Impact of preoperative asymptomatic renal dysfunction on clinical course after pancreatoduodenectomy

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Abstract

Background Although recent large-scale clinical studies have shown that preoperative renal insufficiency is associated with increased risk of postoperative complications after pancreatoduodenectomy (PD), it is unknown whether asymptomatic renal dysfunction has an impact on postoperative course after PD.

Methods Two hundred fifty-four patients who underwent PD between 2007 and 2013 were enrolled. Renal function was evaluated by the preoperative estimated glomerular filtration rate (eGFR). Patients were divided into two groups according to the cutoff value of 55 of eGFR.

Results Thirty-five patients were classified as the low eGFR group, while 219 were as the normal group. There were differences between groups in age, comorbidity and pancreatic texture. The incidence of overall postoperative complication, grade B/C pancreatic fistula and severe complication in the low eGFR group was significantly higher than that in the normal group. Multivariate analysis identified low eGFR as an independent risk factor for severe postoperative complications and grade B/C pancreatic fistula after PD. However, there were no differences in mortality and survival between the low and normal eGFR groups.

Conclusions We have demonstrated for the first time that preoperative asymptomatic renal dysfunction may be a significant risk factor for severe morbidity and clinically relevant pancreatic fistula after PD.

Introduction

Pancreatic resection is generally recognized as highly invasive surgery, although it has become to be relatively safely performed at high volume surgical centers [1-5]. Even at well-experienced institutions, postoperative complications, such as pancreatic fistula and surgical infections, often develop after pancreatoduodenectomy (PD) and occasionally lead to fatal conditions [6, 7]. To date, several risk factors for postoperative complications after PD, such as soft pancreas, gender, intraoperative bleeding, preoperative biliary drainage, and obesity, have been reported [8-12]. The information of such operation risks is important for proper perioperative management and informed consent to patients.

Preoperative renal insufficiency is a well-known risk factor for postoperative complications after cardiac and vascular surgery [8, 13-15]. Furthermore, a few recent large-scale clinical studies have also shown the negative impact of preoperative renal insufficiency on postoperative outcomes after pancreatic resection [16, 17]. Squires et al. have reported severe preoperative renal insufficiency as an independent risk factor associated with increased risk of morbidity and respiratory failure after pancreatic resection in the analysis of 1061 patients who underwent pancreatic resection [17]. In that study, renal insufficiency was defined as serum creatinine (sCr) $\geq$ 1.8 mg/dL or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2. Such patients were less than 3% in whole study population, and also some patients were dialysis dependent preoperatively. Furthermore, Kimura et al. have recently reported that sCr $\geq$ 3 mg/dL

was a significant factor with the highest risk for post-PD mortality by the analysis of 8575 Japanese patients using national clinical database, although patients with sCr $\geq$ 3 mg/dL were only 0.9% in entire study population [18]. Taken together, severe preoperative renal insufficiency should be considered to be a significant risk factor for complications after PD.

There is a subpopulation of patients with asymptomatic renal dysfunction with no need of hemodialysis. However, to our knowledge, no studies have addressed the impact of such asymptomatic renal dysfunction on postoperative outcome after PD. Therefore, this study tried to clarify the short-term and long-term outcomes after PD in patients with such asymptomatic renal dysfunction.

Patients and methods

Patients

A total of 256 patients underwent PD between 2007 and 2013 in Nara Medical University Hospital. Two patients who had undergone hemodialysis or renal transplantation were excluded from this study. The remaining 254 patients were retrospectively analyzed in this study, including 150 males and 104 females, with a mean age of 67.2 years ± 10.0 standard deviation (SD). Patients provided written informed consent before treatment according to the rules and regulations of our institution.

Data and definition

A comprehensive review of the medical records was performed to evaluate various clinicopathological factors including patient demographics, medical comorbidities, preoperative laboratory values, tumor pathological characteristics, and perioperative data. Pathological diagnosis was classified as benign disease, malignant disease other than pancreatic ductal adenocarcinoma (PDAC), and PDAC. As a result, 43 benign primary diseases, 94 malignant tumors other than PDAC, and 117 PDAC were included. The majority of benign diseases were intraductal papillary mucinous adenoma. In non-PDAC malignancy, 41 distal bile duct cancers, 26 ampullary cancers, 11 intraductal papillary mucinous carcinomas, and 8 duodenal cancers were included. Cardiovascular disease included coronary artery disease, atrial fibrillation, and cerebral infarction. Renal disease included renal cell carcinoma, diabetic nephropathy, IgA nephropathy, and chronic kidney disease. Respiratory disorder included chronic obstructive pulmonary disease, bronchial asthma, interstitial pneumonia, and bronchial ectasia. A total of 55 patients with PDAC received neoadjuvant chemoradiotherapy (CRT), as previously reported [19]. Renal function was evaluated by calculating eGFR, based on the results from the latest lab exams preceding operation. eGFR was calculated using the following formulas: eGFR ($mL/min/1.73m^2$) = $194 \times sCr^{-1.094} \times Age^{-0.287}$ ($\times 0.739$; if the patient is female)] [20, 21].

Outcome assessment

The incidence of postoperative complications that occurred within 30 days after surgery

were evaluated in this study, and the severity of complications was defined according to the Clavien-Dindo classification [22]. If more than one complication occurred in a single patient, the most severe grade was considered for the present analysis. In the present study, severe complication was defined as a complication of grade III or greater. Pancreatic fistula was defined according to the definition of the International Study Group on Pancreatic Fistula (ISGPF) [23]. We further evaluated various outcome parameters, including the length of postoperative hospital stay and prognosis. Date of last follow-up was August 2014.

Statistical analysis

The parameters were compared using the Student's t test, the chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as the mean and SD. The logistic regression model was used for multivariate analysis. All significant variables in the univariate analysis were entered into the multivariate analysis. Overall survival (OS) was calculated from the date of initial treatment with either surgery or neoadjuvant cancer therapy until death or last follow-up. The survival curve was estimated according to the Kaplan-Meier method, and differences were analyzed using the log-rank test. All reported P values were two-sided. A P value of < 0.05 was considered statistically significant and confidence intervals (CI) were calculated at the 95% level. The statistical analyses were performed using the SPSS software program, version 19.0 (SPSS, Chicago, IL).

Results

Cutoff value of eGFR

To determine the optimal cutoff value of eGFR to predict postoperative complications, we set and evaluated various values of eGFR (30-60 mL/min/1.73m^2) in relation to either any or severe complications. As a result, we defined 55 as the cutoff value and classified all patients into either low or normal eGFR groups. This was also the same value determined by the receiver operating characteristic curve analysis. As a result, 219 patients (86.2%) with eGFR of 55 and higher were classified as the normal eGFR group, and 35 patients (13.8%) with eGFR of below 55 were classified as the low eGFR group (Fig. 1). Among the low eGFR group, only 3 patients (8.6%) had eGFR of below 30 mL/min/1.73 m^2.

Patient clinicopathological characteristics according to eGFR status

Patient characteristics of each group are summarized in Table 1. The patients in the low eGFR group were significantly older than those in the normal group ($P = 0.009$). The patients in the low eGFR group had more preoperative comorbidities including renal disease (26% vs. 2%), respiratory disorder (14% vs. 5%), and cardiovascular disease (26% vs. 13%). While there were no differences in hemoglobin and albumin levels between two groups, serum creatinine level in the low eGFR group was significantly higher than that in the normal group ($P < 0.001$). The low eGFR group had soft pancreas more frequently compared to the normal group ($P = 0.029$). Finally, benign disease was significantly more common, while PDAC was significantly less common in

the low eGFR group than in the normal group ($P = 0.002$). However, since our surgical indication did not differ between patients with and without renal dysfunction, the reasons for these differences of original diseases are unknown.

Perioperative data

We then compared perioperative data between two groups (Table 2). There were no significant differences between two groups in operating time, intraoperative blood loss, and operative procedure, while blood transfusion was performed more often in the low eGFR group than in the normal group ($P = 0.038$).

Postoperative outcomes

In total, 183 patients (72%) developed postoperative complications (Table 3). The incidence was significantly higher in the low eGFR group than in the normal group ($P = 0.003$). Furthermore, grade B/C pancreatic fistula occurred more frequently in the low eGFR group compared to the normal group ($P = 0.001$). In addition, in patients with soft pancreas, the incidence of grade B/C pancreatic fistula in the low eGFR group is also higher than that in the normal group ($P = 0.012$). The grade B/C pancreatic fistula rates in patients with hard pancreas did not differ between two groups. On the other hand, there were no significant differences between groups in each type of complication, although there was a tendency toward an increase in the low eGFR group, especially for medical complication. Furthermore, the low eGFR group had more severe complications than the normal group (57.1% vs. 28.8%, $P = 0.005$).

Risk factors for severe complications

Next, we analyzed risk factors for severe postoperative complications after PD. In the univariate analysis, malignant disease other than PDAC, no neoadjuvant CRT, soft pancreas, operative time, and low eGFR were found to be significant in relation to the incidence of severe complications (Table 4). The multivariate analysis demonstrated that soft pancreas, operating time, and low GFR were independent risk factors for severe complications (soft pancreas: OR 2.527, 95% CI 1.282 to 4.982; P = 0.007, operating time: OR 1.006, 95% CI 1.002 to 1.009, P = 0.002, GFR: OR 2.898, 95% CI 1.341 to 6.262; P = 0.007).

Risk factors for clinically relevant pancreatic fistula

We further investigated risk factors for grade B/C pancreatic fistula. In the univariate analysis, malignant disease other than PDAC, no neoadjuvant CRT, soft pancreas, portal vein resection, and low eGFR were risk factors significantly associated with grade B/C pancreatic fistula (Table 5). In multivariate analysis, eGFR as well as soft pancreas were independent risk factors for grade B/C pancreatic fistula (eGFR: OR 2.609, 95% CI 1.116 to 6.098, P = 0.027, soft pancreas: OR 3.021, 95% CI 1.162 to 7.853, P = 0.023).

Postoperative survival

Finally, we examined the impact of eGFR status on patient prognosis in each original

disease. As shown in Figure 2, there were no significant differences in the OS rate between two groups in any pathology subgroup.

Discussion

Some studies have reported that preoperative renal insufficiency was associated with increased postoperative complications after various types of surgery including cardiac and general surgery [8, 13-16, 24-26]. Furthermore, large-scale retrospective analyses have also demonstrated severe preoperative renal insufficiency as an independent risk factor associated with increased risk of morbidity after pancreatic resection, although the precise mechanisms are not yet known in any type of surgery [17, 18]. In those studies, the number of patients with such severe renal insufficiency including dialysis dependence was relatively small in the entire study population. In this study, we addressed whether patients with preoperative asymptomatic renal dysfunction might be at an increased risk for morbidity and mortality after PD. Accordingly, we found several important findings as described below.

First, there were significant correlations of low eGFR status with advanced age and preoperative comorbidities including renal disease, respiratory disorder, and cardiovascular disease, while there were no significant correlations between low eGFR status and perioperative variables except for blood transfusion. Although the precise reason for the difference in blood transfusion is unclear, the older age and higher comorbidity rate in patients of the low eGFR group might be related. Data suggest that asymptomatic renal dysfunction may represent patient frailty. Second, there were

significant correlations of eGFR status with the incidence of morbidity, grade B/C pancreatic fistula, and severe complications. The data may be partly consistent with previous studies on severe renal insufficiency [17, 18]. In contrast, the previous study has shown that preoperative severe renal insufficiency was not associated with increased risk for pancreatic fistula in spite of the type of pancreatic resection [17]. Although the reason for this discrepancy is not clear, we assumed that the increased risk for grade B/C pancreatic fistula in the low eGFR group was due to soft pancreas found more frequently in that group. However, even when analyzed in patients with soft pancreas, grade B/C pancreatic fistula occurred more frequently in the low eGFR group compared to the normal group. Furthermore, multivariate analysis indicated that both low eGFR status and soft pancreas were significant independent risk factors for grade B/C pancreatic fistula as well as severe complications. Therefore, data suggest that asymptomatic renal dysfunction had a significant negative impact on clinically relevant postoperative complications after PD.

There are several potential underlying mechanisms for associations of asymptomatic renal dysfunction with increased morbidity after PD. First, the tissue vulnerability in patients with renal dysfunction may be related to increased complications. As described above, patients in the low eGFR group had advanced age and preoperative comorbidity such as cardiovascular disease or respiratory disorder more frequently than those in the normal group. Second, perioperative fluid management may be another reason. To prevent renal insufficiency, excessive fluids may have been administered to patients with mildly elevated serum creatinine. Although it is still controversial, restrictive fluid

management may be beneficial in reduction of complications after PD [27-29]. However, there was no significant association between perioperative fluid volume and postoperative complications in this study (data not shown), while blood transfusion was given more frequently in the low eGFR group than the normal group. Third, a number of studies have shown that renal insufficiency is associated with a variety of impaired immune system in humans [30-32]. For instance, uremia causes inflammation and reduces immune response, thereby resulting in increased susceptibility to infection. Although relatively few studies have addressed the impact of mild renal dysfunction on immunity, potential inadequate immune response may promote the severity of complications after PD [33, 34]. Further studies are required to clarify the underlying mechanisms and to establish the optimal perioperative management after PD.

Finally, we evaluated the impact of asymptomatic renal dysfunction on patient survival. Previous studies have shown that severe renal insufficiency was not related to mortality after pancreatic resection, while there are no reports to address overall survival after pancreatic resection in patients with severe renal insufficiency. Our data also indicated that asymptomatic renal dysfunction had no significant impact on mortality after PD. Furthermore, the results also demonstrated that asymptomatic renal dysfunction had no impact on patient prognosis, regardless of original disease pathology. Taken together, PD may be justified for patients with renal dysfunction, even if there are increased risks of postoperative complications after PD.

To our best of knowledge, this is the first report to address the clinical impact of preoperative asymptomatic renal dysfunction on postoperative clinical course after PD.

Due to the retrospective nature and single-center experience, there are limitations to reach a definitive conclusion. In particular, the cut-off value of eGFR needs to be prospectively validated. However, we should be aware that asymptomatic renal dysfunction may be a significant risk factor for severe morbidity and clinically relevant pancreatic fistula after PD. Although it had no impact on mortality and long-term survival, careful postoperative management and proper informed consent to patients with renal dysfunction are needed.

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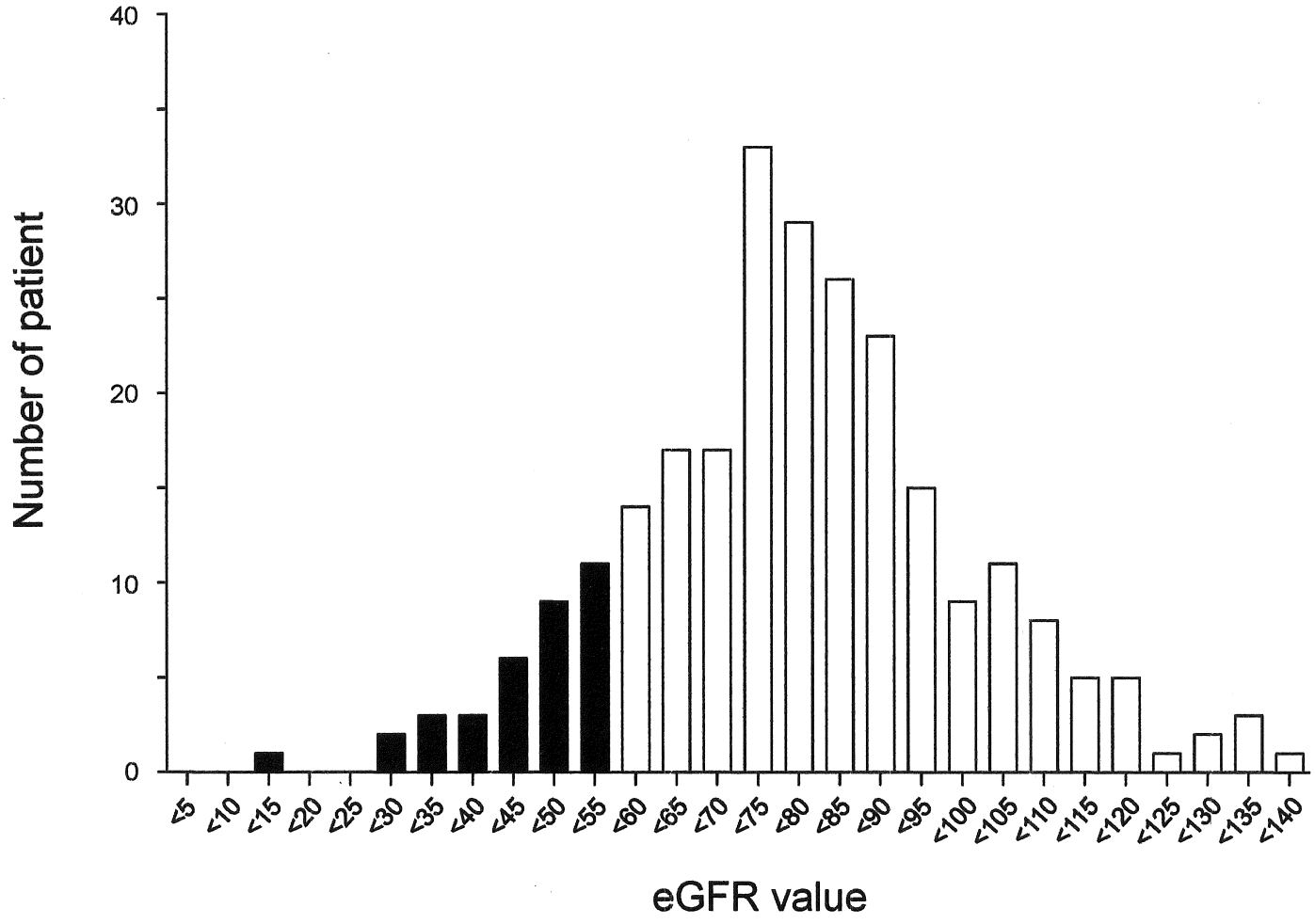
Figure legends

Fig. 1 Distribution of estimated glomerular filtration rate (eGFR) value. Patients with eGFR of below 55 were classified as the low eGFR group (black bar), while those with eGFR of 55 and higher were classified as the normal group (white bar).

Fig. 2 Comparison between the low and normal eGFR groups in the overall survival of each pathology subgroup; (**a**) benign disease, (**b**) malignant disease other than pancreatic ductal adenocarcinoma, and (**c**) pancreatic ductal adenocarcinoma.


Number of patient
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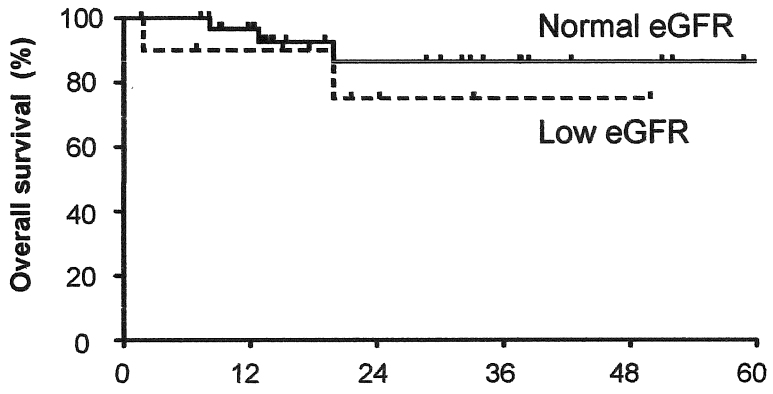
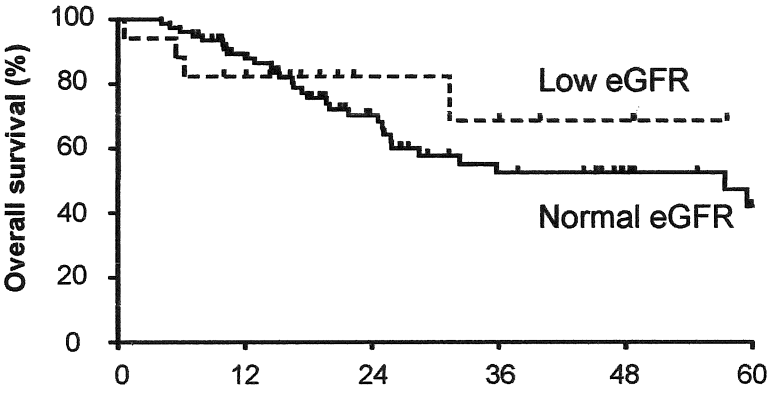
eGFR value

(a)



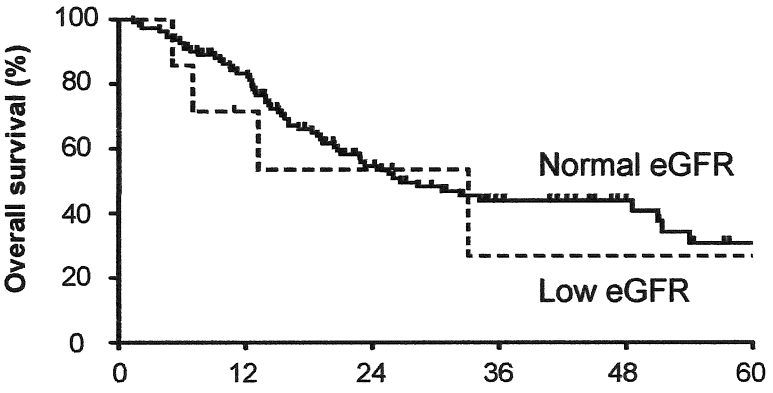
No at risk						
GFR<55	11	8	4	2	2	0
GFR≥55	32	26	14	9	5	2

(b)



No at risk						
GFR<55	17	13	6	5	3	0
GFR≥55	77	62	35	20	13	7

(c)



No at risk						
GFR<55	7	4	3	1	1	1
GFR≥55	110	85	45	26	15	6

Table 1 Patient characteristics

Variables	Normal eGFR[a] ($n = 219$)	Low eGFR[b] ($n = 35$)	*P*-value
Age (years)	66.5 ± 10.3 (33-86)	71.3 ± 7.5 (54-84)	0.009
Gender			0.273
Male	127 (58)	23 (66)	
Female	92 (42)	12 (34)	
Comorbidity			
Any	120 (55)	27 (77)	0.013
Diabetes mellitus	48 (22)	8 (23)	0.901
Hypertension	55 (25)	13 (37)	0.136
Renal disease	4 (2)	9 (26)	<0.001
Respiratory disorder	11 (5)	5 (14)	0.036
Cardiovascular disease	28 (13)	9 (26)	0.044
Hemoglobin, g/dl	11.8 ± 1.7 (8.1-17.1)	11.9 ± 1.5 (8.9-15.7)	0.713
Albumin, g/dl	3.9 ± 0.5 (2.5-5)	4.0 ± 0.3 (2.6-4.6)	0.409
Serum creatinine, mg/dl	0. 67 ± 0.15 (0.36-1.06)	1.17 ± 0.95 (0.79-2.07)	<0.001
Preoperative biliary drainage	110 (50)	13 (37)	0.150
Preoperative cholangitis	50 (23)	7 (20)	0.709
Soft pancreas	113 (52)	25 (71)	0.029
Pathology			0.002
Benign	32 (15)	11 (31)	
Malignant other than PDAC	77 (35)	17 (49)	
PDAC	110 (50)	7 (20)	

Data are presented as Mean ± SD (range) or count (%)

GFR Glomerular filteation rate, *PDAC* Pancreatic ductal adenocarcinoma

[a]defined as eGFR≥55

[b]defined as eGFR<55

Table 2 Perioperative data

Variables	Nomal eGFR ($n = 219$)	Low eGFR ($n = 35$)	*P*-value
Operating time (min)	339.9 ± 87.0 (172-860)	331.6 ± 78.3 (193-535)	0.597
Intraoperative blood loss (ml)	913.1 ± 1834.9 (8-26042)	907.6 ± 881.1 (55-4124)	0.986
Blood transfusion	62 (28)	16 (46)	0.038
Operative procedure			0.264
Pancreatoduodenectomy	136 (62)	24 (69)	
PD combined portal vein resection	71 (32)	7 (20)	
PD combined other organs resection	7 (3)	3 (9)	
PD combined other organs and portal vein resection	5 (2)	1 (3)	

Data are presented as Mean ± SD (range) or count (%).

PD pancreatoduodenectomy, *PV* portal vein

Table 3 Postoperative outcomes

Variables	Normal eGFR ($n = 219$)	Low eGFR ($n = 35$)	P-value
Postoperative complication			0.003
No	68 (31)	3 (9)	
Yes	151 (69)	32 (91)	
Pancreatic fistula[a]			0.001
Grade 0, A	188 (86)	22 (63)	
Grade B, C	31 (14)	13 (37)	
Pancreatic fistula: soft pancreas			0.012
Grade 0, A	88 (78)	13 (52)	
Grade B, C	25 (22)	12 (48)	
Complication			
Intra-abdominal abscess	20 (9)	5 (14)	0.248
Infectious complication[b]	42 (19)	10 (27)	0.201
Medical complication[c]	25 (11)	8 (22)	0.062
Delayed gastric emptying	24 (11)	2 (5)	0.270
Bile leakage	7 (3)	1 (3)	0.696
Bleeding (intra-abdominal, gastrointestinal)	13 (6)	1 (3)	0.399
Severity of complication[d]			0.005
Grade I	35 (16)	6 (17)	
Grade II	53 (24)	6 (17)	
Grade IIIa	57 (26)	15 (43)	
Grade IIIb	3 (1)	2 (6)	
Grade IVa	1 (1)	1 (3)	
Grade IVb	0 (0)	0 (0)	
Grade V	2 (1)	2 (6)	

[a] defined according to International Study Group of Postoperative Pancreatic Fistula

[b] included surgical site infection, catheter infection, cholangitis

[c] included liver dysfunction, pneumonia, heart failure

[d] defined according to Clavien-Dindo classification

Table 4 Analysis of risk factors for severe complications

Variables		Univariate analysis			Multivariate analysis		
		No	Yes	*P*-value	Odds ratio	95%CI	*P*-value
		(n = 171)	(n = 83)				
Age		67.0 ± 10.4 (33-84)	67.6 ± 9.2 (34-86)	0.690			
Gender	Male	94 (55)	56 (68)	0.057			
	Female	77 (45)	27 (32)				
Disease	Benign	28 (16)	15 (18)	0.016	1		
	Malignant non-PDAC	54 (32)	40 (48)		1.416	0.634-3.166	0.396
	PDAC	89 (52)	28 (34)		1.114	0.424-2.923	0.827
Diabetes Mellitus	Absent	129 (75)	69 (83)	0.165			
	Present	42 (25)	14 (17)				
Respiratory disorder	Absent	161 (94)	77 (93)	0.671			
	Present	10 (6)	6 (7)				
Cardiovascular disease	Absent	144 (84)	73 (88)	0.428			
	Present	27 (16)	10 (12)				
Neoadjuvant CRT	Absent	127 (74)	72 (87)	0.024	1		0.307
	Present	44 (26)	11 (13)		0.624	0.253-1.542	
Soft pancreas	Absent	89 (52)	27 (33)	0.003	1		0.007
	Present	82 (48)	56 (67)		2.527	1.282-4.982	
Preoperative biliary drainage	Absent	92 (54)	39 (47)	0.308			
	Present	79 (46)	44 (53)				
Preoperative cholangitis	Absent	138 (81)	59 (71)	0.085			
	Present	33 (19)	24 (29)				
Operative time (min)		330 ± 74	356 ± 103	0.046	1.006	1.002-1.009	0.002
Intraoperative blood loss (ml)		726 ± 621	1300 ± 2883	0.078			
Blood transfusion	Absent	124 (73)	52 (63)	0.110			
	Present	47 (28)	31 (37)				
Portal vein resection	Absent	110 (64)	60 (72)	0.206			
	Present	61 (36)	23 (28)				
Combined organs resection	Absent	162 (95)	76 (92)	0.329			
	Present	9 (5)	7 (8)				
eGFR (ml/min/1.73m^2)	≥55	156 (91)	63 (76)	0.001	1		0.007
	<55	15 (9)	20 (24)		2.898	1.341-6.262	

Data are presented as Mean ± SD (rang or count (%).Data are presented as median (range) or count (%).

CI confidence interval, *C/D* Clavien-Dindo, *CRT* chemoradiotherapy

Table 5 Analyses of risk factors for grade B/C pancreatic fistula

Variable		Uniivariate analysis			Multivariate analysis		
		No (n = 210)	Yes (n = 44)	*P*-value	Odds ratio	95%CI	*P*-value
Age		67.1 ± 10.3 (33-86)	67.6 ± 8.9 (46-81)	0.780			
Gender	Male	121 (58)	29 (66)	0.309			
	Female	89 (42)	15 (34)				
Disease	Benign	30 (14)	13 (30)	<0.001	1		
	Malignant non PDAC	70 (33)	24 (54)		1.070	0.461-2.486	0.875
	PDAC	110 (52)	7 (16)		0.635	0.170-2.369	0.499
Diabetes Mellitus	Absent	163 (78)	35 (80)	0.779			
	Present	47 (22)	9 (20)				
Respiratory disorder	Absent	199 (95)	39 (89)	0.128			
	Present	11 (5)	5 (11)				
Cardiovascular disease	Absent	181 (86)	36 (82)	0.455			
	Present	29 (14)	8 (18)				
Neoadjuvant CRT	Absent	157 (75)	42 (95)	0.001	1		0.351
	Present	53 (25)	2 (5)		0.441	0.079-2.461	
Soft pancreas	Absent	109 (52)	7 (16)	<0.001	1		0.023
	Present	101 (48)	37 (84)		3.021	1.162-7.853	
Preoperative biliary drainage	Absent	106 (51)	25 (57)	0.444			
	Present	104 (49)	19 (43)				
Preoperative cholangitis	Absent	165 (79)	32 (73)	0.398			
	Present	45 (21)	12 (27)				
Operative time (min)		339 ± 85	340 ± 92	0.929			
Estimated blood loss (ml)		897 ± 1850	985 ± 988	0.761			
Blood transfusion	Absent	146 (70)	30 (68)	0.861			
	Present	64 (30)	14 (32)				
Portal vein resection	Absent	130 (62)	40 (90)	<0.001	1		0.197
	Present	80 (38)	4 (9)		0.441	0.127-1.530	
Combined organs resection	Absent	198 (94)	40 (91)	0.293			
	Present	12 (6)	4 (9)				
eGFR (mL/min/1.73m^2)	≥55	188 (90)	31 (70)	0.001	1		0.027
	<55	22 (10)	13 (30)		2.609	1.116-6.098	

Data are presented as Mean ± SD (range) or count (%).

C/D Clavien-Dindo, *CRT* chemoradiotherapy