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ORIGINAL SCIENTIFIC REPORT

Feasibility of an Enhanced Recovery Protocol for Elective Pancreatoduodenectomy: A Multicenter International Cohort Study

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Abstract

Background The first enhanced recovery after surgery (ERAS) guidelines for pancreatoduodenectomy (PD) were developed in 2012. The study aimed to assess compliance and outcomes of an ERAS protocol for PD, to study correlation between compliance and outcomes, and to identify risk factors for complications.

Methods Retrospective cohort analysis is based on a prospective database, including all consecutive patients undergoing elective PD within an ERAS program in four centers: Lausanne University Hospital (Switzerland), Carolinas Medical Center (United States), Edouard Herriot Hospital (France), and University Medical Center Hamburg-Eppendorf (Germany). Patients' characteristics, postoperative outcome and ERAS compliance were assessed. Logistic regression analysis was performed to assess predictors of postoperative complications.

Results Between October 2012 and June 2017, 404 consecutive patients underwent PD. Median length of stay was 14 days with 11.3% readmission rate. Mean overall compliance was 62%, with pre-, intra- and postoperative compliance of 93%, 80% and 30%, respectively. Overall compliance $\geq$ 70% versus $<$ 70% was significantly associated with a reduction in complications ($p = 0.029$) and length of stay ($p < 0.001$). Avoidance of postoperative nasogastric tube (OR = 0.31, $p = 0.043$), mobilization on day of surgery (OR = 0.28, $p = 0.043$), and mobilization more than 6 h on postoperative day 2 (OR = 0.45, $p = 0.001$) were independent predictors of reduced overall complications.

Conclusions Implementation of enhanced recovery for PD is challenging, especially in the postoperative period. Overall compliance with ERAS protocol $\geq$ 70% was associated with decreased complications and length of stay. Specific ERAS elements, such as avoidance of postoperative nasogastric tube and early mobilization, independently improved outcomes.

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Introduction

Enhanced recovery after surgery (ERAS) was initially developed for colorectal surgery in order to reduce the impact of the postsurgical metabolic stress response and improve postoperative outcomes based on the implementation of a multidisciplinary and multimodal pathway. ERAS pathways are composed of multiple individual evidence-based elements which cover the entire patient's journey, from the first referral until the postoperative follow-up [1]. First guidelines for pancreatoduodenectomy (PD) were published in 2012 [2], and the recommendations were mostly based on PD performed outside an ERAS setting or extrapolated from other surgical procedures such as colorectal surgery. Therefore, limited data are currently available on the feasibility and benefits of implementing ERAS pathway according to the existing ERAS guidelines for PD. Moreover, the impact of each individual elements of an ERAS pathway for PD has not been studied yet.

This study aimed to assess the feasibility of an enhanced recovery program for PD in a multicenter setting by analyzing the compliance to each ERAS items. The secondary aim was to analyze the effect of compliance on outcomes, and to identify predictors of complications.

Material and methods

Inclusion

Retrospective cohort analysis is based on a prospective database, including all consecutive patients undergoing open, laparoscopic or robotic elective PD (classic Whipple or pylorus preserving PD) within an ERAS pathway in four tertiary centers: Lausanne University Hospital (Switzerland), Carolinas Medical Center (United States), Edouard Herriot Hospital (France), and University Medical Center Hamburg-Eppendorf (Germany). Inclusion started from the date of the first patient operated within an implemented ERAS pathway in each center (8th October 2012 at Lausanne University Hospital, 1st September 2015 at Carolinas Medical Center, 17th February 2016 at University Medical Center Hamburg-Eppendorf, and 26th June 2016 at Edouard Herriot Hospital) until 30th June 2017. Patients less than 18 years old, operated in an emergency setting, or without consent were not included. In each center, the surgeon leader (J.I., M. A., D. V. and N. D.) built up a multidisciplinary ERAS team including surgeons, anaesthetists and nurses champions [3].The ERAS pathway in the four centers was based on the perioperative elements as described in Table 1 according to the ERAS recommendations for PD [2].

Table 1 Definitions of enhanced recovery elements used for compliance calculation

ERAS elements	Compliance definition
Preadmission patient education	Dedicated preoperative counseling and education
Oral bowel preparation	No bowel preparation
Preoperative oral carbohydrate	Carbohydrate drink until 2 h before surgery, except in case of mechanical obstruction, gastroparesis, or uncontrolled diabetes
No preoperative long-acting sedative medication	No preoperative long-acting sedatives on day of surgery
Thrombotic prophylaxis	Preoperative low-molecular-weight heparin ± sequential compression device
Antibiotic prophylaxis	Antibiotic prophylaxis before skin incision
PONV prophylaxis	PONV prophylaxis if two or more risk factors (female, non-smoker, previous PONV/motion sickness)
Epidural	Thoracic epidural, except when contra-indicated
Upper-body heating cover	Use of upper-body forded-air heating cover intraoperatively
No postop nasogastric tube	Removal of nasogastric tube before end of surgery
Early abdominal drain removal	Early drain removal on POD 3 if low risk
Termination urinary drainage POD 2	Transurethral catheter removal on POD 2
Stimulation of gut motility	Oral laxatives and/or chewing gum given postoperatively
Increase weight POD 1	Increase in weight of less than 2 kg
Balanced iv fluids POD 0	Less than 3500 ml intravenous fluid on day of surgery
Termination iv fluids	Termination of intravenous infusion less than 2 postoperative nights
Mobilization on day of surgery	Any mobilization (to walk, to sit on a chair or rising from bed)
Mobilization on POD 1	Mobilization in total for more than 4 h
Mobilization on POD 2	Mobilization in total for more than 6 h

PONV postoperative nausea and vomiting, *POD* postoperative day

Data collection

Data on patients' characteristics, surgery, compliance and outcome were collected prospectively by each center from the preoperative period until postoperative day 30. Data were coded and entered on an online web-based central database, the ERAS Interactive Audit System (www.erassociety.org, ENCARE, Krista, Sweden) as previously described [4]. An extraction of the data from the ERAS Interactive Audit System was performed in December 2017 and data from each center were merged in a single database for analysis. Ethical committee approval was individually obtained by each center (Lausanne University Hospital: # 2016-01815, Carolinas Medical Center: # 06-12-34E, University Medical Center Hamburg-Eppendorf: # PV 5779, and Edouard Herriot Hospital: # 16/09/06). The study was performed and reported according to the STROBE statement [5] and to the Reporting on ERAS Compliance Outcomes, and Elements Research (RECOvER) checklist [6].

Definitions

Compliance to pre-, intra-, and postoperative elements was assessed as specified in the ERAS society guidelines for PD [2] and reported as compliant, non-compliant, or missing. Overall compliance was calculated as the total of compliant elements divided by all 19 ERAS perioperative elements (Table 1). *Primary length of stay* was the total number of days in hospital from the operation until discharge. *Total length of stay* was the total number of days following readmission within 30 postoperative days added to the primary length of stay. Complications were defined as any adverse event occurring in the postoperative period until 30 days after surgery, and were graded according to the Dindo–Clavien classification [7]. Clavien grade I–II were considered as minor, and grade IIIa to IVb as major complication. Pancreas surgery specific complications, such as post-pancreatectomy hemorrhage, delayed gastric emptying or pancreatic fistula were graded A to C according to the respective International Study Group of Pancreatic Surgery classifications (ISGPS) [8–10].According to the 2016 ISGPS update [11], only clinically relevant pancreatic fistula (Grade B–C) were reported. Patients were also classified according to the American Society of Anesthesiologists (ASA) grade (low, I–II; high III–V) [12], preoperative World Health Organization (WHO) performance status [13] (good, 0; reduced I–III) and body mass index (BMI).

Statistical analysis

To assess the correlation between compliance and postoperative outcome, complications (overall and major) as well as length of stay (primary and total) were compared between patients with less or more than 70% of compliance. An overall compliance rate of 70% or more was defined as cutoff according to previous studies [14, 15] The Fischer test for complications and the Mann–Whitney *U* test for length of stay were used.

Binary logistic regression analysis with overall complication and major complication as dependent variable was performed with following independent variables: patient (age, gender, BMI, ASA grade, preoperative WHO performance score, surgery (procedure, approach, length of surgery) and ERAS specific elements. Only factors with at least 10% of patients differing from the rest of the cohort (i.e., $n \geq 39$) were included in the regression analysis. Multiple logistic regression analysis was further performed including all previous independent variables with a p value < 0.1. $p < 0.05$ was considered statistically significant. SPSS version 25 (IBM Corp., Armonk, NY) was used for data analysis.

Results

A total of 404 patients undergoing elective PD at the four academic centers were prospectively entered into the ERAS Interactive Audit System between 1st October 2012 and 30th June 2017. Fourteen patients refused the use of their data and were excluded. The number of included patients per center was as following: $n = 164$ at Lausanne University Hospital; $n = 105$ at Carolinas Medical Center; $n = 38$ at University Medical Center Hamburg-Eppendorf; and $n = 83$ at Edouard Herriot Hospital.

The characteristics of included patients are displayed in Table 2. The study population was in general elderly with a mean age of 65 years and with more than 70% of patients with reduced WHO performance status. The classical Whipple was performed in 52% of the patients, and 93% of the operations were performed by open surgery. Vascular resection, including venous, arterial and combined, was performed in 21% of patients ($n = 81$).

Compliance

The compliance to each ERAS element is described in Fig. 1. Mean overall compliance was 62%, with a compliance in the pre-, intra-, and post- operative period of 93%, 80% and 30%, respectively. No significant difference in compliance between centers was observed. Missing data for compliance items were on average 10%. Difficult

Table 2 Baseline characteristics of patients undergoing elective pancreatoduodenectomy within an ERAS pathway (n = 390)

Category	*N*	%
Gender, male	217	55.6
Age, mean (SD), years	65.3 (11.6)	
BMI, mean (SD), kg/m^2	25.5 (4.7)	
ASA		
1–2	186	47.7
3–4	203	52.0
Neoadjuvant chemotherapy	549	12.6
Preoperative WHO performance status		
0	112	28.7
1–3	275	70.6
Procedure type		
Pancreaticoduodenectomy (PD)	203	52.1
Pylorus-preserving PD	187	47.9
Surgical approach		
Open/converted	362	92.9
Laparoscopic	6	1.5
Robotic	22	5.6
Vascular resection		
Venous	66	16.9
Arterial	7	1.8
Arterial and venous	8	2.1
Missing	3	0.8
Diagnosis		
Primary adenocarcinoma	297	76.2
Other primary malignancy	34	8.7
Metastasis or recurrence of malignant disease	3	0.8
Benign tumor	25	6.4
Chronic pancreatitis	6	1.5
Others	24	6.2
Missing	1	0.3

SD standard deviation, *BMI* body mass index, *WHO* World Health Organization, *ASA* American Society of Anesthesiologists

elements to achieve (with a compliance less than 50%) were mainly found in the postoperative period. They concerned two main areas: fluid balance and urinary drainage removal (average compliance = 19%) as well as adequate postoperative mobilization (average compliance for day 0, 1, and 2 = 40%).

Outcomes

Postoperative outcomes are summarized in Table 3. Overall, complications within 30 postoperative days occurred in 83.7% of the patients, with a major complications rate of 36.9%. The 30-day mortality rate was 3.1%.

A compliance with ERAS pathway $\geq$ 70% was associated with an improved postoperative outcome as detailed in Table 4. Patients achieving a compliance above 70% had a significantly reduced primary and total length of stay ($p < 0.001$) and underwent significantly less overall and major complications ($p = 0.029$ and $p = 0.012$, respectively). The reduction in complications with compliance $\geq$ 70% was significant for respiratory ($p = 0.022$) and infectious ($p = 0.030$) complications.

Predictive factors of overall complications

No patient's or surgical characteristics affected the overall complications rate on multivariable logistic regression analysis. Avoidance of postoperative nasogastric tube (OR 0.31; 95% CI 0.14–0.97; $p = 0.043$), mobilization on day 0 of surgery (OR 0.28; 95% CI 0.14–0.97; $p = 0.043$) and mobilization more than 6 h on the second postoperative day (OR 0.45; 95% CI 0.22–0.93; $p = 0.001$) were independent predictors of decreased overall complications (Table 5).

Predictive factors of major complications

Female patients were associated with reduced major complications (OR 0.53; 95% CI 0.33–0.85; $p = 0.009$) (Table 6). Altered preoperative WHO performance (more than 0) was an independent predictor of increased major complications (OR 2.43; 95% CI 1.35–4.36; $p = 0.003$). Early mobilization on the day of surgery was the only independent predictor among ERAS items and was associated with reduced major complications (OR 0.42; 95% CI 0.22–0.77; $p = 0.005$).

Discussion

In this international multicenter study including patients undergoing PD without any selection criteria, high compliance to ERAS was obtained only in the pre- and intraoperative period. As expected, a high overall compliance (defined as more than 70%) was associated with significant reduction in complications and length of stay. Specific postoperative ERAS elements, such as avoidance of nasogastric tube, as well as early mobilization at postoperative day 0 and 1 were independent factors associated with decreased complications.

Postoperative outcomes such as LOS, readmission and clinically relevant pancreatic fistula were in the range of benchmark cutoffs as recently defined for pancreatic surgery [16]. Postoperative complications Grade $\geq$ 3 and mortality was 37%, and 3.1% in the present study, which is above the benchmark cutoffs of $\leq$ 30%, and $\leq$ 1.6%,

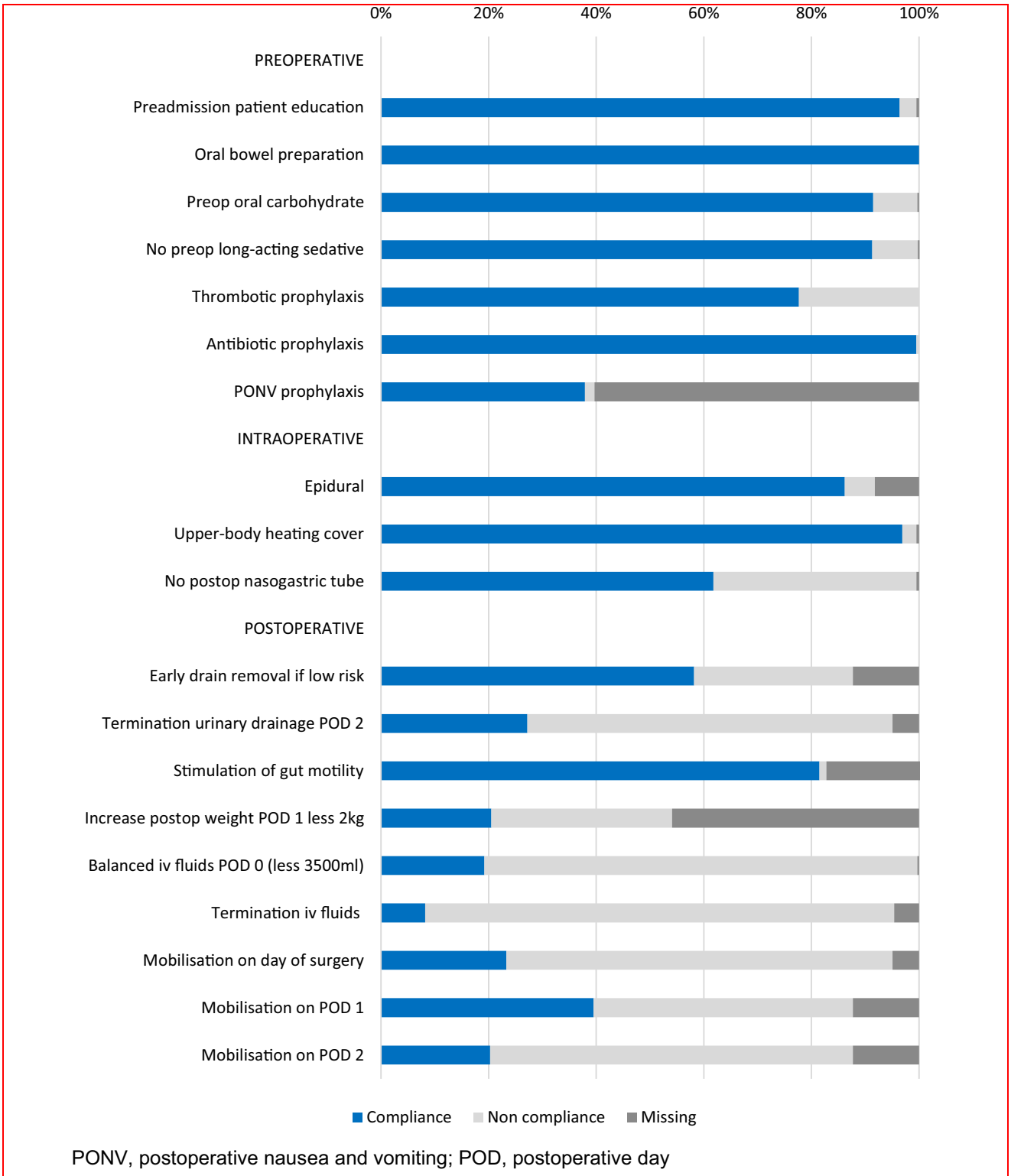

Fig. 1 Compliance by ERAS element in patients undergoing pancreatoduodenectomy. ERAS protocol compliance by element in the preoperative, intraoperative and postoperative phases for patients undergoing elective pancreatoduodenectomy. *PONV* postoperative nausea and vomiting, *POD* postoperative day

Table 3 Postoperative outcomes of patients undergoing elective pancreatoduodenectomy within an ERAS pathway (n = 390)

Category	*N*	%
Primary length of stay, median (IQR)	14 (9–22)	
Readmission	44	11.3
Total length of stay, median (IQR)	15 (10–24)	
Overall complications	338	83.7
Grading of most severe complication		
1–2 (minor)	180	46.2
3–4 (major)	144	36.9
Mortality	12	3.1
Pancreatic surgery specific complications		
Delayed gastric emptying	130	33.3
Clinically relevant pancreatic fistula (Grade B-C)	74	19.0
Post-pancreatectomy hemorrhage	34	8.7

IQR interquartile range

respectively [16]. However, this benchmark was established for low-risk patient excluding those with ASA IV, as opposed to our non-selected study population, which also included high-risk patients.

Several studies [17–21] reported successful outcome following implementation of ERAS for PD. However, only few single center studies reported the obtained compliance to each ERAS element [21–23]. Comparison of compliance between these studies is difficult as the number and definitions of elements included in the enhanced recovery pathway were heterogeneous. Williamsson et al. [21] reported an overall compliance, varying over time from 65 to 72%, similar to the overall compliance observed in this study. The compliance for the pre- and intra-operative periods was consistently high in three previous studies ranging from 84 to 100% per element [21–23]. Similarly, we observed high compliance in the pre- and intraoperative period with a mean compliance of 93% and 80%, respectively. Elements with $\geq$ 90% compliance were preoperative patient education, avoidance of bowel preparation, carbohydrate loading, avoidance of long-acting sedating medication, antibiotic prophylaxis and use of upper-body forced air heating cover. Only systematic postoperative nausea and vomiting prophylaxis (PONV) was a difficult element in the present study with a compliance of only 38%. Compliance to PONV prophylaxis was previously described in colorectal surgery and lack of prescription by the anesthetist in charge was identified as its reason [24]. If pre- and intra- operative elements are mostly easily achieved, similar conclusion cannot be drawn for the postoperative period. Indeed, the postoperative period contained the most challenging elements to apply in clinical practice. In the present study three main postoperative objective raised concern: fluid balance, urinary drainage removal (average compliance 18.8%), and adequate postoperative mobilization (average compliance 40.4%).

Braga et al. reported a compliance of 38% to 66% in the postoperative period, with mobilization (47%) and intravenous fluid withdrawal (38%) being the most difficult targets [22]. Williamsson et al. [21] also obtained low compliance in the postoperative period (48–58%). In the study of Zouros et al. [23] higher compliance was reported in the postoperative period, with 87% of patients achieving more than 2 h of mobilization on first postoperative day, but no data were reported on urinary drainage or weight gain. Postoperative elements are the most demanding, as they require supplementary combined effort from caregivers and patients. However, postoperative ERAS elements are essential as they have the greatest impact on optimal recovery as recently shown by a multicenter study in colorectal surgery [25]. In the latter study, the

Table 4 Compliance with ERAS pathway and postoperative outcomes

	Compliance < 70% n = 305	Compliance $\geq$ 70% n = 85	p value
Primary length of stay, median (IQR)	15 (10–23)	11 (7–16)	< 0.001
Total length of stay, median (IQR)	15 (11–25)	12 (7–19)	< 0.001
Overall complications, *n* (%)	271 (88.9)	67 (78.8)	0.029
Major complications (3–4), *n* (%)	132 (43.6)	24 (28.2)	0.012
Clinically relevant pancreatic fistula (Grade B–C), *n* (%)	63 (20.7)	11 (12.9)	0.119
Delayed gastric emptying, *n (%)*	103 (34.0)	27 (31.8)	0.795
Post-pancreatectomy hemorrhage, *n (%)*	28 (9.2)	6 (7.1)	0.666
Respiratory complications, *n (%)*	96 (31.6)	16 (18.8)	0.022
Infectious complications, *n (%)*	118 (38.8)	22 (25.9)	0.030
Cardiovascular complications, *n* (%)	63 (20.7)	13 (15.3)	0.284

IQR interquartile range

Table 5 Predictive factors for overall complications at 30 postoperative days

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
Age > 70 years	0.89	0.49–1.63	0.710			
Gender (female)	0.92	0.51–1.65	0.780			
BMI > 30 kg/m^2	2.54	0.88–7.31	0.075	1.45	0.47–4.50	0.517
ASA III/IV	2.71	1.44–5.08	0.001	1.72	0.80–3.70	0.169
WHO performance > 0	1.65	0.90–3.03	0.104			
Length surgery > 300 min	1.69	0.94–3.05	0.077	0.90	0.45–1.81	0.766
Malignant tumor	0.48	0.17–1.39	0.166			
Patient education	0.59	0.08–4.69	0.616			
Thrombotic prophylaxis	2.79	1.51–5.17	0.001	1.17	0.50–2.75	0.718
No postop nasogastric tube	0.31	0.15–0.66	0.001	0.31	0.14–0.97	0.043
Early drain removal if low risk	1.03	0.49–2.16	0.930			
Termination urinary drainage POD 2	1.40	0.69–2.86	0.353			
Laxatives	1.00	0.46–2.17	0.995			
Increased weight POD 1 < 2 kg	0.73	0.32–1.66	0.454			
Balanced iv fluids POD 0	0.58	0.30–1.14	0.113			
Mobilization on POD 0	0.31	0.16–0.58	< 0.001	0.28	0.14–0.97	0.043
Mobilization on POD 1	0.72	0.39–1.34	0.295			
Mobilization on POD 2	0.49	0.25–0.95	0.033	0.45	0.22–0.93	0.001

OR odds ratio, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *WHO* World Health Organization, *POD* postoperative day

Table 6 Predictive factors for major complications at 30 postoperative days

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
Age > 70 years	1.16	0.76–1.76	0.501			
Gender (female)	0.55	0.36–0.83	0.004	0.53	0.33–0.85	0.009
BMI > 30 kg/m^2	1.23	0.71–2.12	0.453			
ASA III/IV	1.73	1.14–2.61	0.009	1.47	0.87–2.48	0.150
WHO performance > 0	2.17	1.35–3.51	0.001	2.43	1.35–4.36	0.003
Length surgery > 300 min	0.88	0.58–1.35	0.563			
Malignant tumor	0.85	0.48–1.52	0.587			
Patient education	0.47	0.15–1.50	0.192			
Thrombotic prophylaxis	1.83	1.09–3.07	0.022	1.05	0.48–2.31	0.905
No postop nasogastric tube	0.64	0.42–0.97	0.033	0.69	0.39–01.22	0.201
Early drain removal if low risk	1.64	1.03–2.62	0.037	1.50	0.91–2.46	0.114
Termination urinary drainage POD 2	0.82	0.51–1.30	0.387			
Laxatives	0.69	0.41–1.18	0.174			
Increased weight POD 1 < 2 kg	0.69	0.39–1.23	0.207			
Balanced iv fluids POD 0	0.84	0.50–1.42	0.520			
Mobilization on POD 0	0.38	0.22–0.65	< 0.001	0.42	0.22–0.77	0.005
Mobilization on POD 1	0.94	0.61–1.46	0.782			
Mobilization on POD 2	1.12	0.67–1.87	0.688			

OR odds ratio, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *WHO* World Health Organization, *POD* postoperative day

compliance for postoperative elements was 40.3% among 2876 patients undergoing colorectal surgery [25].

The relationship between increased ERAS compliance and reduced postoperative complication was clearly established in a large international observational study for colorectal surgery [4]. For PD, previous series with 75 to 160 patients [21, 23] also reported that an increasing ERAS compliance was associated with reduced morbidity and shortened length of stay. We observed more favorable postoperative outcome when patient overall compliance was more than 70%, especially for respiratory complications and infectious complications. Of note, only less than a quarter of patients achieved such a good compliance and more efforts are still needed to increase compliance rates as well as to adapt the existing guidelines to the specificity of pancreatic resections.

Surprisingly, patients' characteristics and surgery related factors did not interfere with overall complication. With a majority of elderly patients, age itself was not a predictive factor for complications. The preoperative performance status, frequently altered in elderly patients, was an independent factor of major complication. A careful screening of the nutritional status and potential prehabilitation program might be of importance in these patients with altered preoperative performance [26]. Female gender was associated with a reduced risk of major complications, which is consistent with previous studies, which identified male gender as a predictor of complications as well as clinically relevant pancreatic fistula [27, 28].

Considering the impact of each individual ERAS element, only postoperative parameters were independent predictors of complications. For overall complications, avoidance of nasogastric tube as well as sufficient mobilization on the day of surgery and on postoperative day 2 were associated with reduced overall complications. Mobilization on postoperative day 2 was the only independent factor for reduced major complication. To our knowledge, no preexisting study analyzed the impact of each individual ERAS element in PD. Despite these postoperative elements are independently correlated with favorable outcome, they are partially modifiable factors, as postoperative complication itself can impinge proper postoperative mobilization. Therefore, mobilization elements can reflect the occurrence of complication. However, patient not able to be mobilized on the day of surgery definitely need more attention since they are more prone to develop complications.

One of the limitations of this study is the missing data, especially for compliance elements, which reached up to ten percent. Data were provided by four tertiary referral centers in four different countries. Since each participating center included in the database the patients, a potential limitation is selection bias. However, each center entered consecutive patients prospectively. A further limitation is that no details on compliance for liquid or solid feeding could be provided due to lack of consensus in the current guidelines and no specific data were available on postoperative diet. However, early diet at will was encouraged.

This large international cohort study suggested that high compliance to ERAS protocol is difficult to achieve for PD, particularly in the postoperative period. When achieved, high compliance was associated with improved outcome.

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