Article

Early and Long-Term Morbidity and Mortality Following Pancreaticoduodenectomy for Periampullary Tumors in Elderly Patients

Ann. Ital. Chir., 2024 95, 2: 235–245
https://doi.org/10.62713/aic.3380

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Aim: The growing elderly population is facing an increasing risk of cancers, consequently raising the pancreatic cancer surgery rate. This study aimed to determine whether advanced age is a risk factor for morbidity and mortality following pancreaticoduodenectomy (PD) for periampullary tumors.

Materials and Methods: The present study included 90 patients who underwent PD for periampullary tumors. Patients were divided into two age-related groups, including those aged 60–74 years (n = 60) (Group 1) and those aged ≥75 years (n = 30) (Group 2). Each patient's characteristics, perioperative features, morbidity, and long-term results were evaluated retrospectively.

Results: In both univariate and multivariate logistic regression analyses, old age (≥75 years) was not a risk factor for morbidity and hospital mortality. The multivariate analysis demonstrated that male gender (p = **0.008**), pancreatic duct diameter (<3 mm) ($p <$ **0.001**), and length of hospital stay (p = 0.005) were independent risk factors for pancreatic fistula post-operation and reoperation. Additionally, hospital mortality was significantly associated with reoperation (p = **0.011**). The overall median survival was 27 ± 4.1 (18.8–35.1) months. Lymph node positivity ($p <$ **0.001**), neural tumor invasion (p = **0.026**), and age ≥75 years (p = **0.045**) were risk factors affecting the overall survival rate. Moreover, there was no statistically significant difference in terms of PD rates during the Coronavirus disease-19 (COVID-19) period among groups, and PD during this period was not related to the occurrence of pancreatic fistula.

Conclusion: PD can be performed effectively in selected elderly patients with tolerable morbidity and mortality rates.

Keywords: elderly; morbidity; mortality; pancreaticoduodenectomy; periampullary tumor

Introduction

Advancements in research and healthcare have led to an increase in average lifespan, age, and life expectancy globally [1,2]. Nevertheless, there has been an increase in digestive system cancers, especially pancreatic cancer, attributed to environmental, dietary, and genetic factors [3]. Pancreatic cancer in periampullary tumors is associated with a poor prognosi, including a five-year survival rate ranging from 2–11%, mainly due to delayed diagnosis, molecular heterogeneity, and resistance to systemic treatment [3,4,5]. The annual incidence of pancreatic cancer has increased in recent decades. In 2022 alone, approximately 62,210 new diagnoses were reported among adults in the USA, resulting in 49,830 deaths across genders [6].

Pancreaticoduodenectomy (PD) is a complex surgical technique primarily used to remove periampullary tumors or masses [5,6,7]. However, the Coronavirus disease-19 (COVID-19) pandemic has recently affected world, especially in the health field, with highly damaging results. In this period, there have been delays in cancer diagnosis and treatment due to restricted public access [8,9]. Patients generally prefer to attend low- or medium-volume centers for pancreatic surgery due to financial concerns, long waiting lists at high-volume centers (over 28 cases per year), the prevalence of low-volume intensive care units, high hospital occupancy rates, and the impact of the COVID-19 pandemic [10,11,12,13,14]. However, research suggests that low-volume centers have increased morbidity and mortality (11.4–14.5% mortality) rates in the elderly [14]. Furthermore, Bathe *et al.* [15] reported that those aged ≥75 years have a mortality rate of 25% compared to only 3.7% for those aged <75 years. Therefore, this study aimed to identify whether old age represents a risk factor for morbidity and mortality following PD for periampullary tumors.

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Materials and Methods

Patients and Methodology

This multidisciplinary study was conducted at our hospital from August 2010 to August 2021. A total of 90 patients who had been curatively treated for periampullary tumors, including cancers of the head and uncinate of the pancreas, distal choledochal, and ampulla of Vater without metastasis, were enrolled in the study. The study retrospectively evaluated clinical and perioperative findings as well as long-term survival. The patients were divided into two groups, one comprising those aged 60–74 years (n = 60) (Group 1) and another with those aged ≥75 years (n = 30) (Group 2).

Inclusion and Exclusion Criteria

This study included patients diagnosed with periampullary area tumors who underwent PD, were >18 years of age, and had normal hemodynamic parameters. The exclusion criteria included the identification of metastasis in the preoperative evaluation and lack of follow-up or if operated on at another hospital.

Assessment of the COVID-19 Infection

All patients underwent the COVID-19 polymerase chain reaction (PCR) test during the preoperative period of the COVID-19 pandemic. The surgery was postponed in patients who tested positive for the COVID-19 test in PCR or thoracal computed tomography (CT). Subsequently, those patients underwent PD two weeks after a negative COVID-19 PCR test. Symptomatic patients underwent the COVID-19 PCR test or thorax CT in the postoperative period.

Surgery Management

Following general anesthesia, most patients underwent direct laparotomy. Laparoscopy was performed in patients with distant metastasis or peritoneal cancer. After abdominal entry, PD was performed in the absence of metastasis in the liver, splenic hilum, or pelvis (Fig. 1).

Volume Center, Postoperative Care, Anticoagulation, and Follow-up

Over five years, we consistently conducted over 15 pancreaticoduodenectomies (PDs) annually, with the number of cases steadily rising each year. Following PD, all patients were transferred to the intensive care unit (ICU) for comprehensive monitoring of vital signs, and early postoperative drainage was performed. Oral feeding was initiated after the gastrointestinal tract functions resumed. Drainage amylase levels were measured for pancreatic fistula three days postoperatively. Pancreatic fistula after the operation (PFAO) was managed according to the pancreatic fistula grade. All patients were discharged with low-molecular-weight heparin during the first postoperative month. Subsequent follow-up appointments were scheduled at three-month intervals during the first year postoperatively, followed by visits every six months thereafter in the outpatient clinic.

Chemotherapy and Radiotherapy

Adjuvant therapy aims to prevent long-term disease recurrence and provide prolonged survival. Various studies have investigated different adjuvant treatment modalities, including bolus 5-fluorouracil (5FU), gemcitabine, 5FU/folinic acid, gemcitabine/capecitabine, S-1 (tegafur), modified 5FU/irinotecan/oxaliplatin (mFOLFIRINOX), and gemcitabine/nab-Paclitaxel, either alone or in combination with radiotherapy [16,17]. In the current study, chemotherapy, the application method, and the dosing schedule for adjuvant or palliative purposes were decided post-surgery [18]. No patient in this study received preoperative palliative radiation.

Statistical Analysis

The Kolmogorov-Smirnov test was used to investigate whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentages (%), while quantitative data were given as mean ± standard deviation (SD) or median (min-max), where applicable. Student's *t*-test was used to compare mean differences between age groups, and the Mann-Whitney U test was applied for comparisons involving non-normally distributed data. Pearson's χ^2 test was used to analyze qualitative data unless otherwise specified. In 2 × 2 contingency tables comparing categorical variables, the Continuity corrected χ^2 test was used when one or more cells had an expected frequency of 5–25; otherwise, Fisher's exact test was used when one or more cells had an expected frequency of 5 or less. For all R × C contingency tables comparing categorical variables, the Fisher Freeman Halton test was used when ¼ or more of the cells had an expected frequency of 5 or less. Associations between patients' demographic and clinical characteristics with main outcomes (i.e., pancreatic fistula, reoperation, and hospital mortality) were assessed using univariate logistic regression analyses to determine statistical significance. Multiple logistic regression models were constructed to determine the best independent predictor(s) of the main outcomes. Variables with a univariable test *p*-value of <0.25 were considered candidates for the multivariable model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each independent variable. Univariate Cox proportional hazard regression models were generated to determine which factor(s) affect overall survival (OS). The Multiple Cox proportional hazard regression model was then employed to identify the most influential independent predictor(s) of OS. Variables with a univariable test *p*-value of <0.25 were accepted as candidates for the multivariable model. Hazard ratios (HR) and 95% confidence intervals (CI) were also obtained. Data were analyzed with IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). A *p*-value of less than 0.05 was considered statistically significant.

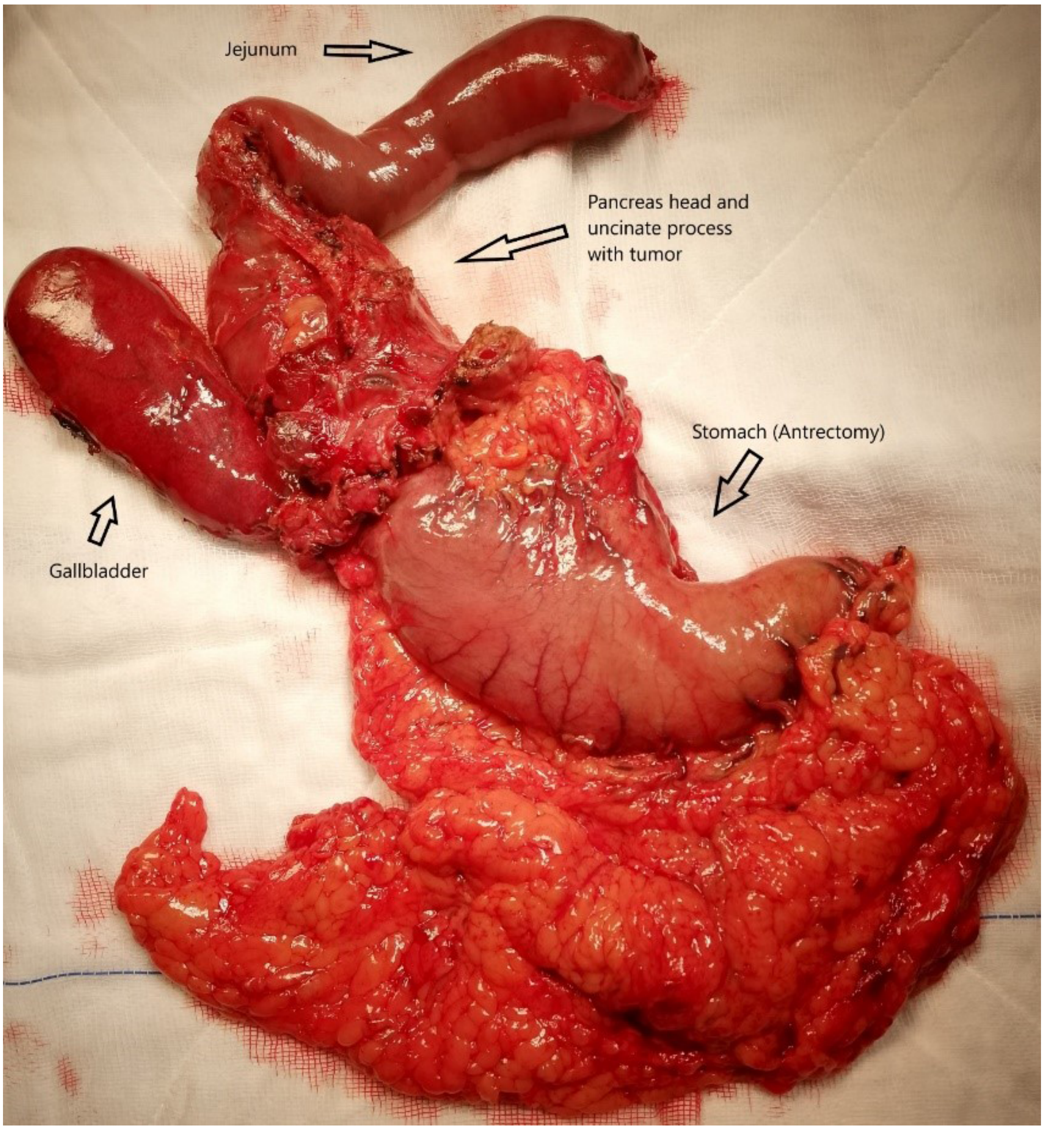

Fig. 1. Pancreaticoduodenectomy specimen.

Results

Patient Characteristics, Diagnosis, and Perioperative Findings

Out of the 134 total patients, 90 were enrolled in the study, with 44 excluded for failing to meet the inclusion criteria (unsuitable age, follow-up, or inadequate clinical/operative features). The median age was 69 (63.75–75) years ($p < \mathbf{0.001}$). Of these, 33 (36.7%) were female and 57 (63.3%) were male, with no significant gender difference ($p = 0.486$). The prevalence of comorbidities was similar across groups, with the most common being hypertension (48.8%), diabetes mellitus (33.3%), and coronary artery disease (12.2%). Body mass index (BMI) values were comparable between groups ($p > 0.999$). The ASA score in the elderly group was significantly higher compared to their younger counterparts ($p < \mathbf{0.001}$) (Table 1).

The most common diagnoses were pancreas head cancer (43.3%), ampulla of Vater tumors (28.9%), and distal choledochal tumors (18.9%) ($p = 0.903$). The median follow-up was 13.2 (0.07–150.6) months, with a notably longer follow-up period observed in Group 1 compared to Group 2 [25.1 (0.07–150.6) vs. 8 (0.16–67.1)]. The prolonged follow-up occurred because those aged 75 years and above underwent surgery later in the study period ($p = \mathbf{0.008}$) (Tables 1,2).

There is a numerical difference between the two groups in our study (n = 60 vs n = 30). The leading cause of this distinction is that the PDs performed during the COVID-19 period decreased, resulting in a reduced sample size in the elderly group.

Preoperative Laboratory, Histopathological Features, and Treatment Protocol

The median preoperative carcinoma-embryogenic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were 3.2 (0.6–57.9) µg/L and 57.5 (0–12,000) U/mL ($p >$

Table 1. Patient's characteristics and perioperative features.

	Total (n = 90)	Group 1 (60–74 years) (n = 60)	Group 2 (≥75 years) (n = 30)	*p* value
Gender (F/M) (%)	33 (36.7)/57(63.3)	24 (40.0)/36 (60.0)	9 (30.0)/21 (70.0)	0.486†
Body mass index (kg/m^2)	28 (26–28)	27 (20–35)	27 (18–40)	0.612‡
Comorbidity	52 (58.4)	34 (57.6)	18 (60.0)	>0.999†
ASA				**<0.001**¶
2	36 (40.0)	31 (51.7)	5 (16.7)	
3	56 (58.9)	29 (48.3)	24 (80.0)	
4	1 (1.1)	-	1 (3.3)	
ASA>3	54 (60.0)	29 (48.3)	25 (83.3)	**0.003**†
Diagnosis				0.903¶
Pancreas head	39 (43.3)	25 (41.7)	14 (46.7)	
Ampulla Vatery	26 (28.9)	18 (30.0)	8 (26.7)	
Distal Choledochal	17 (18.9)	11 (18.3)	6 (20.0)	
Duodenum	6 (6.7)	5 (8.3)	1 (3.3)	
Pancreas uncinate	2 (2.2)	1 (1.7)	1 (3.3)	
Pancreas tissue nature				0.551¥
Soft	32 (35.6)	19 (31.7)	13 (43.3)	
Hard	27 (30.0)	19 (31.7)	8 (26.7)	
Normal	31(34.4)	22 (36.7)	9 (30.0)	
Pancreatic anastomosis				0.629¶
Wirsungojejunostomy	67 (74.4)	46 (76.7)	21 (70.0)	
Dunking pancreatojejunostomy	22 (24.4)	13 (21.7)	9 (30.0)	
Blumgart anastomosis	1 (1.1)	1 (1.7)	-	
Growth in culture	28 (31.1)	19 (31.7)	9 (30.0)	>0.999†
Preoperative biliary drainage	49 (54.4)	31 (51.7)	18 (60.0)	0.600†
Length of the hospital stay	17.5 (11–25.25)	19.5 (15.7–30)	19 (13–30.5)	0.861‡
Operation in the COVID-19 period	15 (16.6)	7 (11.6)	8 (26.6)	0.134†
Positive COVID-19 test in postop.	1 (1.1)	-	1 (3.3)	N/A
Operation time (min)	325 (300–420)	320 (300–420)	320 (300–420)	0.458‡
Portal vein resection or repair	5 (5.6)	5 (8.3)	-	0.165§
Pancreatic duct diameter	3 (2.88–6)	3 (2–4.5)	4 (3–9)	0.071‡
<3 mm	50 (55.6)	37 (61.7)	13 (43.3)	0.154†
Octreotide	29 (32.2)	19 (31.7)	10 (33.3)	>0.999†
Internal stent	44 (48.9)	30 (50.0)	14 (46.7)	0.941†
Postop pancreatitis	8 (8.9)	3 (5.0)	5 (16.7)	0.078§
Number of the removed LN	15 (2–43)	15 (3–43)	10 (2–24)	**0.038**‡
Percutaneous drainage	9 (10.3)	7 (12.1)	2 (6.9)	*0.712*§
Reoperation	18 (20.0)	14 (23.3)	4 (13.3)	0.402†
Curative resection	83 (92.2)	55 (91.7)	28 (93.3)	>0.999§
Follow up (month)	13.2 (0.07–150.6)	25.1 (0.07–150.6)	8.0 (0.1–67.1)	**0.008**‡
Complication				
Surgical site infection (SSI)	28 (31.1)	17 (28.3)	11 (36.6)	0.573†
Superficial SSI (sSSI)	15 (16.6)	8 (13.3)	7 (23.3)	0.368†
Deep SSI	13 (14.4)	9 (15.0)	4 (13.3)	>0.999§
Pancreas fistula	35 (38.9)	26 (43.3)	9 (30.0)	0.320†
Grade A	20 (22.2)	14 (23.3)	6 (20.0)	
Grade B	6 (6.7)	4 (6.7)	2 (6.7)	
Grade C	9 (10.0)	8 (13.3)	1 (3.3)	
Hemorrhage	9 (10.0)	8 (13.3)	1 (3.3)	0.262§
Clavien & Dindo ≥3A	29 (32.2)	19 (31.7)	10 (33.3)	>0.999†

ASA, American Society of Anesthesiologists; Clavien & Dindo, Clavien and Dindo complication classification; F/M, Female/Male; sSSI, Superficial surgical site infection; COVID-19, Coronavirus disease-19; LN, Lymph node.

† Continuity correceted χ^2 test; ‡ Mann Whitney U; ¶ Fisher Freeman Halton test; ¥ Pearson's χ^2 test; § Fisher's exact test; N/A: Not applicable. Bold words of *p* value is statistical significant.

Table 2. Diagnosis, histopathological finding and treatment protocols in groups.

	Total (n = 90)	Group 1	Group 2	*p* value
		(60–74 years) (n = 60)	(≥75 years) (n = 30)	
Laboratory				
CEA (μg/L)	3.2 (0.6–57.9)	3.4 (0.6–11.4)	2.9 (0.9–57.9)	0.558†
CA19-9 (U/mL)	57.5 (0–12,000)	41.5 (1.0–4253.0)	170 (0–12,000)	0.073†
Neutrophil to lymphocyte ratio	245 (19–4522)	226.0 (19.0–4522.0)	296.0 (109.0–2825.0)	0.056†
Platelet to lymphocyte ratio	15,136 (3958–82,000)	14,318.5 (3958.0–62,609.0)	16,291.5 (7956.0–82,000.0)	0.238†
Total bilirubin (mg/dL)	3.0 (0.2–29.8)	2.1 (0.2–27.4)	3.3 (0.3–29.8)	0.611†
Albumin (mg/dL)	3.4 (2.4–30.8)	3.5 (2.5–29.6)	3.1 (2.4–30.8)	0.054†
Histopathological features (n) (%)				0.898¶
Adenocarcinoma	72 (80.0)	50 (83.3)	22 (73.3)	
NET	3 (3.3)	2 (3.3)	1 (3.3)	
Carcinoma *in situ*	4 (4.4)	2 (3.3)	2 (6.7)	
Chronic pancreatitis	4 (4.4)	2 (3.3)	2 (6.7)	
IPMN	3 (3.3)	2 (3.3)	1 (3.3)	
Others *	4 (4.4)	2 (3.3)	2 (6.7)	
Malignancy rate (%)	77 (85.5)	54 (90)	23 (76.6)	0.205¥
TNM staging				**0.007**¶
In situ or benign	13 (14.4)	6 (10.0)	7 (23.3)	
1	27 (30.0)	23 (38.3)	4 (13.3)	
2	41 (45.6)	23 (38.3)	18 (60.0)	
3	7 (7.8)	7 (11.7)	-	
4	2 (2.2)		1 (3.3)	
T				0.397¶
0	13 (14.4)	6 (10.0)	7 (23.3)	
1	5 (5.6)	3 (5.0)	2 (6.7)	
2	42 (46.7)	28 (46.7)	14 (46.7)	
3	26 (28.9)	20 (33.3)	6 (20.0)	
4	4 (4.4)	3 (5.0)	1 (3.3)	
Lymph node positivity	40 (44.4)	24 (40.0)	16 (53.3)	0.330¥
Metastasis	2 (2.2)	1 (1.7)	1 (3.3)	>0.999§
Tumor grade				0.923#
Well	30 (38.0)	20 (37.0)	10 (40.0)	
Moderate	31 (39.2)	22 (40.7)	9 (36.0)	
Poor	18 (22.8)	12 (22.2)	6 (24.0)	
Lymphovascular invasion	37 (41.1)	23 (38.3)	14 (46.7)	0.596¥
Nerve invasion	42 (46.7)	27 (45.0)	15 (50.0)	0.823¥
Treatment protocol				
Gemcitabine	31 (36.5)	25 (43.9)	6 (21.4)	0.075¥
Folfirinox	15 (17.6)	13 (22.8)	2 (7.1)	0.128§
Gemcitabine and Folfirinox	11 (12.9)	10 (17.5)	1 (3.6)	0.092§
Cisplatin, paclitaxel, oxaliplatin	10 (11.8)	8 (14.0)	2 (7.1)	0.486§
Capecitabine	11 (12.9)	6 (10.5)	5 (17.9)	0.493§
Radiotherapy	21 (24.1)	16 (27.1)	5 (17.9)	0.500¥
Hospital mortality	10 (11.1)	6 (10.0)	4 (13.3)	0.726§

CEA, carcinoma-embryogenic antigen; CA19-9, carbohydrate antigen 19-9; IPMN, Intraductal papillary mucinous neoplasm; NET, Neuroendocrine tumor; TNM, tumor node metastasis. * Reactive hyperplasia, Schwannoma/Granulomatosis disease, † Mann Whitney U test, ¶ Fisher Freeman Halton test, ¥ Continuity corrected χ^2 test, § Fisher's exact test, # Pearson's χ^2 test. Bold words of *p* value is statistical significant.

0.05), respectively (Table 2). Furthermore, no significance was observed in neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, total bilirubin, or albumin levels ($p >$ 0.05).

The histopathological examination showed 80% adenocarcinoma, 4.4% carcinoma *in situ*, and 4.4% chronic pancreatitis (p = 0.898). The malignancy rate was 85.5% in all patients (p = 0.205). The median of clinical stage and T-score

Table 3. Assessment of the risk factors on the pancratic fistula, reoperation, and multivariate logistic regression analysis.

	Univariate Analysis				Multivariate Analysis			
	OR	95% CI for OR		*p*-value	OR	95% CI for OR		*p*-value
		Lower	*Upper*			*Lower*	*Upper*	
Pancreatic Fistula								
Age >75 years	0.560	0.220	1.425	0.224	0.469	0.121	1.819	0.273
Gender (Male)	3.586	1.342	9.584	**0.011**	5.909	1.593	21.914	**0.008**
ASA score	0.650	0.282	1.499	0.312	-	-	-	-
Co-morbidity (>1)	1.833	0.761	4.413	0.177	1.549	0.483	4.974	0.462
Malignancy	0.306	0.100	0.939	**0.038**	0.217	0.044	1.078	0.062
Elevated Bilirubin account (>2 mg/dL)	1.689	0.693	4.116	0.249	2.160	0.608	7.670	0.233
Location of tm / pancreas head	1.000	-	-	-	-	-	-	-
Ampulla Vatery	0.847	0.301	2.382	0.753	-	-	-	-
Distal common biliary duct	0.873	0.267	2.856	0.822	-	-	-	-
Duodenum	3.200	0.521	19.668	0.209	-	-	-	-
Uncinate	1.600	0.093	27.547	0.746	-	-	-	-
Anastomosis type / Wirsungo-jejunostomy	1.000	-	-	-	-	-	-	-
Dunking / External catheter	2.659	1.009	7.010	**0.048**	2.173	0.605	7.808	0.234
Operation during the Covid-19 period	1.469	0.481	4.488	0.500	-	-	-	-
Pancreatic duct diameter (≤3 mm)	25.770	4.158	159.728	**<0.001**	10.657	2.640	43.018	**<0.001**
Pancreatic tissue nature	0.276	0.051	1.478	0.133	0.388	0.105	1.435	0.156
Length of hospital stay	1.095	1.032	1.162	**0.003**	1.064	1.019	1.112	**0.005**

	Univariate Analysis				Multivariate Analysis			
	OR	95% CI for OR		*p*-value	OR	95% CI for OR		*p*-value
		Lower	*Upper*			*Lower*	*Upper*	
Reoperation								
Age >75 years	0.505	0.151	1.697	0.269	-	-	-	-
Gender (Male)	0.665	0.233	1.898	0.446	-	-	-	-
ASA score	0.767	0.279	2.104	0.606	-	-	-	-
Co-morbidity (>1)	2.609	0.909	7.486	0.075	2.474	0.666	9.196	0.176
Malignancy	0.323	0.099	1.056	0.062	0.395	0.086	1.811	0.232
Elevated Bilirubin account (>2 mg/dL)	0.750	0.264	2.132	0.589	-	-	-	-
Location of tumor / pancreas head	1.000	-	-	-	-	-	-	-
Ampulla Vatery	0.435	0.106	1.790	0.249	-	-	-	-
Distal common biliary duct	1.389	0.385	5.005	0.615	-	-	-	-
Duodenum	0.667	0.069	6.470	0.727	-	-	-	-
Uncinate	N/A	N/A	N/A	N/A	-	-	-	-
Anastomosis type / Wirsungo-jejunostomy	1.000	-	-	-	-	-	-	-
Dunking / External catheter	3.040	1.022	9.041	**0.046**	2.279	0.565	9.199	0.247
Pancreatic duct diameter (≤3 mm)	5.286	1.408	19.845	**0.014**	8.202	1.439	46.735	**0.018**
Pancreatic tissue nature	1.144	0.363	3.602	0.818	-	-	-	-
Length of hospital stay	1.079	1.032	1.129	**<0.001**	1.087	1.036	1.141	**<0.001**

OR, Odds ratio; CI, Confidence interval; ASA, American Society of Anesthesiologists; N/A, Not applicable.

Bold words of *p* value is statistical significant.

were 2 (1–2) and 2 (2–3), respectively. Elderly patients exhibited the highest tumor, lymph node, and tumor node metastasis (TNM) staging in the two groups (p = **0.007**). The lymph node positivity, metastasis, tumor grade, lymphovascular invasion, and nerve invasion were similar between the two groups ($p > 0.05$) (Table 2).

Most patients received gemcitabine-based chemotherapy agents (36.5%) in adjuvant chemotherapy, with no statistically significant in groups ($p > 0.05$).

Morbidity and COVID-19 Infection

There was no significant difference in the total complication rate between the two groups. The surgical site infection (SSI) rate was 31.1% (28.3% in Group 1 vs. 36.6% in Group 2). Patients with superficial SSI (16.6%) received wound care with medical agents or in hospital beds. However, patients with deep SSI were taken into the ICU, with or without surgery, depending on the underlying factors.

Table 4. Assessment of the risk factors on hospital mortality and overall survival via logistic and Cox's proportional hazard regression analysis.

	Univariate Analysis				Multivariate Analysis			
	OR	95% CI for OR		*p*-value	OR	95% CI for OR		*p*-value
		Lower	*Upper*			*Lower*	*Upper*	
Hospital mortality								
Age >75 years	1.385	0.359	5.335	0.636	-	-	-	-
Gender (Male)	0.538	0.144	2.020	0.359	-	-	-	-
ASA (>3)	1.638	0.394	6.804	0.497	-	-	-	-
Malignancy	0.159	0.040	0.642	**0.010**	0.131	0.016	1.087	0.060
Operation during the Covid-19 period	0.524	0.061	4.474	0.555	-	-	-	-
Tissue nature (soft)	4.333	0.521	36.040	0.175	6.892	0.576	82.394	0.127
Duration of operation	0.996	0.986	1.005	0.376	-	-	-	-
Albumin	0.535	0.134	2.136	0.376	-	-	-	-
Neutrophil to lymphocyte ratio	1.000	0.999	1.001	0.454	-	-	-	-
Hematocrit	0.961	0.813	1.137	0.645	-	-	-	-
Reoperation	28.000	5.191	151.020	**<0.001**	23.731	2.039	276.265	**0.011**
Hemorrhage	5.286	1.080	25.865	**0.040**	2.339	0.181	30.183	0.515
Pancreatic duct diameter (≤3 mm)	3.619	0.723	18.113	0.117	0.562	0.060	5.246	0.613
Pancreatic fistula grade	1.777	0.994	3.179	0.053	0.983	0.464	2.079	0.964

	Univariate Analysis				Multivariate Analysis			
	HR	95% CI for HR		*p*-value	HR	95% CI for HR		*p*-value
		Lower	*Upper*			*Lower*	*Upper*	
Overall survival								
Age >75 years	2.312	1.237	4.322	**0.009**	2.219	1.016	4.846	**0.045**
Gender (Male)	1.016	0.542	1.902	0.962	-	-	-	-
ASA score	1.406	0.764	2.590	0.274	-	-	-	-
CA19-9 *	1.000	1.000	1.000	0.564	-	-	-	-
Albumin	1.075	0.985	1.174	0.106	1.060	0.955	1.176	0.276
Operation during the Covid-19 period	0.913	0.276	3.024	0.882	-	-	-	-
TNM Staging	1.667	1.183	2.349	**0.004**	0.647	0.255	1.640	0.359
T score	1.403	1.028	1.913	**0.033**	1.187	0.596	2.360	0.626
Lymph node positivity	4.161	2.151	8.050	**<0.001**	6.633	2.350	18.722	**<0.001**
Metastasis	3.657	0.481	27.792	0.210	2.190	0.137	34.894	0.579
Lymphovascular invasion	2.434	1.313	4.515	**0.005**	0.506	0.201	1.272	0.147
Neural invasion	2.391	1.297	4.408	**0.005**	2.356	1.108	5.010	**0.026**
Tumor differentiate grade	1.997	1.285	3.105	**0.002**	1.291	0.804	2.074	0.290
Chemotherapy	0.757	0.415	1.379	0.363	-	-	-	-
Gemcitabine	0.858	0.449	1.637	0.641	-	-	-	-
Folfirinox	0.642	0.268	1.541	0.321	-	-	-	-
Folfirinox and gemcitabine	0.620	0.220	1.750	0.367	-	-	-	-
Cisplatin or paclitaxel or Ox	1.141	0.477	2.730	0.767	-	-	-	-
Capecitabine	1.474	0.648	3.353	0.355	-	-	-	-
Radiotherapy	1.250	0.647	2.416	0.506	-	-	-	-

OR, Odds ratios; HR, Hazard ratios; CI, Confidence intervals; ASA, American Society of Anesthesiologists; CA19-9, Carbohydrate antigene 19-9.

* The effect of each 100-unite increase in pre-operative.

Bold words of *p* value is statistical significant.

The total pancreatic fistula rate was 38.9%, with 22.2% classified as grade A, 6.7% as grade B, and 10% as grade C in all patients ($p = 0.320$). A total of 26 grade A or B PFAO were treated with endoscopic or percutaneous drainage in nine patients, octreotide agent in 17 patients, and only follow-up in 16 patients. For grade C PFAO (9 cases, 10%) four patients underwent external Wirsung-ostomy, four underwent ligated arteries or branches of pancreatic vessels, and a Bogota bag was placed in 1 patient. Moreover, 29 (32.2%) patients received an octreotide agent during the perioperative period. Among the 90 patients, five experienced massive hemorrhages, excluding those with grade C PFAO who underwent laparotomy for bleeding. Additionally, 29 patients (32.2%) had complications classified as grade 3 or higher according to the Clavien-Dindo classification rate [19], and the classification rate of ≥3 was ordinary in both groups ($p > 0.05$) (Tables 1,2).

The multivariate logistic regression analysis investigated the combined effects of potential factors on the development of pancreatic fistula, considering variables with *p*-values < 0.25 from univariate analyses and those deemed clinically significant. As a result of multivariate logistic regression analysis, it was determined that the most influential factors for the development of pancreatic fistula are pancreatic duct diameter ≤3 mm, prolonged hospital stay, and male gender. Regardless of other factors, a pancreatic duct diameter of ≤3 mm continued to increase the probability of pancreatic fistula development statistically significantly (OR = 10.657, 95% CI: 2.640–43.018, $p < 0.001$). Additionally, prolonged hospital stay (OR = 1.064, 95% CI: 1.019–1.112, $p = 0.005$) and male gender (OR = 5.909, 95% CI: 1.593–21.914, $p = 0.008$) increased the probability of fistula development statistically after adjusting for other factors (Table 3).

Regarding reoperation, univariate statistical analysis reoperation revealed that operation types (dunking or external catheter application), pancreatic duct diameter of ≤3 mm, and prolonged hospitalization were found to be statistically significant ($p < 0.05$).

After conducting univariate statistical analyses, multivariate logistic regression analysis investigated the combined effects of all possible factors affecting reoperation. All variables found to be $p < 0.25$ as a result of univariate statistical analyses and assumed to be clinically significant were included in the regression model as candidate risk factors. The results of the multivariate logistic regression analysis revealed that the most influential factors on reoperation were prolonged hospital stay and a pancreatic duct diameter of ≤3 mm. An increased hospital stay (OR = 1.087, 95% CI: 1.036–1.141, $p < 0.001$) and pancreatic duct diameter ≤3 mm (OR = 8.202, 95% CI: 1.439–46.735, $p = 0.018$) continued to increase the probability of statistical significance independent of factors. During the COVID-19 period, we performed surgery on 15 cases (16.6%), with seven cases (11.6%) in Group 1 and eight cases (26.6%) in Group 2 (≥75 years) ($p = 0.134$). One patient tested positive for COVID-19 two weeks after the operation. The patient was an 83-year-old man who received medical treatment and was successfully discharged after two weeks (Table 3).

Hospital Mortality

Hospital mortality occurred in 10 patients (11.1%) postoperatively within the first 30 days. The main causes of hospital mortality were sepsis due to grade C PFAO or massive hemorrhage (affecting seven patients, 7.7%), lung or acute renal failure (two patients, 2.2%), and acute myocardial infarction (one patient, 1.1%). Multivariate logistic regression analysis was conducted to investigate the combined effects of all potential factors on hospital mortality, based on the results of univariate statistical analyses. All variables found to be $p < 0.25$ as a result of univariate statistical analyses and thought to be clinically significant were included in the regression model as candidate risk factors. As a consequence of multivariate logistic regression analysis, reoperation was the most significant factor associated with in-hospital mortality. The probability of hospital mortality continued to increase statistically in patients who underwent reoperation, regardless of other factors (OR = 23,731, 95% CI: 2.039–276.265, p = **0.011**) (Table 4).

Overall Survival

In the current study, 44 deaths (48.8%) were recorded after a median follow-up of 13.2 months (range: 50.07–150.6 months). The median overall survival rate for all patients was 27 ± 4.1 (18.8–35.1) months, and the cumulative proportions of one-, three-, and five-year survival without hospital mortality were 97.5%, 76.2%, and 48.5%, respectively. Meanwhile, the cumulative proportions of one-, three-, and five-year survival with hospital mortality were 87.7%, 68.5%, and 43.7%, respectively. The median overall survival rate of patients aged 60–75 years (44 ± 11.03 (22.3–65.6) months) was significantly higher than for elderly patients (12 ± 1.6 (8.7–15.2) months) (log-rank, p = **0.007**) (Fig. 2).

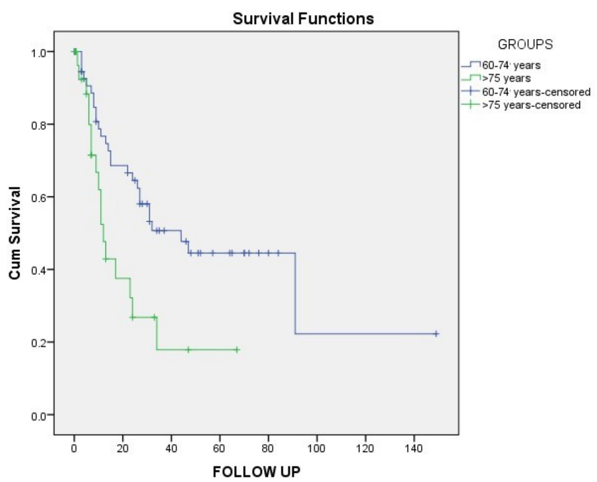

Fig. 2. Kaplan-Meier curve for overall survival in groups.

The univariate analysis examined factors affecting overall survival and found that age ≥75 years ($p = 0.009$), TNM staging ($p = 0.004$), T score ($p = 0.033$), lymph node positivity ($p < 0.001$), lymphovascular invasion ($p = 0.005$), neural invasion ($p = 0.005$), and differential tumor grade ($p = 0.002$) were statistically significant. Finally, multivariate analysis showed that lymph node positivity (HR: 6.633, 95% CI: 2.350–18.722, $p < \mathbf{0.001}$), tumor neural invasion (HR: 2.356, 95% CI: 1.108–5.010, $p = \mathbf{0.026}$), and age (≥ 75 years) (HR: 2.219, 95% CI: 1.016–4.846, $p = \mathbf{0.045}$) were the independent factors affecting the overall survival rate (Table 4).

Discussion

Pancreatic cancer is the second most common digestive system cancer, presenting as an insidious, late-diagnosed, initially synchronous tumor with an aggressive course and resistance to chemotherapy and a high risk of recurrence and metastasis [3,4,16,17,18]. The average annual percent changes in pancreatic cancer incidence have increased over the past two decades, now ranking fourth among all cancers for its death rates across age groups [5,6].

The expanding elderly population is predicted to significantly affect surgical practice, and there has been a 25–30% increase in general surgeries performed over the past two decades, coinciding with a consistent increase in the number of geriatric cancers [1,7]. Despite the PD or Whipple procedure representing a curative treatment modality in periampullary tumors, this procedure is accompanied by high morbidity and mortality rates [7,10,11]. In elderly patients, the rate of dramatic complications may be double, even when surgeries are performed at high-volume centers. PFAO, reoperation, and bleeding are the most common postoperative complications of PD. The PFAO rate varies from 13% to 45%, influenced by various factors including center proficiency, tissue characteristics, vascular supply, tumor location, pancreatic duct diameter, body mass index (BMI), intra-abdominal hemorrhage, residual pancreatic tissue volume, preoperative nutrition status, and surgeon and center experience [12,13,14]. Facility experience or volume is essential, and van der Geest *et al.* [12] described the effect of its volume as follows: low-volume centers have <15 PDs per year, medium-volume have 15–28 PDs, and high-volume have >28 PDs.

PFAO can lead to life-threatening complications such as intra-abdominal hemorrhage and sepsis, with a hospital mortality rate as high as 25% for grade B and C patients [19,20]. Despite advanced suture and operation techniques to reduce PFAO, the rate of pancreatic fistula remains high [7,21]. Chen *et al.* [21] detected a total complication rate of 39.6%, PFAO rate of 20.1%, severe complication rate of 16.8%, and reoperation rate of 4% in patients aged over 65 years, demonstrating that aging is a significant risk factor for serious postoperative complications following pancreatic resection. Moreover, they supported more careful patient selection criteria for surgery. Melis *et al.* [22], meanwhile, detected a total morbidity rate of 68% in octogenarians, with comparable 30-day mortality and survival to those observed in non-elderly patients, concluding that PD may be offered to carefully selected octogenarians. Similarly, Makary *et al.* [23] reported complications in 53% of very elderly patients, with pancreatic fistula in 21%, and reoperation in 5.6%. Elsewhere, Liang *et al.* [24] presented a major complication rate of 41% and a grade B or C PFAO rate of 21% in elderly patients undergoing laparoscopic PD (LPD), indicating increased postoperative complications compared to younger patients. However, for an aging population undergoing PD, LPD might have advantages over open PD [24]. The current study exhibited a total complication rate of 61.1%, with most complications being minor, such as superficial surgical site infection (28.8%) and grade A PFAO (22.2%). Major complications included grade B or C PFAO (10%) and hemorrhage (10%). We identified male gender, pancreatic duct diameter (<3 mm), and length of hospital stay as risk factors for PFAO. Aside from affecting the postoperative morbidity as a reoperation, pancreatic duct diameter (<3 mm) and length of the hospital affected the likelihood of patients requiring reoperation as independent risk factors.

The COVID-19 pandemic has negatively affected health systems globally [25]. Pancreatic surgery frequently requires a careful preoperative diagnosis, oncology council, third-level ICU admission, and prolonged hospitalization. Furthermore, in complicated patients, hospitalization times can increase. While the precise impact of the COVID-19 pandemic on high-volume pancreatic cancer surgery centers remains unclear, it may cause significant disruptions in activity in some centers [26]. Despite slight delays in pancreatic surgeries during the restriction period, we proceeded with pancreatic cancer surgeries in the present study. Consequently, half of the elderly patients (15 cases) underwent PD during the COVID-19 pandemic. COVID-19 affected only one patient, with no mortality attributed to the virus.

According to existing literature, mortality may occur following PD due to multiple risk factors, including patient characteristics, perioperative conditions, and the experience of the surgeon or medical center [7,12,18,21,22,23,24]. PFAO is a significant risk factor, with hospital mortality rates for grade B and C patients as high as 25% [7,19]. Various studies have reported a mortality rate of 1.6–2.5 times greater in elderly patients who underwent pancreatic surgery, particularly notable in the centralization of procedures in high-volume hospitals [12,13]. In addition, Chen *et al.* [21] reported higher postoperative mortality rates in elderly patients versus non-elderly patients (5.5% vs. 0.9%). Melis *et al.* [22] showed that, compared to non-elderly groups, elderly patients had a significantly greater hospital mortality rate (4% vs 0.6%). Moreover, they found that the median survival time was 17.3 months in elderly patients. Meanwhile, Liang *et al.* [24] reported a 90-day mortality of 10% in patients who underwent open PD. Additionally, Adham *et al.* [27] showed that elderly patients exhibited higher postoperative mortality rates (12.9% vs. 3.9%) after pancreatic resection. Furthermore, Bathe *et al.* [15] showed that elderly patients had a higher hospital mortality rate (25%) and required extended treatment in the surgical ICU postoperatively. However, long-term survival was comparable between the two age groups. They suggested that curative resection for periampullary tumors is effective in appropriately selected elderly patients. The present study observed a hospital mortality rate of 11.1% (10% in Group 1 vs. 13.3% in Group 2), consistent with existing literature. Multivariable statistical analysis showed that reoperation was the most important independent risk factor for hospital mortality. Moreover, the overall median survival was 27 ± 4.1 (18.8–35.1) months following a median follow-up of 13.5 months for all patients. Age >75 years, lymph node positivity, and neural invasion were significant factors influencing long-term survival according to the multivariable analysis.

There were some limitations to the present study. First, this was a retrospective study with a small sample size. Second, there was heterogeneity among the operating surgeons, with PD performed by different senior surgeons. Finally, PD performed in elderly cases was commonly achieved during the latter half of the study period.

Conclusion

Medical advancements have led to increased lifespans and life expectancies. The present study concluded that PD can be effectively performed with tolerable morbidity and mortality rates in appropriate elderly patients.

Availability of Data and Materials

The authors in present article confirm that the data supporting the findings of this study are available within the article.

Author Contributions

Concept – MA, AİK; Design – ME, MA; Supervision – FA; Data Acquisition and Processing – FA, MT, DS, FAU; Analysis and Interpretation – MA, AD; Literature Search – AİK, MA; Writing Manuscript – MA; Critical Reviews – FA. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Ethical Committee of University of Sakarya, Faculty of Medicine approved the present study protocol number (E-71522473-050.01.04-83253-497). The consent of the patients was taken prior to the writing of the manuscript. The study is in accordance with the Declaration of Helsinki.

Acknowledgment

We would like to thank Mrs. Münire Demirci (operation nursing) and M.D. Zeynep Aziret for helping us in this study.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Anisimov VN. Life span extension and cancer risk: myths and reality. Experimental Gerontology. 2001; 36: 1101–1136.

[2] Chang AY, Skirbekk VF, Tyrovolas S, Kassebaum NJ, Dieleman JL. Measuring population ageing: an analysis of the Global Burden of Disease Study 2017. Lancet Public Health. 2019; 4: e159–e167

[3] McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World Journal of Gastroenterology. 2018; 24: 4846–4861.

[4] Qian Y, Gong Y, Fan Z, Luo G, Huang Q, Deng S, *et al.* Molecular alterations and targeted therapy in pancreatic ductal adenocarcinoma. Journal of Hematology & Oncology. 2020; 13: 130.

[5] Kim SM, Eads JR. Adjuvant and Neoadjuvant Therapy for Resectable Pancreatic and Periampullary Cancer. The Surgical Clinics of North America. 2016; 96: 1287–1300.

[6] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a Cancer Journal for Clinicians. 2022; 72: 7–33.

[7] Aziret M. Pancreaticojejunostomy Anastomosis Techniques After Pancreaticoduodenectomy: A Critical Review. Erciyes Medical Journal. 2022; 44: 123–128.

[8] COVIDSurg Collaborative. Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: an international, prospective, cohort study. The Lancet. Oncology. 2021; 22: 1507–1517.

[9] Kuzuu K, Misawa N, Ashikari K, Kessoku T, Kato S, Hosono K, *et al.* Gastrointestinal Cancer Stage at Diagnosis Before and During the COVID-19 Pandemic in Japan. JAMA Network Open. 2021; 4: e2126334.

[10] Riall TS. What is the effect of age on pancreatic resection? Advances in Surgery. 2009; 43: 233–249.

[11] Erdem H, Çetinkünar S, Aziret M, Reyhan E, Sözütek A, Sözen S, *et al.* Can isolated pancreaticojejunostomy reduce pancreas fistula after pancreaticoduodenectomy with Roux-en-Y reconstruction? Ulusal Cerrahi Dergisi. 2016; 32: 248–251.

[12] van der Geest LG, Besselink MG, Busch OR, de Hingh IH, van Eijck CH, Dejong CH, *et al.* Elderly Patients Strongly Benefit from Centralization of Pancreatic Cancer Surgery: A Population-Based Study. Annals of Surgical Oncology. 2016; 23: 2002–2009.

[13] de Wilde RF, Besselink MGH, van der Tweel I, de Hingh IHJT, van Eijck CHJ, Dejong CHC, *et al.* Impact of nationwide centralization of pancreaticoduodenectomy on

hospital mortality. The British Journal of Surgery. 2012; 99: 404–410.
[14] Riall TS, Reddy DM, Nealon WH, Goodwin JS. The effect of age on short-term outcomes after pancreatic resection: a population-based study. Annals of Surgery. 2008; 248: 459–467.
[15] Bathe OF, Levi D, Caldera H, Franceschi D, Raez L, Patel A, *et al*. Radical resection of periampullary tumors in the elderly: evaluation of long-term results. World Journal of Surgery. 2000; 24: 353–358.
[16] Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, *et al*. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. The New England Journal of Medicine. 2018; 379: 2395–2406.
[17] Macarulla T, Hendifar AE, Li CP, Reni M, Riess H, Tempero MA, *et al*. Landscape of Health-Related Quality of Life in Patients with Early-Stage Pancreatic Cancer Receiving Adjuvant or Neoadjuvant Chemotherapy: A Systematic Literature Review. Pancreas. 2020; 49: 393–407.
[18] Tempero MA, Malafa MP, Al-Hawary M, Behrman SW, Benson AB, Cardin DB, *et al*. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2021; 19: 439–457.
[19] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, *et al*. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of Surgery. 2009; 250: 187–196.
[20] Pedrazzoli S. Pancreatoduodenectomy (PD) and postoperative pancreatic fistula (POPF): A systematic review and analysis of the POPF-related mortality rate in 60,739 patients retrieved from the English literature published between 1990 and 2015. Medicine. 2017; 96: e6858.
[21] Chen YT, Ma FH, Wang CF, Zhao DB, Zhang YW, Tian YT. Elderly patients had more severe postoperative complications after pancreatic resection: A retrospective analysis of 727 patients. World Journal of Gastroenterology. 2018; 24: 844–851.
[22] Melis M, Marcon F, Masi A, Pinna A, Sarpel U, Miller G, *et al*. The safety of a pancreaticoduodenectomy in patients older than 80 years: risk vs. benefits. HPB: the Official Journal of the International Hepato Pancreato Biliary Association. 2012; 14: 583–588.
[23] Makary MA, Winter JM, Cameron JL, Campbell KA, Chang D, Cunningham SC, *et al*. Pancreaticoduodenectomy in the very elderly. Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract. 2006; 10: 347–356.
[24] Liang Y, Zhao L, Jiang C, Hu P, Wang H, Cai Z, *et al*. Laparoscopic pancreaticoduodenectomy in elderly patients. Surgical Endoscopy. 2020; 34: 2028–2034.
[25] WHO Coronavirus (COVID-19) Dashboard. 2021. Available at: https://covid19.who.int (Accessed: 16 July 2021).
[26] Marchegiani G, Perri G, Bianchi B, Esposito A, Landoni L, Casetti L, *et al*. Pancreatic surgery during COVID-19 pandemic: major activity disruption of a third-level referral center during 2020. Updates in Surgery. 2022; 74: 953–961.
[27] Adham M, Bredt LC, Robert M, Perinel J, Lombard-Bohas C, Ponchon T, *et al*. Pancreatic resection in elderly patients: should it be denied? Langenbeck's Archives of Surgery. 2014; 399: 449–459.

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