Role of Early Mobilization on the Clinical Course of Patients who Underwent Pancreaticoduodenectomy: A Retrospective Cohort Study

Takuya Fukushima,^{1,2} Tomohiko Adachi,³ Masatoshi Hanada,^{1,4} Takayuki Tanaka,³ Masato Oikawa,^{1,4} Hiroki Nagura,^{1,4} Susumu Eguchi³ and Ryo Kozu^{1,4}

¹Department of Rehabilitation Medicine, Nagasaki University Hospital, Nagasaki, Nagasaki, Japan
²Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center, Tokyo, Japan
³Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Nagasaki, Japan

⁴Department of Cardiopulmonary Rehabilitation Science, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Nagasaki, Japan

The length of hospital stay is an important outcome measure in patients who have undergone pancreaticoduodenectomy. Although postoperative complications are known to adversely affect the length of hospital stay (LOS), the influence of early mobilization on LOS has not been clarified yet. This study aimed to examine the impact of the initial ambulation day, which is one of the components of early mobilization, on LOS after pancreaticoduodenectomy. We retrospectively enrolled patients who underwent pancreaticoduodenectomy between January 2013 and December 2017. Postoperative complications were evaluated using the Clavien–Dindo classification (CDC) system. Patients were divided into two groups based on the median LOS (early and late-discharge groups) and compared to determine their characteristics. Multivariate logistic regression analysis was performed with LOS as the dependent variable. Patients in the late-discharge group were significantly older, had an initial ambulation delay, and had higher rates of advanced disease stages and a CDC grade ≥ IIIa than those in the early discharge group. In the multivariate logistic regression analysis, CDC grade ≥ IIIa, initial ambulation day, and age were found to be significant independent factors associated with LOS. Our results demonstrated that not only postoperative complications, but also the initial ambulation day, could affect LOS after pancreaticoduodenectomy, emphasizing the importance of early ambulation for patients who undergo this surgery.

Keywords: early mobilization; initial ambulation day; length of stay; pancreaticoduodenectomy; postoperative complication

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Introduction

Pancreaticoduodenectomy is a well-established surgical procedure for the management of pancreatic and biliary tract neoplasms. With advancements in surgery, the mortality rate after pancreaticoduodenectomy has decreased to less than 5% in high-volume centers (Narayanan et al. 2018). However, pancreaticoduodenectomy is an invasive procedure that involves vessel and/or other organ resection, requires a longer operation time, and is associated with more blood loss than other abdominal surgeries; furthermore, its postoperative complication rate remains high (up to approximately 50%) (Gouma et al. 2000; Tani et al. 2005).

Postoperative complications have adverse effects on the length of hospital stay (LOS) (Chaudhary et al. 2015; Jiang et al. 2019), hospital readmission (Howard et al. 2019), overall survival (Pugalenthi et al. 2016), and medical costs (Brown et al. 2014). Therefore, the analysis of LOS after pancreaticoduodenectomy is a crucial issue. In recent years, not only postoperative complications but also other factors such as age, body mass index (BMI), blood

Correspondence: Takuya Fukushima, Ph.D., Department of Musculoskeletal Oncology and Rehabilitation, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.

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e-mail: takuyafukushima321@yahoo.co.jp

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transfusion, surgical procedure, and fluid intake have been reported to be associated with LOS (Xie et al. 2013), suggesting the importance of a multifaceted perspective. Thus, enhanced recovery after surgery (ERAS) pathways, which are multimodal, and evidence-based approaches to optimize patient outcome after surgery are recommended. ERAS involves a multidisciplinary team approach and careful review of all aspects of operative and perioperative care such as optimal pain control (including regional anesthesia), minimally invasive techniques, early mobilization, and nutritional support (Xiong et al. 2016).

Early mobilization, including postoperative sitting, standing, and ambulation, has been advocated for patients undergoing major surgery to enhance recovery. Previous studies have revealed that early mobilization could improve functional capacity (de Almeida et al. 2017), reduce postoperative complications (Hanada et al. 2018), and shorten LOS after abdominal and thoracic surgery (Castelino et al. 2016). Although early mobilization is strongly recommended in the guidelines for successful surgical outcomes after pancreaticoduodenectomy, there is a lack of evidence due to the lack of scientific data (Lassen et al. 2013; Xu et al. 2018). To the best of our knowledge, there is only one study that claims reduced pulmonary complications and a shortened LOS after pancreaticoduodenectomy because of that perioperative rehabilitation (Kitahata et al. 2018). However, although the importance of ERAS after pancreaticoduodenectomy is recognized in clinical settings, the specific impact of early mobilization in patients who have undergone pancreaticoduodenectomy has not been clarified with regard to postoperative LOS. We hypothesized that early mobilization in patients who have undergone pancreaticoduodenectomy may have an impact on postoperative complications and LOS. Hence, this study aimed to identify the impact of early mobilization on postoperative LOS in patients who underwent pancreaticoduodenectomy.

Materials and Methods

Study design and study population

This was a single-center, retrospective cohort study conducted at Nagasaki University Hospital. Ethical approval was obtained from the Human Ethics Review Committee of Nagasaki University Hospital (approval number: 18011515) and carried out according to the Declaration of Helsinki. Patients who underwent pancreaticoduodenectomy between January 2013 and December 2017, consecutively, were enrolled in this study. The inclusion criteria were as follows: patients diagnosed with pancreatic and pancreatic head cancer, intraductal papillary mucinous adenoma, intraductal papillary mucinous neoplasm, pancreatic neuroendocrine tumor, intraductal papillary mucinous carcinoma, serous cystic tumors, and gastrinomas; patients who underwent pancreatectomy, including pancreaticoduodenectomy, pylorus-preserving pancreaticoduodenectomy, and subtotal stomach-preserving pancreaticoduodenectomy; patients with preoperative ambulation who were independent; patients with confirmed early mobilization from medical records. Patients in whom early mobilization could not be confirmed were excluded from the study.

Operative procedure

During the study period, the operative procedure was the same as that described in a previous study (Adachi et al. 2019). In cases of portal invasion with invasive carcinoma of the pancreatic head, portal vein reconstruction with endto-end anastomosis was performed. For this reconstruction, pancreatic anastomosis was performed using pancreaticojejunostomy with duct-to-mucosa anastomosis in all patients. Additionally, a short 5-Fr lost stent was inserted in all cases. All choledochojejunostomies were performed via the retrocolic route, and all gastrojejunostomies were performed via the antecolic route. Two closed-suction drains were placed behind the area of choledochojejunostomy and near the area of pancreaticojejunostomy and pulled out from both sides of the abdominal wall. Laparoscopic procedures are often performed for low-grade malignant tumors.

Perioperative management and early mobilization protocol

Preoperative physiotherapy education facilitated by a physiotherapist provided information on the importance of postoperative early mobilization, deep diaphragmatic breathing exercises, and airway clearance techniques for the prevention of postoperative pulmonary complications. The physiotherapist began conducting early mobilization on postoperative day (POD) 1 with due precaution. In accordance with a previous study (Conceicao et al. 2017), the starting criteria of early mobilization was defined as follows: 40 bpm < heart rate < 130 bpm; 90 mmHg < systolic arterial pressure < 200 mmHg; 60 mmHg < mean arterial pressure < 110 mmHg; 5 breaths per minute < respiratory rate < 40 breaths per minute, peripheral oxygen saturation \geq 90%; and sufficient level of consciousness that allowed correct understanding and execution of commands. The physiotherapist checked the vital signs and level of consciousness with the patient in the supine position, and head-up was performed if no abnormalities were observed. The patient was then shifted to sitting on the edge of the bed with the lower extremities hanging. In this study, sitting was defined as maintaining this position for more than 5 minutes at least once a day. Then, in the next step of the mobilization protocol, the patient progressed to a standing position. Afterwards, we decided to start ambulation if there were no recognized abnormal vital signs such as tachycardia or orthostatic hypotension, and symptoms such as nausea and vomiting when the patient took a standing position. The patient's subjective and objective findings were assessed during ambulation. In this study, ambulation was defined as the ability to leave the hospital room regardless of the use of walking aids.

Measurements

General and clinical data such as age, sex, BMI, disease type, disease stage, and preoperative blood biochemistry were obtained from medical records. Preoperative nutritional status was evaluated using the geriatric nutritional risk index (GNRI) formula: GNRI = [1.489 × albumin (g/dL)] + [41.7 × (weight/ideal weight)], where the ideal weight was calculated using the formula [height (m²) × 22 (BMI)] (Yamada et al. 2008). Data on the surgical type, laparoscopic usage, operation time, and operative blood loss were collected as operative parameters.

The parameters of early mobilization (the initial sitting, standing, and ambulation days) and LOS after pancreaticoduodenectomy were evaluated. Based on a previous study (Xie et al. 2013), we defined the discharge criteria as follows: independent in activities of daily living, oral intake ability, normal body temperature for 3 consecutive days, no obvious discomfort, and normal tiredness. We classified patients into early- and late-discharge groups according to the median LOS (Ripetti et al. 2019).

Postoperative complications until discharge were evaluated using the Clavien-Dindo classification (CDC) system, which consists of five grades: grade I, any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions; grade II, requiring pharmacological treatment with drugs; grade III, requiring surgical, endoscopic, or radiological intervention (grade IIIa, intervention without general anesthesia; grade IIIb, intervention under general anesthesia); grade IV, life-threatening complications requiring intensive care unit management (grade IVa, single-organ dysfunction; grade IVb, multiorgan dysfunction); and grade V, patient death (Dindo et al. 2004). Postoperative complications with a CDC grade of IIIa or higher were considered clinically significant (Neeman et al. 2020). Based on the criteria of the International Study Group for Pancreatic Fistula (Bassi et al. 2017), even a single instance of drain reinsertion or exchange was deemed grade B, and a grade of B or C was considered to represent the presence of pancreatic fistula in this study (Adachi et al. 2019). Delayed gastric emptying was defined according to the definition given by the International Study Group for Pancreatic Surgery (Wente et al. 2007).

LOS and the effect of early mobilization on LOS were examined, with patient characteristics compared between the two groups.

Statistical analysis

Data were analyzed using IBM SPSS Statistics software version 26 (IBM Corp., Chicago, IL, USA). To verify the characteristics of the early- and late-discharge groups, the two groups were compared. The Shapiro–Wilk test was used to analyze the normality of the data. Normally distributed data were analyzed using Student's t-test, nonnormally distributed data were analyzed using the Mann– Whitney U test, and categorical data were analyzed using

the chi-square test for between-group comparison. Multivariate logistic regression analysis was performed to identify the effect of the independent factors on LOS after pancreaticoduodenectomy, adjusting for risk factors that showed least significance (P < 0.1) between the two groups. Multivariate analysis was performed to determine the independent factors associated with the initial ambulation day, adjusting for risk factors that showed least significance (P < 0.1) in the univariate analysis. P values < 0.05 were considered statistically significant. Additionally, comparisons were made between the early- and latedischarge groups among patients with delayed mobilization, defined as the inability to start ambulating by POD 3 (Kitahata et al. 2018). Data were expressed as median (interquartile range [IQR]) or numbers and percentage of patients.

Results

Of the 85 eligible patients, five were excluded because of missing data on early mobilization. Consequently, 80 patients were analyzed in this study (Fig. 1). The demographic data and clinical characteristics and a comparison of the early- and late-discharge groups are presented in Tables 1 and 2. The surgical type was mostly subtotal stomach-preserving pancreaticoduodenectomy, and approximately 25% of the patients underwent laparoscopic surgery. The patients were divided into two groups according to the median LOS (21.0 days): the early-discharge (n = 41; median, 16.0 days) and late-discharge groups (n = 39; median, 33.0 days) (Fig. 1). The medians of the initial sitting, standing, and ambulation days were PODs 1, 2, and 2, respectively.

Patients in the late-discharge group were significantly older, had a higher rate of advanced disease stages, and a CDC grade of \geq IIIa compared than those in the earlydischarge group. The late-discharge group with CDC grade \geq IIIa consisted of three patients with pancreatic fistula (23.1%), two patients with bile leakage (15.4%), one patient with lymph leakage (7.7%), one patient with gastric emptying leakage (7.7%), one patient with hemorrhage (7.7%), and five patients with other conditions (38.4%). There was no significant difference between the two groups in the initial sitting and standing days (sitting: median of both groups, 1.0 days; P = 0.452; standing: median of both groups, 2.0 days; P = 0.261). Meanwhile, the initial ambulation day showed statistically significant differences between the two groups (median of both groups, 2.0 days; P = 0.043; actual average, 1.8 and 4.4 days, respectively). Although the clinical characteristics, such as disease and surgical type, were varied, there was no significant difference between the two groups.

We included variables with P < 0.1 in the betweengroup comparison of the multivariate logistic regression analysis, adjusted by surgical procedure. It revealed that CDC grade \geq IIIa, initial ambulation day, and age were significant independent factors associated with LOS (Table 3).

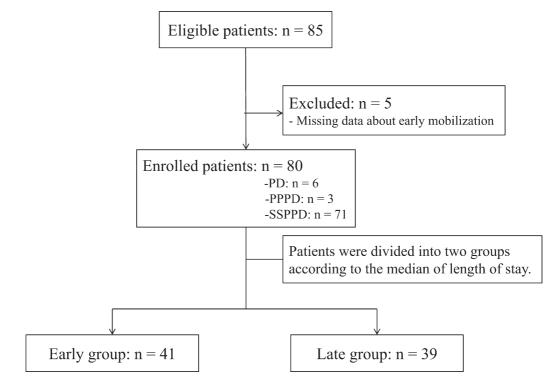


Fig. 1. Flowchart of the enrollment procedure.

PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

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Characteristics	Total $(n = 80)$	Early group $(n = 41)$	Late group $(n = 39)$	P-value
Age (years)	69.5 [63.0-75.5]	67.0 [61.5-73.5]	71.0 [67.0-76.0]	0.037
Male	47 (55.0%)	25 (61.0%)	22 (56.4%)	0.678
BMI (kg/m ²)	20.7 [19.2-23.2]	20.5 [19.0-22.5]	21.1 [19.4-24.1]	0.235
Preoperative blood biochemistry				
Total bilirubin (g/dL)	0.8 [0.8-1.3]	0.8 [0.6-1.5]	0.8 [0.6-1.3]	0.643
White blood cell ($\times 10^3$ /mm ³)	5.3 [4.3-6.3]	5.4 [4.4-6.8]	4.9 [4.3-6.3]	0.326
Serum albumin (g/dL)	3.8 [3.5-4.2]	3.8 [3.7-4.2]	3.8 [3.3-4.2]	0.148
Lymphocytes (×10 ³ /mm ³)	1.4 [1.0-1.8]	1.4 [1.1-1.8]	1.4 [1.0-1.8]	0.456
Creatinine (mg/dL)	0.7 [0.6-0.9]	0.8 [0.7-0.9]	0.7 [0.6-0.9]	0.204
Preoperative GNRI	96.4 [92.0-103.8]	96.8 [93.1-103.5]	96.0 [89.5-107.7]	0.593
Preoperative physiotherapy	48 (60.0%)	21 (51.2%)	27 (69.2%)	0.100
Preoperative comorbidity				
Diabetes mellitus	27 (33.8%)	15 (36.6%)	12 (30.8%)	0.582
Chronic obstructive pulmonary disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Interstitial lung disease	1 (1.3%)	0 (0.0%)	1 (2.6%)	0.302
Heart disease	1 (1.3%)	0 (0.0%)	1 (2.6%)	0.302
Atrial fibrillation	1 (1.3%)	1 (2.4%)	0 (0.0%)	0.326
Chronic kidney disease	2 (2.5%)	0 (0.0%)	2 (5.1%)	0.142
Cerebrovascular disease	5 (6.3%)	3 (7.3%)	2 (5.1%)	0.686

Table 1.	Demographic	and blood	biochemical	data of	patients.
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Values are presented as median [interquartile range] or n (%). BMI, body mass index; GNRI, geriatric nutritional risk index.

Characteristics	Total $(n = 80)$	Early group $(n = 41)$	Late group $(n = 39)$	P-value
Diagnosis				0.491
Pancreatic cancer	49 (61.3%)	24 (58.5%)	25 (64.1%)	
Pancreatic head cancer	8 (10.0%)	7 (17.1%)	1 (2.6%)	
Intraductal papillary mucinous adenoma	7 (8.8%)	2 (4.9%)	5 (12.8%)	
Intraductal papillary mucinous neoplasm	4 (5.0%)	2 (4.9%)	2 (5.1%)	
Pancreatic neuroendocrine tumor	4 (5.0%)	2 (4.9%)	2 (5.1%)	
Intraductal papillary mucinous carcinoma	3 (3.7%)	1 (2.4%)	2 (5.1%)	
Serous cystic tumors	3 (3.7%)	2 (4.9%)	1 (2.6%)	
Gastrinoma	2 (2.5%)	1 (2.4%)	1 (2.6%)	
Disease stage				0.028
0	22 (27.5%)	9 (22.0%)	13 (33.3%)	
Ι	4 (5.1%)	3 (7.3%)	1 (2.6%)	
II	12 (15.0%)	10 (24.4%)	2 (5.2%)	
III	18 (22.5%)	11 (26.8%)	7 (17.9%)	
IV	21 (26.3%)	5 (12.2%)	16 (41.0%)	
Unknown	3 (3.8%)	2 (2.5%)	0 (0.0%)	
Type of surgery				0.778
PD	6 (7.5%)	2 (4.9%)	4 (10.3%)	
PPPD	3 (3.8%)	2 (4.9%)	1 (2.6%)	
SSPPD	71 (88.8%)	37 (90.3%)	34 (87.2%)	
Laparoscopic surgery	13 (16.3%)	7 (17.1%)	6 (15.4%)	0.838
Operation time (min)	430.5 [375.0-510.5]	419.0 [368.0-496.0]	454.0 [378.0- 519.0]	0.381
Operative blood loss (mL)	860.0 [410.0-1,347.3]	666.0 [485.0-1,265.0]	1050.0 [360.0-1,652.0]	0.244
CDC grade ≥ IIIa	14 (17.5%)	1 (2.4%)	13 (33.3%)	< 0.001
Pancreatic fistulas	3 (3.8%)	0 (0.0%)	3 (7.7%)	0.070
Delayed gastric empty	4 (5.0%)	1 (2.4%)	3 (7.7%)	0.281
Initial sitting (days)	1.0 [1.0- 2.0]	1.0 [1.0- 2.0]	1.0 [1.0-2.0]	0.452
Initial standing (days)	2.0 [1.0-2.0]	2.0 [1.0-2.0]	2.0 [1.0-3.0]	0.261
Initial ambulation (days)	2.0 [2.0- 2.0]	2.0 [1.0-2.0]	2.0 [1.0-3.0]	0.043
LOS (days)	21.0 [15.5-33.0]	16.0 [12.0- 19.0]	33.0 [7.0- 43.0]	< 0.001

Values are presented as median [interquartile range] or n (%).

CDC, Clavien–Dindo classification; LOS, length of stay; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

Table 3.	Factors	associated	with	length	of stay	(LOS).
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Parameters	Multivariate logistic regression analysis		
Farameters	OR (95% CI)	P-value	
Age	1.784 (1.015-3.137)	0.018	
CDC grade ≥ IIIa	23.979 (2.011-285.931)	0.012	
Initial ambulation	1.784 (1.015-3.137)	0.044	

95% CI, 95% confidence interval; CDC, Clavien–Dindo classification; LOS, length of stay; OR, odds ratio.

Meanwhile, disease stage (P = 0.384) and pancreatic fistula (P = 0.999) were not significant factors.

In a subanalysis of patients with delayed mobilization, early discharge was only observed in one patient, while all others were discharged late (n = 8, 88.9%). Although it was not possible to perform a full statistical analysis of the two groups, the late-discharge group was characterized by a higher rate of CDC grade of \geq IIIa (62.5%).

In the univariate analysis, only the GNRI had a P-value < 0.1, but no factors were found to be significantly different. Therefore, multivariate analysis was not performed (Table 4).

Table 4. Factors associated with initial ambulation.

Parameters	Univariate analysis			
Parameters	β	P-value		
Age	0.052	0.648		
Sex	0.134	0.235		
BMI	-0.115	0.309		
Total bilirubin	-0.062	0.582		
White blood cell	-0.107	0.345		
Lymphocytes	-0.100	0.379		
Creatinine	-0.176	0.119		
GNRI	-0.205	0.069		
Preoperative PT	0.094	0.405		
Diabetes mellitus	0.089	0.431		
Disease type	0.059	0.605		
Disease stage	0.167	0.139		
Type of surgery	0.099	0.385		
Laparoscopic surgery	0.081	0.474		
Operation time	-0.136	0.230		
Operative blood loss	-0.009	0.938		

BMI, body mass index; GNRI, geriatric nutritional risk index; PT, physical therapy.

Discussion

To the best of our knowledge, this is the first study that attempted to evaluate the specific impact of initial ambulation-centered early mobilization on LOS in patients who underwent pancreaticoduodenectomy. LOS is an important outcome measure for postoperative progress as well as for readmission, overall survival, and medical costs incurred in health-care systems (Lingsma et al. 2018; Court et al. 2020). Although the need for a multifaceted perspective of LOS after pancreaticoduodenectomy was inferred in previous studies, the effect of early mobilization on LOS remains to be determined. The main findings are as follows: early mobilization significantly affected LOS in patients who underwent pancreaticoduodenectomy; patients in the late-discharge group were significantly older, had a higher rate of CDC grade \geq IIIa, and delayed initial ambulation day than those in the early-discharge group.

Regarding the relationship between early mobilization and LOS, the initial ambulation day was one of the significant independent factors associated with LOS. A previous study showed that perioperative rehabilitation shortens LOS after pancreaticoduodenectomy, but the role of early mobilization has not been clarified (Kitahata et al. 2018). Stethen et al. (2018a, b) demonstrated that failure to ambulate early after bowel resection was associated with prolonged LOS, and our results were consistent with those of the previous report. Daskivich et al. (2019) also revealed that a lower step count on POD 1 was associated with higher odds of prolonged LOS after major surgery, suggesting that both the ambulation distance and frequency in the early postoperative period and the initial day of ambulation are important factors. In addition, our subanalysis revealed that delayed initial ambulation was associated with higher complication rates and prolonged LOS. These results also indicate that delay in mobilization after surgery strongly affects discharge, indicating that early mobilization could be one of the key components determining the clinical course after pancreaticoduodenectomy. This finding is beneficial to the implementation of rehabilitation in patients who had undergone pancreaticoduodenectomy.

We determined that patients in the late-discharge group were significantly older and had a higher rate of CDC grade \geq IIIa than those in the early-discharge group. Previous studies have shown that age and postoperative complications were associated with longer LOS (Xie et al. 2013; Chaudhary et al. 2015; Kim et al. 2017; Kobayashi et al. 2018; Pedziwiatr et al. 2018; Jiang et al. 2019). Our results were also consistent with those of the previous reports. The prolonged postoperative recovery probably reflects the decreased physical fitness and physiological capacity in older patients, as represented by frailty, in comparison with younger patients (Xie et al. 2013; Kobayashi et al. 2018). Therefore, it is anticipated that a higher rate of complications will occur in the late-discharge group than in the early-discharge group. Although it has been demonstrated that pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy were not affected by age (Kim et al. 2017), the complications, including pneumonia and atelectasis, after pancreaticoduodenectomy were associated with older age in previous studies (Lee et al. 2014; Kim et al. 2017; Yuan et al. 2018). Our results cannot clarify the relationship between age and postoperative complications, similar to a previous study (Yuan et al. 2018). However, preoperative morbidities (Kim et al. 2017) and poor physiological capacity such as musculoskeletal and cardiopulmonary function may contribute to postoperative complications. Therefore, the characteristics of the patients in the late-discharge group may be related to the physiological capacity decrease due to aging and complications.

Furthermore, CDC grade \geq IIIa was also a significant independent factor associated with LOS, similar to previous studies (Chaudhary et al. 2015; Jiang et al. 2019). It is easy to assume that LOS is prolonged due to postoperative complications such as pneumonia, pancreatic fistula, and delayed gastric emptying. In addition, given that delayed ambulation is associated with complications and prolonged LOS, and that pancreatic duodenectomy-specific complications such as pancreatic fistula and delayed gastric emptying are unlikely to occur on POD 1, the initial ambulation date may influence subsequent complications, and in turn, the LOS. In other words, this suggests that early mobilization may be effective in preventing postoperative complications and shortening LOS. Therefore, while paying full attention to cardiovascular reactions and symptoms, it is necessary to actively practice ambulation-based early mobilization after pancreaticoduodenectomy.

Unfortunately, we were not able to detect factors influencing the initial ambulation day. In the previous study, patients who develop delirium within the first 2 days of surgery were less likely to mobilize (Said et al. 2021). The study did not provide an objective assessment of delirium, which should be further investigated in a future study.

This study has several limitations. First, the sample size was relatively small. Second, this study was conducted at a single facility. From the viewpoint of generalization, we believe that a larger multicenter investigation will be necessary. Third, this was a retrospective study. LOS may be influenced by a variety of factors, including national cultural differences, facility policies, and insurance issues. Therefore, we cannot completely eliminate confounding factors, and further randomized controlled trials are required. Lastly, preoperative physical function and performance cannot be evaluated, which can affect the results. Although we focused on postoperative initial ambulation day as a marker of early mobilization in this study, further research will be necessary to consider the preoperative physical function in the future.

In conclusion, our study showed that early mobilization could affect LOS after pancreaticoduodenectomy, suggesting that it could be one of the key components determining LOS after pancreaticoduodenectomy. Consequently, it is necessary to initiate ambulation-based early mobilization as soon as possible after surgery. In the future, the effects of early mobilization should be verified in a randomized controlled trial.

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Conflict of Interest

The authors declare no conflict of interest.

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