in view of small sample size in each subgroup, with odds ratio > 1,000 or < 0.01 and were statistically insignificant.

[b)]Other morbidity refers to other post-operative complications such as urinary tract infection, septic shock, atrial fibrillation, acute kidney injury, severe hyperglycaemia, derangement in electrolytes and delirium.

operative outcomes between PP and no-PP groups, showing no statistically significant differences (Table 3). LOS was also comparable between PP and no-PP groups (PP: 12.5 days, IQR = 8.8–18.0 days versus no-PP: 10.0 days, IQR = 7.5–15.5 days; $p = 0.138$). Multivariate analysis similarly showed that PP was not independently predictive of reduced intra-abdominal collections (OR: 0.43, 95% CI: 0.03–6.11, $p = 0.532$), any morbidity (OR: 2.80, 95% CI: 0.38–20.88; $p = 0.315$), major morbidity (OR: 1.31, 95% CI: 0.09–19.47; $p = 0.845$), ileus (OR: 2.31, 95% CI: 0.06–86.29; $p = 0.650$) or 30-day readmission (OR: 3.16, 95% CI: 0.26–38.27; $p = 0.365$).

There was one (1.4%) unplanned return to operating theatre. This patient underwent open PD for moderately differentiated pancreatic ampullary cancer with persistently high drain fluid amylase > 1,500 IU/L and postoperative fever spike on postoperative day (POD) 7. The patient was diagnosed with pancreaticojejunostomy disruption. The decision was made for relook laparotomy and repair of pancreaticojejunostomy on POD 11. This patient was discharged well on POD 37. There was one (1.4%) 90-day mortality in a patient who underwent open PD for pT2N1 moderately differentiated pancreatic ductal adenocarcinoma. However, the patient had complication caused by superficial surgical site infection on POD 9 which was managed conservatively with antibiotics. He was discharged well on POD 15. However, he demised on POD 17 after returning to the community. We were unable to identify the cause as there was no post-mortem conducted.

DISCUSSION

Prehabilitation is an important facet of the ERAS protocol that has been increasingly used in elective surgeries to optimise patients' medical conditions to achieve good postoperative outcomes [8]. Our study demonstrated the feasibility of an outpatient PP in a real-world scenario. However, we failed to demonstrate any benefit in postoperative outcomes of an outpatient PP compared to no-PP.

A meta-analysis in 2019 on 15 randomized controlled trials (RCTs) with 907 patients (457 in a prehabilitation group and 450 in a control group) who underwent major abdominal surgery showed significant reduction in overall morbidity (OR: 0.63, 95% CI: 0.46–0.87, $I^2 = 34\%$, $p = 0.005$) and pulmonary morbidity (OR: 0.4, 95% CI: 0.23–0.68, $I^2 = 0\%$, $p = 0.0007$) with prehabilitation [25]. Although there is evidence supporting for the use of prehabilitation in major abdominal surgery including liver resection, its role in pancreatic surgery remains uncertain [26]. A recent systematic review by Bundred et al. [12] in 2020 only identified six studies (one randomized controlled trial, three prospective cohort studies, one retrospective cohort study, and one case series) that examined the role of prehabilitation in pancreatic surgery. Included studies reported PPs ranging from two to four weeks for upfront surgery and from two to six months for patients who require neoadjuvant therapy, comprising aerobic and strengthening exercises. However, only two studies (Nakajima et al. [10] and Ausania et al. [11]) included reported postoperative outcomes, of which postoperative outcomes were mainly comparable except for the shorter LOS in prehabilitation by Nakajima et al. [10] (median: 23 days vs. 30 days, $p = 0.045$) and lower incidence of DGE by Ausania et al. [11] (1% vs. 9%, $p = 0.01$). Of note, more than half of patients in the study of Nakajima et al. [10] underwent hepatic resection. Thus, outcomes could not be generalized to PD patients. Furthermore, the study of Ausania et al. [11] was small, including only 20 patients in each arm. Thus, it was not adequately powered. Our study excluded patients with liver resection and distal pancreatectomy. We did not find any significant difference in LOS. Our study is relevant to prehabilitation outcomes in PD. Further studies on PD alone should be conducted to validate this.

Although fixed exercise regime is not prescribed for prehabilitation, most existing literature on the effectiveness of PPs uses a scheduled exercise regime with varying amounts of supervision and clear intensity targets (e.g., duration of a session, maximum inspiratory pressure, and heart rate) [12,25]. To the best of our knowledge, our study is the first to evaluate an outpatient PP versus no-PP in pancreas cancer patients undergoing PD. A plausible explanation for the lack of improved outcomes following PP might be due to selection bias. Patients were selected for either PP versus no-PP based on clinical judgment of medical teams. Thus, patients selected for PP might have been intrinsically at higher risk of worse outcomes due to underlying medical comorbidity or frailty. Several studies have established risk factors for perioperative morbidity following pancreatic resections. Braga et al. [22] have developed a 4-item scoring system including ASA score, pancreas texture, PD diameter, and EBL (area under the curve: 0.711, $p < 0.001$). Venkat et al. [23] have identified age, male sex, tumor size, and albumin levels as predictors of all-cause mortality following PD or total pancreatectomy. In view of these possible confounding factors, multivariate analysis was performed to reduce bias. Our study also included patients who had minimally-invasive surgery (MIS). Difference in surgical access (MIS vs. open) might have confounded peri-operative outcomes (incidence of totally laparoscopic PD: 4.0% in PP vs. 9.5% in no-PP). However, a recent meta-analysis including 3 RCTs and 224 patients has reported that laparoscopic PD has similar postoperative outcomes to open PD [27]. Another plausible explanation for not achieving improved outcomes following PP might be because we included patients aged < 65 years and pre-frail elderly (FRAIL score < 3 and age of 65–74 years) who might be less vulnerable than frail elderly patients. Our selected group of patients might have more physiological reserves and hence achieve less benefit from the PP to reach statistical significance. This might also be attributed to the small sample size of our study. While patients with age ≥ 65 years and FRAIL score < 3 are considered robust or pre-frail, elderly patients are associated with increased

re-operation, cardiovascular complications, LOS, and postoperative mortality in PD [28,29]. Hence, we still included those with age ≥ 65 years in our outpatient PP.

We adopted a different type of PP than those described in the existing literature [12,25]. We adopted an outpatient PP with a single session of supervised physiotherapy, with remaining prehabilitation sessions done via self-administration by patients. Unlike supervised PPs, our approach of single-session physiotherapy with subsequent self-empowered prehabilitation is prone to compliance issues. Patients might have not adhered fully to prescribed exercise regimes which might have impacted outcomes. During prehabilitation, phone consultations were provided to ensure compliance with the exercise programme and nutrition regime. Although phone calls are not direct substitutes for face-to-face meetups, they provide an avenue of communication and encouragement to patients during the preoperative period. Importantly, a phone call demonstrates to patients that the medical team cares about their health and illness. It also provides an avenue for patients to ask any questions or seek clarification. Furthermore, this hybrid programme is highly relevant in the COVID-19 pandemic as it reduces contact of a patient with healthcare worker and hospital premises, thus reducing exposure to COVID-19. There has been an increasing number of studies exploring alternatives to outpatient physiotherapy clinics for prehabilitation. A systematic review by Driessen et al. [30] in 2017 summarized the adherence, treatment tolerance, and recovery of a home-based prehabilitation and rehabilitation in patients with non-small cell lung cancer. Three studies have examined the use of unsupervised home-based training alone and reported good adherence (72%, 100%, and 100%, respectively) [31-33]. In our study, patients verbalized that they were compliant to both 30 minutes walking and four sessions of deep breathing exercises (× 10 times each). Although healthcare workers should trust patients, a directly supervised PP is more reliable to validate compliance. The supervision can be done via hospital or community-based outpatient PP or inpatient PP. However, such initiatives require resources. They might not be cost-effective due to low incidence of PD. In our institution, inpatient PP is reserved for frail elderly patients. Other measures of compliance include activity diaries [34], which similarly require patient honesty.

Prehabilitation has been shown to be able to reduce LOS in HPB surgery. However, studies thus far are heterogeneous. A meta-analysis of three RCTs and one propensity score-matched case-control study including 419 patients by Dagorno et al. [21] showed a non-significant reduction in LOS using a random-effects model (mean difference: -4.37 days, 95% CI: -8.86-0.13, p = 0.0595), whereas a significant reduction in LOS was shown using a fixed-effects model (mean difference: -1.19 days, 95% CI: -1.56 to -0.81, p = 0.0071). The report of Dagorno et al. [21] also included studies of Nakajima et al. [10] and Ausania et al [11]. In addition, another two included studies focused on liver resection [35,36]. Thus, results could not be applied to patients undergoing PD. We have also previously reported improved overall morbidity (30% vs. 52.9%, p = 0.02) with standardized outpatient PP (for 2 to 4 weeks) vs. standard hospital protocol in elective liver resection patients (PP: n = 70, no-PP: n = 34) [25]. Dagorno et al. [21] have concluded that it is not possible to determine any beneficial impact of prehabilitation on LOS in patients following HPB surgery. Their report is interesting as the authors have calculated an estimated sample size that might guide future clinical studies. The authors made assumptions of α at 5% (type I error) and β at 80% (type II error). They computed a sample size of 56 patients (n = 28 in each arm) to reduce LOS by 25% (corresponding to an effect size of six days) and a sample size of 174 patients (n = 87 in each arm) to reduce postoperative morbidity by 20%. We calculated sample size with aim to reduce postoperative morbidity from 50% to 30% (i.e., effect size difference of 20%). However, due to 2:1 group allocation, a smaller sample was feasible to detect the difference.

This study has its strengths. To the best of our knowledge, this is the first study to assess a home-based outpatient PP in patients undergoing PD alone. The majority of existing studies either evaluated a home-based outpatient PP in a combined group of patients undergoing HPB surgery or evaluated a supervised outpatient program in PD [10,11]. Furthermore, we used multivariate analysis to address confounding factors that might affect postoperative outcomes. However, this study also has a few limitations. Firstly, this was a single-center study, thus limiting generalizability of results. We calculated sample size based on the assumptions according to published literature and the recent prospective randomized controlled trial. However, sample size was insufficient. Thus, we might not be able to detect differences in individual organ-specific morbidity [11]. Our study found an overall morbidity of 54.9%. Thus, the study was not underpowered to detect differences. Due to the small sample size in the no-PP arm, we did not perform propensity score matching. We did not study objective measures such as improvement in functional quality of life (e.g., activity of daily living) or use of surrogate markers such as handgrip strength to assess compliance to home-based PP [37]. Furthermore, we did not collect data on the duration between the start of outpatient PP to the date of surgery, although this was estimated to be between 2 to 4 weeks for most patients. Data on respiratory and cardiac function before and after a home-based outpatient PP were not collected either as the main aim of our study was to compare clinical outcomes between PP and no-PP. Lastly, selection bias might have influenced postoperative outcomes and might not truly reflect the impact of a home-based outpatient PP. Despite these limitations, this study adds to the current body of evidence related to home-based prehabilitation initiatives in PD.

In conclusion, our outpatient home-based PP with a single physiotherapy session followed by unsupervised breathing

exercises and walking before elective PD is feasible with good compliance. However, this PP did not show improvement in postoperative outcomes. Further studies should report compliance, surrogate biochemical markers of nutritional assessment, functional activity outcomes, quality of life indicators, and cost-effectiveness data. Multi-center collaboration is necessary to recruit a large sample of pancreatic surgery patients to generate evidence if prehabilitation initiatives are worth implementing in all patients or only in selected groups of patients (e.g., frail patients) scheduled for an elective pancreatic neoplasm surgery, especially PD.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix 1. Components of the FRAIL (fatigue, resistance, aerobic, illnesses, loss of weight) questionnaire

Indicators	Scoring	Please circle
Fatigue: How much time during the previous 4 weeks did you feel tired?	Not at all	0
	Yes (all of time / most of the time)	1
Resistance: Do you have difficulty walking up 1 flight of stairs alone without resting and without aids?	No	0
	Yes	1
Aerobic: Do you have any difficulty walking 1 block without aids?	No	0
	Yes	1
Illnesses: Do you have more than 5 illnesses*?	No	0
*The illnesses include hypertension, diabetes, cancer (other than minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease	Yes	1
Loss of weight: Have you lost more than 5% of your original weight in the past 6 months?	No	0
	Yes	1
Total score[a)]		

[a)]Patients with a FRAIL score < 3 were selected for our home-based outpatient prehabilitation program, and score of ≥ 3 were selected for our inpatient prehabilitation program: Recovery of Surgery in the Elderly (ROSE) program.

Appendix 2

Description of the Recovery of Surgery in the Elderly (ROSE) program

The ROSE program is an inpatient prehabilitation program for patients ≥ 75 years old or 65–74 years old with FRAIL score ≥ 3. Patients enrolled in the ROSE program were arranged for inpatient admission for at least 2 weeks prior to day of surgery. A standardized physiotherapy regime was prescribed for all patients under the ROSE program, with physiotherapy sessions for at least 1 hour per day, and six days per week. Exercises taught during the physiotherapy sessions are similar to that of our outpatient prehabilitation program (details are described in our main manuscript).