Personalized multimodal prehabilitation reduces cardiopulmonary complications after pancreatoduodenectomy

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Personalized multimodal prehabilitation reduces cardiopulmonary complications after pancreatoduodenectomy: results of a propensity score matching analysis

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Abstract

Background: The purpose of prehabilitation is to improve postoperative outcomes by increasing patients' resilience against the stress of surgery. This study investigates the effect of personalized multimodal prehabilitation on patients undergoing pancreatoduodenectomy.

Methods: Included patients were screened for six modifiable risk factors: (1) low physical fitness, (2) malnutrition, (3) low mental resilience, (4) anemia and hyperglycemia, (5) frailty, and (6) substance abuse. Interventions were performed as needed. Using 1:1 propensity score matching (PSM), patients were compared to a historical cohort.

Results: From 120 patients, 77 (64.2%) performed a cardiopulmonary exercise test to assess their physical fitness and provide them with a preoperative training advice. Furthermore, 88 (73.3%) patients received nutritional support, 15 (12.5%) mental support, 17 (14.2%) iron supplementation to correct for iron deficiency, 18 (15%) regulation support for hyperglycemia, 14 (11.7%) a comprehensive geriatric assessment, and 19 (15.8%) substance abuse support. Of all patients, 63% required $\geq$2 prehabilitation interventions. Fewer cardiopulmonary complications were observed in the prehabilitation cohort (9.2% versus 23.3%; $p = 0.002$). In surgical outcomes and length of stay no differences were observed.

Conclusion: Our prehabilitation program is effective in detecting risk factors in patients; most patients required multiple interventions. Consequently, a reduction in cardiopulmonary complications was observed.

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Introduction

In the past decades, developments in perioperative care have significantly enhanced the safety and efficacy of surgery for patients with pancreatic cancer, resulting in a decrease in perioperative mortality and an increase in the 5-year survival rate.[1] However, pancreatic surgery is highly complex, and the complication rate following pancreatic resections remains high.[2] The risk of postoperative complications depends in part on patient-related modifiable risk factors. Preoperative screening and optimization of these risk factors (i.e., prehabilitation) can strengthen patients' resilience to the stress of surgery, ultimately reducing postoperative morbidity.[3]

In the coming decades, the incidence of pancreatic malignancies is expected to increase alongside aging and the rising obesity rates of the western population.[4,5] Multimorbidity is especially prevalent in older patients, who are therefore considered as high-risk candidates for surgery. With the optimization of the perioperative care pathway, prehabilitation programs are gaining ground as an effective method of preparing (high-risk)

patients for major abdominal surgery.[6–15] Since prehabilitation programs were initially implemented for patients with colorectal cancer, the majority of literature on the effects of prehabilitation programs pertains to patients undergoing colorectal surgery. In their systematic review, Bruns et al. examined the effect of prehabilitation in colorectal surgery and found that prehabilitation enhanced patients' physical condition preoperatively.[14] Concerning prehabilitation in pancreatic surgery, Bundred et al. reviewed six studies (three prospective cohort studies, one retrospective cohort study, one randomized controlled trial, and one case series) on prehabilitation programs for patients undergoing surgery for pancreatic cancer.[11] The authors concluded that prehabilitation was safe and feasible for patients with pancreatic cancer, with two reviewed studies also demonstrating a lower rate of delayed gastric emptying (DGE) and a shorter hospital stay compared to standard care.[11] Prehabilitation programs reducing postoperative morbidity might help enhance postoperative recovery in patients. Adequate postoperative recovery is essential for timely commencement of adjuvant therapy, an important treatment modality to achieve optimal survival outcomes in pancreatic cancer patients.[16] Hence, prehabilitation might be beneficial for both the perioperative as adjuvant treatment phase.[17]

Although previous studies demonstrate that a prehabilitation program may improve postoperative outcomes in pancreatic surgery, some important considerations must be taken into account when evaluating these results. First, there is significant heterogenicity in the reported prehabilitation regimens, with the majority of programs predominantly focusing on improving patients' preoperative physical fitness through a unimodal exercise program. Second, patient selection remains an important issue when assessing the effect of a prehabilitation program. High-risk patients appear to benefit the most from prehabilitation that is tailored specifically to their identified risk factors.[3,18] In this study, we aim to characterize the prehabilitation needs of patients undergoing a pancreatoduodenectomy, thereby identifying those at high risk. In addition, we will investigate the effect of a multimodal prehabilitation program with a personalized approach on the postoperative course, including 30-day morbidity and mortality rates.

Methods

Study design and participants

This longitudinal prospective cohort study was conducted between May 2019 and August 2022 at the University Medical Center Groningen in the Netherlands. In this study, the effect of a multimodal personalized prehabilitation program was investigated in pancreatic surgery patients undergoing pancreatoduodenectomy (i.e., pylorus-preserving pancreaticoduodenectomy (PPPD), pylorus-resecting pancreaticoduodenectomy (PRPD), or Whipple procedure). This study is part of the "Frail-study," in which a new preoperative care pathway was developed and implemented for patients scheduled to undergo hepato-pancreato-biliary (HPB) surgery.[3] All patients undergoing the prehabilitation program completed the informed consent process, which was approved by the Institutional Review Board of the University Medical Center Groningen (Netherlands research registration number 201800293). The postoperative outcomes of patients undergoing the prehabilitation program (multimodal prehabilitation cohort) were compared to those of a historical cohort receiving conventional care. Patients in the historical cohort underwent pancreatoduodenectomy at the University Medical Center Groningen between January 2013 and April 2019. Since age is an important predictor of patients' frailty and the prehabilitation cohort comprised a larger number of older patients, only patients aged 55 years or older were included in the final analysis. Furthermore, we observed a discrepancy in our cohort, with more patients receiving neoadjuvant chemotherapy in the prehabilitation cohort compared to the historical cohort, which significantly influences patients' physical fitness. Therefore, to analyze a homogenous cohort and limit bias, patients receiving neoadjuvant chemotherapy were excluded from the statistical analysis.

Prehabilitation outpatient clinic

Since May 2019, all patients referred for pancreatic surgery have been preoperatively screened and assessed for patient-related modifiable risk factors by a trained nurse at our prehabilitation outpatient clinic. Screening and assessment were performed on six different domains; a detailed description was published previously.[3] In summary, the risk of low physical fitness (1) was assessed using the following screening questions: (i) Does the patient not comply with the World Health Organization recommendations for physical activity?[19] (ii) Does the patient have a poorly regulated comorbidity (e.g., poorly controlled diabetes mellitus)? (iii) Is the patient receiving neoadjuvant treatment? (iv) Is the patient aged 80 years or older? When one or more questions were answered in the affirmative, patients were referred to a sports physician for an objective assessment of their physical fitness using a cardiopulmonary exercise test (CPET). Based on the results of the CPET, the sports physician provided each patient with personalized training advice to maintain or improve their physical fitness during the preoperative waiting period. Because the oxygen uptake (VO_2) at the ventilatory anaerobic threshold (VAT) and VO_2 at peak exercise (VO_2peak) have been found to have a consistent relationship with postoperative outcomes in major abdominal surgery, the sports physician's preoperative training advice aimed to optimize these physiological indicators of physical fitness.[20,21] Patients with very low physical fitness (i.e., VO_2 at VAT $\leq$11 mL/kg/min) were enrolled in a supervised training program consisting of home-based high-intensity interval training and endurance training.[22] In addition, patients were screened for risk of malnutrition (2)

using the Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire and were referred to a specialized dietician for dietary advice, including at least 1.5 g/kg/day of proteins and/or nutritional supplements and pancreatic enzyme replacement therapy (PERT), as needed. Using the Hospital Anxiety and Depression Scale (HADS) questionnaire, patients were screened for low mental resilience (3) and, if necessary, rereferred for mental support to their general practitioner or the medical psychology department. A blood sample was drawn from each patient to screen for (causes of) anemia (4) (e.g., iron, vitamin B12, or folic acid deficiency) and poorly controlled diabetes (HbA1c). Subsequently, patients were referred to the internal medicine department for anemia treatment (e.g., iron supplementation in the case of iron deficiency anemia [IDA]). In the case of poorly controlled diabetes, they were referred either to the internal medicine department (in the case of new-onset diabetes) or to their general practitioner (in the case of preexisting diabetes) for blood glucose regulation support. Frailty (5) was assessed using the Robinson Frailty Index (RFI) and Groningen Frailty Indicator (GFI). Patients were referred to a geriatrician in the hospital for a full comprehensive geriatric assessment as appropriate. Finally, substance abuse (6) (i.e., tobacco use and/or alcohol consumption) was assessed and patients were strongly advised to stop. Appropriate professional support to stop substance abuse was offered as necessary. In our hospital, the median waiting time for surgery is 4–6 weeks; therefore, the multimodal prehabilitation program did not delay surgery.

Perioperative procedure

During the inclusion period (2013–2022), no significant differences in surgical procedures were implemented; therefore, patients in both cohorts received the same surgical treatment. During this period, however, our hospital switched from PPPD to PRPD due to its reported ability to reduce the incidence of DGE.[23] For the pancreatojejunostomy a double-layer continuous suturing and duct-to-mucosa technique was used. All patients received the same postoperative care, which consisted of placing two abdominal drains and testing them for amylase, following a fixed postoperative protocol. Depending on the amylase level, either the drains were removed or additional diagnostic procedures were performed. The patients were transferred to the Intensive Care Unit (ICU) or Post-Anesthesia Care Unit (PACU) immediately after surgery. Depending on the patient's clinical condition, they were transferred to the surgical ward beginning the second postoperative day. In addition to our prehabilitation program, all patients received perioperative care in accordance with the most recent Enhanced Recovery After Surgery protocols for pancreatic surgery.[24] During the inclusion period a shift in postoperative anesthetic management of patients took place, meaning if their clinical condition allowed for it, patients were discharged to the PACU instead of ICU. No other changes in anesthetic management were implemented.

Data collection and study endpoints

Baseline demographic data, including age, gender, body mass index (BMI), comorbidities, American Society of Anesthesiologists (ASA) classification, Charlson Comorbidity Index, tumor origin, histological diagnosis, and preoperative biliary drainage, were recorded. Concerning intraoperative details, the type of surgical procedure, estimated intraoperative blood loss, and complementary (vascular) resections were recorded. The risk of postoperative pancreatic fistula was calculated using the Dutch Pancreatic Cancer Group fistula risk score for pancreatoduodenectomy.[25] According to the definitions of the International Study Group of Pancreatic Surgery, 30-day postoperative complications were recorded and graded.[26] Subsequently, postoperative complication severity was graded using the Clavien–Dindo classification system.[27] The total hospital stay was calculated from the day of surgery until discharge. Postoperative cardiopulmonary complications (CPC) were defined as any cardiological (e.g., heart rhythm disorder, myocardial infarction, and decompensated heart failure) or pulmonary complication (e.g., pneumonia, pulmonary embolus, and chronic obstructive pulmonary disease [COPD] exacerbation).

Statistical analysis

Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR), based on the normality of distribution. Categorical data are presented as number and percentage. Differences between groups were calculated by using Student's t-test and the Mann–Whitney U test or the chi-squared test and Fisher's exact test, as appropriate. Using 1:1 nearest neighbor propensity score matching, patients in the prehabilitation group were matched with a historical cohort. The following variables were used in the model: age, gender, BMI, ASA classification, Charlson Comorbidity Index, and known medical history of diabetes mellitus and heart or respiratory disease. Subsequently, patient characteristics and postoperative outcomes were compared between the multimodal prehabilitation and historical cohorts. The R software packages "car" and "MatchIt" (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Statistical significance was defined as $p < 0.05$.

Results

Multimodal prehabilitation program

Based on eligibility criteria, 120 patients undergoing pancreatoduodenectomy were included for analysis in the multimodal prehabilitation cohort (Fig. 1). An overview of the number of performed interventions is provided in Fig. 2. The majority of patients (n = 77 [64.2%]) were referred for a CPET and subsequently received personalized training advice from the sports physician. Of these patients, 14 (18.2%) were enrolled in a supervised training program. Moreover, a large number of patients

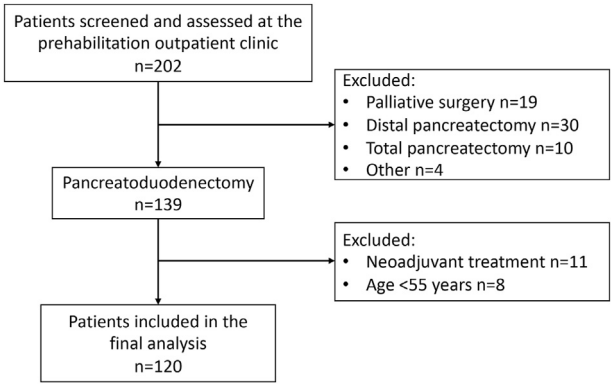

Figure 1 Inclusion flow chart

(n = 88 [73.3%]) were referred for nutritional support to a specialized dietician. For the remaining risk factors, 15 (12.5%) patients received mental support, 17 (14.2%) were referred for iron supplementation to correct for IDA, 18 (15%) were referred for regulation of poorly controlled diabetes, 14 (11.7%) underwent a comprehensive geriatric assessment for frailty, and 19 (15.8%) received professional support to stop substance abuse. Regarding the number of interventions required per patient, only a minority of the patients (8%) required no interventions, whereas the majority (29%) required one intervention or two or more (63%) interventions (Fig. 3).

Baseline characteristics

Using 1:1 propensity score matching, 120 historical cohort patients were matched with the multimodal prehabilitation cohort. The cohorts were successfully matched with a mean age of 68.7 years, a mean BMI of 25.5 kg/m^2 versus 25.8 kg/m^2, and a female gender ratio of 46.7% versus 51.7% for the historical and multimodal prehabilitation cohorts, respectively (Table 1). Moreover, ASA classification, Charlson Comorbidity Index, medical history, substance abuse, and preoperative biliary decompression were equally distributed between the study cohorts.

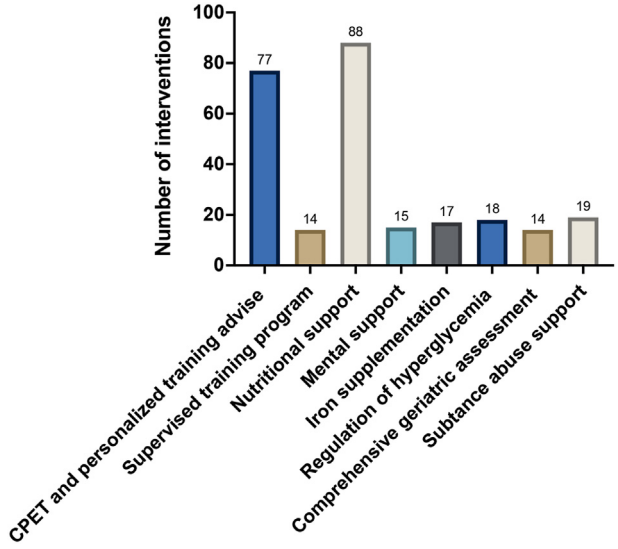

Figure 2 Overview of all prehabilitation interventions in 120 patients preoperatively screened and assessed at our prehabilitation outpatient clinic

Abbreviations: CPET = cardiopulmonary exercise test

Intraoperative characteristics

As a result of our hospital switching from PPPD to PRPD, we observed a significant difference in the type of pancreatoduodenectomies performed between cohorts, with more PRPDs performed in the multimodal prehabilitation cohort (24.2% versus 1.7% in the historical cohort) (Table 2). The number of complementary (7.5% versus 3.3%, respectively; $p = 0.253$) and vascular resections (10.8% versus 16.7%, respectively; $p = 0.189$) was similar between the historical cohort and the multimodal prehabilitation cohort, and no difference in median intraoperative blood loss was observed (525 mL [350–825] versus 500 mL [300–706], respectively, in the historical cohort and the multimodal prehabilitation cohort; $p = 0.051$). No differences existed between tumor origin and histological diagnosis. Lastly, the calculated risk scores for postoperative pancreatic fistula were similar between groups ($p = 0.807$).

Postoperative outcomes

All relevant postoperative outcomes are summarized in Table 3. The median length of stay was not statistically different between the historical and multimodal prehabilitation cohorts (12 days [9–17] and 12 days [9–20], respectively; $p = 0.449$). Furthermore, no differences in the rate of complications specific to pancreatic surgery (i.e., postoperative pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhage, bile leakage, and chyle leakage) were observed between the cohorts. Nonetheless, a significant reduction in the rate of CPC was observed in the multimodal prehabilitation cohort (9.2% versus 23.3% in the historical cohort; $p = 0.002$). Heart rhythm disorders and pneumonias were the most common complications contributing to the number of CPC observed. Between the historical and multimodal prehabilitation cohort no differences were observed in 90-day mortality (4.2% versus 3.3%, respectively) and unplanned readmissions rates (22.5% versus 16.7%, respectively). Finally, the time to commencement of adjuvant chemotherapy for patients with a pancreatic ductal adenocarcinoma (PDAC) was 4 days shorter in the multimodal prehabilitation cohort, although this effect did not reach statistical significance (58 days versus 62 days in the historical cohort, $p = 0.378$).

Discussion

In this study, the majority of patients undergoing pancreatoduodenectomy required two or more preoperative interventions to optimize their identified preoperative risk factors. In the

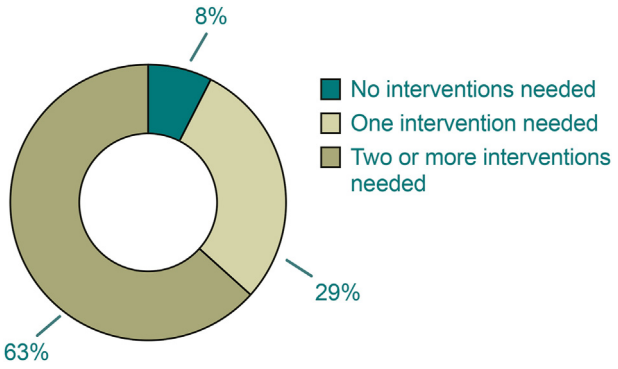

Figure 3 Proportions of prehabilitation interventions necessary in 120 patients preoperatively screened and assessed at our prehabilitation outpatient clinic

majority of patients, these interventions included an assessment of their physical fitness to provide them with personalized training advice to maintain or improve physical fitness, as well as nutritional support by a specialized dietician. Personalized multimodal prehabilitation resulted in a significant reduction in the rate of CPC. Particularly, the number of heart rhythm disorders and pneumonias decreased. Nevertheless, no differences were observed in the median length of hospital stay, surgery-specific complications, or unplanned readmission rates. Pancreatic fistulas constitute the most serious complications of pancreatic surgery and have a significant impact on the length of hospital stay and readmission rates. Meanwhile, the risk of developing a pancreatic fistula depends largely on the pancreatic texture and pancreatic duct size and is therefore not affected by prehabilitation. In our multimodal prehabilitation cohort, the relatively high rate of pancreatic fistulas significantly influenced the length of hospital stay and readmission rates, thereby diminishing the effect of a decrease in CPC.

This study is the first of its kind to enroll a large cohort of pancreatic surgery patients in a personalized multimodal prehabilitation program, in which they underwent interventions specifically tailored to their preoperatively identified risk factors. Only validated screening methods were used in this study (e.g., physical fitness was assessed by performing a CPET, the gold standard for aerobic capacity assessment[28]), which improved the efficacy of preoperative screening in identifying patient-related risk factors, especially in high-risk patients. Previous studies evaluating the effect of prehabilitation programs in pancreatic surgery only used small sample sizes and were highly heterogenous in terms of screening methods and performed interventions. Ausania et al., for instance, enrolled 18 patients in their prehabilitation program, which included nutritional support, control of diabetes and pancreatic insufficiency, and physical and respiratory training; they observed a reduction in the incidence of DGE as a result.[15] Similarly, in Nakajima et al.'s prehabilitation program, patients (n = 76) were subjected to preoperative exercise and nutritional therapy.[13] The authors reported a reduction in nutritional deterioration, an improvement in physical fitness, and subsequently a shorter hospital stay.[13] However, because only 25 out of 76 patients in their study cohort underwent pancreatic surgery, these findings are difficult to generalize to pancreatic surgery patients. Lastly, Chan et al. enrolled 50 patients who were considered to be frail (based on the FRAIL questionnaire) in their unimodal prehabilitation

Table 1 Baseline characteristics of patients in the historical cohort and multimodal prehabilitation cohort

	Historical cohort (n = 120)	Multimodal prehabilitation (n = 120)	*p*-value
Mean age: years	68.7 ± 7.1	68.7 ± 7.3	0.972
Mean BMI: kg/m^2	25.5 ± 4.9	25.8 ± 4.8	0.632
Female sex	56 (46.7)	62 (51.7)	0.438
ASA classification ≥3	38 (31.7)	40 (33.3)	0.782
CCI ≥4	58 (48.3)	56 (46.7)	0.796
Medical history			
Diabetes mellitus	26 (21.7)	27 (22.5)	0.876
Hypertension	54 (45)	55 (45.8)	0.896
Heart disease	16 (13.3)	16 (13.3)	1.000
Respiratory disease	9 (7.5)	16 (13.3)	0.139
Substance abuse			
Tobacco	37 (30.8)	32 (26.7)	0.475
Alcohol	56 (46.7)	63 (52.5)	0.366
Biliary decompression	72 (60)	62 (51.7)	0.276

Legend: Data are presented as mean ± standard deviation, median (IQR), or number (%).
Abbreviations: BMI = body mass index; ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index.

Table 2 Intraoperative characteristics of patients in the historical cohort and multimodal prehabilitation cohort

	Historical cohort (n = 120)	Multimodal prehabilitation (n = 120)	*p*-value
Type of pancreatoduodenectomy			**<0.001**
PPPD	92 (76.7)	82 (68.3)	
PRPD	2 (1.7)	29 (24.2)	
Whipple	26 (21.6)	9 (7.5)	
Complementary resection	9 (7.5)	4 (3.3)	0.253
Vascular resection	13 (10.8)	20 (16.7)	0.189
Median intraoperative blood loss: ml	525 (350–825)	500 (300–706)	0.051
Origin of tumor			0.302
Pancreas	58 (48.3)	56 (46.7)	
Distal CBD	19 (15.9)	28 (23.3)	
Ampulla of Vater	21 (17.5)	24 (20)	
Duodenum	16 (13.3)	9 (7.5)	
Other	6 (5)	3 (2.5)	
Histological diagnosis			0.338
Adenocarcinoma	92 (76.7)	81 (67.5)	
Neuroendocrine	5 (4.2)	5 (4.2)	
IPMN	7 (5.8)	10 (8.3)	
Intestinal adenoma	8 (6.7)	7 (5.8)	
Other	8 (6.7)	17 (14.2)	
Calculated POPF-risk[a,b]	n = 89	n = 116	0.807
Low	18 (20.2)	21 (18.1)	
Intermediate	52 (58.4)	73 (62.9)	
High	19 (21.4)	22 (19)	

Legend: Data are presented as median (IQR) or number (%).
Abbreviations: PPPD = pylorus-preserving pancreaticoduodenectomy; PRPD = pylorus-resecting pancreaticoduodenectomy; CBD = common bile duct; IPMN = intraductal papillary mucinous neoplasm; POPF = postoperative pancreatic fistula.
[a] Dutch Pancreatic Cancer Group fistula risk score for pancreatoduodenectomy.[25]
[b] The risk of POPF was only calculated for patients in which all prognostic factors for POPF were available.

program, which consisted of unsupervised breathing and lower-limb strengthening exercises, and a walking program. However, they were unable to demonstrate a difference in postoperative outcomes in comparison to conventional care. The lack of a multimodal and personalized approach in this vulnerable patient population may influence the efficacy of prehabilitation programs. Therefore, we believe that a multimodal approach is preferable to a unimodal or bimodal approach, addressing all known patient-related risk factors, to achieve optimal results in the relatively short preoperative waiting period.

In major abdominal surgery, the incidence of CPC is high and is associated with increased morbidity, prolonged hospital stays, and frequent unplanned readmissions, leading to high hospital costs.[29–33] Specific patient-related risk factors have been linked to the incidence of CPC. First, malnutrition and associated (respiratory) muscle weakness are linked to an increased risk of pulmonary complications.[29,34] Tobacco use and hazardous alcohol consumption are additional risk factors directly associated with pulmonary complications.[29] Moreover, multiple studies demonstrated an association between untreated preoperative anemia and the incidence of postoperative pulmonary and cardiac complications.[35,36] In addition, the postoperative outcomes of nearly 6600 patients who underwent major liver resection indicated that the risk of CPC is age related, with higher incidences observed in older patients.[37] In light of an aging population with significant patient-related modifiable risk factors and the profound effects of CPC on postoperative outcomes, interventions are required to effectively address this issue. Our results demonstrate that a multimodal prehabilitation program focusing on optimizing patient-related risk factors can help in reducing CPC. Timely commencement of adjuvant therapy is important to achieve optimal treatment results in pancreatic cancer.[16] Although the rate of surgery-specific complications remained relatively high in this study, we observed a somewhat shorter time to commencement of adjuvant therapy for patients with PDAC. This might indicate that the impact of complications was less for patients in the prehabilitation cohort, resulting in faster postoperative recovery. However, further research is

Table 3 Postoperative outcomes of patients in the historical cohort and multimodal prehabilitation cohort

	Historical cohort (n = 120)	Multimodal prehabilitation (n = 120)	*p*-value
Median length of hospital stay: days	12 (9–17)	12 (9–20)	0.449
Surgery-specific complications			
POPF grade ≥ B	24 (20)	25 (20.8)	0.872
DGE grade ≥ B	30 (25)	31 (25.8)	0.882
PPH grade ≥	6 (5)	11 (9.2)	0.208
BL grade ≥ B	2 (1.7)	2 (1.7)	1.000
CL grade ≥ B	16 (13.3)	13 (10.8)	0.552
Cardiopulmonary complication ≥1	28 (23.3)	11 (9.2)	**0.002**
Heart rhythm disorder	11 (9.2)	6 (5)	0.208
Myocardial infarction	0	1 (0.8)	1.000
Decompensated heart failure	5 (4.2)	2 (1.7)	0.446
Pneumonia	9 (7.5)	3 (2.5)	0.136
Pulmonary embolus	5 (4.2)	1 (0.8)	0.213
COPD exacerbation	0	1 (0.8)	1.000
Wound infection	20 (16.7)	29 (24.2)	0.149
Clavien-Dindo complication grade ≥3	28 (23.3)	26 (21.7)	0.762
Readmission ICU	8 (6.7)	9 (7.5)	0.802
Deceased during primary hospital stay	1 (0.8)	3 (2.5)	0.621
90-day mortality	4 (3.3)	5 (4.2)	1.000
Unplanned readmission <30 days	27 (22.5)	20 (16.7)	0.267
Time to commencement of adjuvant chemotherapy for patients with PDAC: days	n = 25 (20.8) 62 (55–70)	n = 23 (19.2) 58 (43–69)	0.378

Legend: Data are presented as median (IQR) or number (%).
Abbreviations: POPF = postoperative pancreatic fistula; DGE = delayed gastric emptying; PPH = postpancreatectomy hemorrhage; BL = bile leakage; CL = chyle leakage; COPD = chronic obstructive pulmonary disease; PDAC = pancreatic ductal adenocarcinoma; ICU = intensive care unit.

needed to objectively elucidate the effect of prehabilitation on the impact of complications.

The strengths of this study include the multimodal and personalized approach of our prehabilitation program, its incorporation in the perioperative care pathway, and well-matched study cohorts. However, this study has some limitations. First, due to its pragmatic approach, the effect of the prehabilitation program was not evaluated for all performed interventions (e.g., the effect of nutritional support in malnourished patients). Nevertheless, the effect of iron supplementation was evaluated prior to surgery. In patients participating in the supervised training program, the adherence rate was monitored and the CPET was repeated to assess the change in physical fitness.[22] Second, low health literacy (HL) was not screened for. Recently, Driessens et al. investigated the effect of low HL in patients undergoing HPB surgery and concluded that low HL leads to poor postoperative outcomes.[38] Low HL should be included in preoperative screening, and interventions should focus on preoperative education and guidance for patients with low HL. Lastly, in this study, we evaluated only surgical outcome measures. Although these are important, global outcome measures of patients' quality of recovery focusing on long-term disability-free survival should be incorporated to better define postoperative recovery.[39] A representative example is the time to functional recovery, which has been found in previous pancreatic surgery studies to be a valid outcome measure of the quality of recovery.[40] We think that our multimodal prehabilitation program may reduce the time to functional recovery by simultaneously reducing the number of postoperative complications and increasing patients' resilience to the adverse effects of complications on postoperative recovery. Future studies with larger sample sizes may need to further elucidate this.

In conclusion, this study demonstrates that our multimodal prehabilitation program is effective at identifying patient-related risk factors. The majority of patients required two or more preoperative interventions, which resulted in a reduction in CPC. In light of an aging population with associated multimorbidity and an expected increase in pancreatic cancer incidence, the time has come to implement personalized multimodal prehabilitation programs in pancreatic surgery.

Ethical approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of the UMCG in the Netherlands (Netherlands research registration number 201800293). This study was performed in accordance with the ethical standards set by the Declaration of Helsinki. All patients provided written consent before enrollment in the study.

Authors' contributions

A.G.W. study design, data collection, data analysis, writing and reviewing the manuscript. F.J.H. writing and reviewing the manuscript. M.W.N. writing and reviewing the manuscript. J.M.K. study design, writing and reviewing the manuscript.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

None to declare.

Availability of data and materials

The datasets generated or analyzed in the present study are not publicly available because the data are linked to a vulnerable patient population. However, these data are available upon reasonable request from the corresponding author (a.g.wijma@umcg.nl).

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