Digestive Surgery

Research Article

Dig Surg 2021;38:166–174
DOI: 10.1159/000513223

Received: July 15, 2020
Accepted: November 17, 2020
Published online: February 1, 2021

Albumin Difference as a New Predictor of Postoperative Complications following Pancreatectomy

Jian Shen[a] Feng Guo[a] Yan Sun[a] Dianyun Ren[a] Jingyuan Zhao[a] Jin Hu[b] Yushun Zhang[a] Xin Jin[c] Heshui Wu[a]

[a]Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [b]Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [c]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Keywords
Pancreas surgery · Complications · Predictors · Albumin · Fluid transfusion

Abstract
Background: Postoperative complications after pancreatectomy are a challenging problem due to their high incidence and serious consequences. The majority of studies have focused on a specific complication, but data on predictors of overall postoperative complications (OPCs) are limited. ***Methods:*** The data of patients who underwent pancreatectomy at a single institute between 2017 and 2019 were analyzed retrospectively. Univariate and multivariate logistic regression were used to investigate predictors of the outcomes of interest. The Clavien-Dindo classification and comprehensive complication index (CCI) were used to assess postoperative complications and the severity of postoperative complications. The relationship between predictors and the CCI was evaluated by linear regression. ***Results:*** A total of 490 patients were divided into a training group (n = 339) and a validation group (n = 151). The rate of OPCs was 44.25%. Fluid transfusion and albumin difference (AD) were predictors of OPCs. AD showed a good discrimination (AUC = 0.70) and good calibration in the validation cohort. AD was associated with complications, including pancreatic fistula, intra-abdominal hemorrhage, intra-abdominal infection, delayed gastric emptying, and re-intervention, and was positively correlated with complication severity. Intraoperative blood loss and preoperative albumin were independent predictors of AD. ***Conclusions:*** AD, a variable that reflects dynamic physiological changes is a new and accessible predictor of OPCs following pancreatectomy.

Introduction

An increasing trend in the incidence of pancreatic neoplasms has occurred in recent years [1, 2]. Surgical resection remains the only potentially curative treatment for neoplasms and pancreatic surgery is increasingly performed [3]. Although great progress has been made in medical management, pancreatic surgery remains one of the most high-risk procedures with an incidence of overall postoperative complications (OPCs) of up to 70% [4, 5] and a 90-day postoperative mortality rate of up to 10% in a low-volume center [6]. The occurrence of OPCs can

karger@karger.com
www.karger.com/dsu

Karger

Heshui Wu
Department of Pancreatic Surgery, Union Hospital, Tongji Medical College
Huazhong University of Science and Technology
1277 Jiefang Avenue, Wuhan 430022 (China)
heshuiwu@hust.edu.cn

increase not only the economic burden and workload but also psychological pressure. Pancreatic surgeons must maintain a high level of vigilance to ensure an uneventful postoperative course for the patients. Postoperative pancreatic fistula (POPF), abdominal hemorrhage, sepsis, and intra-abdominal collections are common OPCs [7, 8]. POPF has attracted much attention from researchers, and the majority of current predictors are mainly based on distal pancreatectomy (DP) or pancreaticoduodenectomy (PD). The predictors of OPCs after pancreatectomy are a topic of continuing interest and could help doctors stratify patients and make clinical decisions [7].

Serum albumin is a widely used clinical indicator and is generally considered to be a useful marker of the liver function and nutritional status. The preoperative serum albumin level was demonstrated to be closely associated with OPCs; however, with changes in quality of life and progress in perioperative management, preoperative hypoproteinaemia is no longer a concern, especially in elective major surgery. However, the albumin difference (AD) is associated with postoperative complications [7, 9] and evidence on the relationship between the AD and OPCs following pancreatic surgery is scarce. This study aimed to evaluate the value of ADs for predicting OPCs following the pancreatic surgery.

Materials and Methods

Patient Population

The electronic medical records of patients who underwent pancreatic surgery between 2017 and 2019 at a single institution were retrospectively analyzed. The cohort included patients undergoing DP or PD. Patients were excluded if they met one of the following criteria: complicated by chronic organ insufficiency; total pancreatectomy or segmental pancreas resection; younger than 18 years; history of pancreatectomy; and presence of infection at admission. The patients were divided into 2 cohorts: the training cohort included patients diagnosed in 2017, and the validation cohort contained patients from 2018 to 2019. Written informed consent forms were obtained before the operation.

Data Collection and Definition

The primary end point of this study was OPCs, and OPCs were defined as any deviation from the normal postoperative course, which also includes some asymptomatic complications such as arrhythmia [10]. The records were examined manually, and data on patient demographics, medical history, biochemical markers, intraoperative variables, and OPCs were collected. The following main OPCs were identified: POPF, readmission, intra-abdominal hemorrhage, pneumonia, reintervention, intra-abdominal infection, reoperation, and delayed gastric emptying. The Clavien-Dindo classification (CDC) was used to stratify OPCs. The comprehensive complication index (CCI), a continuous scale used to measure OPCs, was calculated for each patient via the online tool provided at https://www.assessurgery.com/[11].

The prognostic nutritional index (PNI) was calculated on the basis of admission data as follows: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3) [12]. The AD was defined as the level of preoperative albumin minus the level of postoperative albumin on the postoperative day (POD) 1 [7]. POPF, intra-abdominal hemorrhage, and delayed gastric emptying were classified according to the 2016, 2007, and 2007 International Study Group of Pancreatic Surgery guidelines, respectively. Reintervention refers to various interventions, including endoscopy, intervention, or minor surgery, that need to be performed under local anesthesia [11]. Reoperation refers to an unplanned operation carried out under general anesthesia due to an OPC [11]. Infection was diagnosed by clinical features or microbiologic confirmation. Readmission was defined as unplanned return to hospital within 90 days of surgery. The fluid balance was defined as total fluid input minus total fluid output.

Perioperative Management

Routine blood tests and imaging examinations were performed preoperatively. Physiological and psychological adjustments were made for all patients. Antibiotic prophylaxis was given half an hour before the operation. The surgical approaches, including open or minimally invasive surgery, were carried out by surgeons with extensive experience in pancreatic surgery, and specific surgery principles and guidelines were followed. The Child's type digestive tract reconstruction technique and an end-to-side duct-to-mucosa pancreaticojejunostomy were performed in patients who underwent PD. DP was performed when the tumor was located at the body or tail of the pancreas. Except for artificial blood vessels, no additional biological materials were used. Routine peritoneal drainage tubes were placed near the stump or anastomosis.

Gastric acid suppression was routinely administered, while somatostatin and its analogs were not. Additional tests or examinations were performed when a possible complication was suspected. Early oral intake, ambulation, and withdrawal of drainage tubes were recommended. Patients in good clinical condition but with a high concentration of amylase in the drainage fluid were discharged home with drainage tubes, which were removed during their follow-up when the fistula had disappeared. The patients were followed up for at least 90 days.

Statistical Analysis

Normally distributed data were presented as means and standard deviations and evaluated by *t* tests; nonnormally distributed data were presented as medians and interquartile ranges and compared with the Mann-Whitney test; categorical variables were expressed as frequencies and analyzed with the χ^2 or Fisher's exact test. Variables with $p < 0.10$ were incorporated into the multivariable logistic regression analysis, and the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). In order to discriminate patients with and without the outcome of interest, the optimal cutoff value of continuous variable was calculated by Cutoff Finder [13]. The correlations between the AD and CCI were evaluated by linear regression models. Statistical analysis was carried out using SPSS (version 22; IBM Corp., Armonk, NY, USA) and R software (version 3.6.2). $p < 0.05$ were considered statistically significant.

Table 1. Relationship between clinicopathologic characteristics and OPCs

Variables	Overall (*n* = 339)	OPCs		Univariate analysis	Multivariate analysis	
		no (*n* = 189)	yes (*n* = 150)	*p* value	OR (95% CI)	*p* value
Age, years	54.42±12.53	54.67±12.52	54.11±12.58	0.683		
BMI, kg/m^2	22.53±3.29	22.39±3.38	22.70±3.18	0.382		
Sex						
Female	157	82	75	0.225		
Male	182	107	75			
Smoking						
Yes	95	55	40	0.620		
No	244	134	110			
Drinking						
Yes	69	38	31	0.893		
No	270	151	119			
Diabetes						
Yes	43	20	23	0.250		
No	296	169	127			
Hypertension						
Yes	83	45	38	0.746		
No	256	144	112			
Epigastric operation history						
Yes	67	40	27	0.467		
No	272	149	123			
Preoperative albumin, g/L	38.99±5.20	38.91±5.12	39.09±5.31	0.714		
Preoperative glucose, mmmol/L	5.28 (4.70–6.30)	5.28 (4.70–6.32)	5.27 (4.70–6.30)	0.988		
Preoperative total bilirubin, μmol/L	13.30 (9.00–30.60)	13.20 (8.75–29.85)	13.30 (9.47–30.70)	0.393		
Preoperative biliary drainage						
Yes	325	183	142	0.321		
No	14	6	8			
Preoperative white blood cell, 10^{12}/L	5.76±1.92	5.75±1.86	5.77±1.98	0.914		
Operative time, min	294.01±94.12	287.10±91.82	302.72±96.53	0.129		
PNI	46.57±6.91	46.63±6.97	46.51±6.86	0.018		
Pancreas duct size, mm	2.62 (2.03–4.30)	2.62 (1.99–4.39)	2.63 (2.03–4.20)	0.537		
Intraoperative red cell transfusion, U	0 (0–2)	0 (0–0.75)	0 (0–3)	0.046		
Fresh frozen plasma infusion, mL	0 (0–0)	0 (0–0)	0 (0–150)	0.015		
Intraoperative blood loss, mL	460.00 (350.00–650.00)	450.00 (350.00–600.00)	500.00 (350.00–700.00)	0.119		
Intraoperative urine output, mL	800.00 (550.00–1,275.00)	800 (550–1,225)	850 (650–1,300)	0.142		
Total fluid input, mL	4,000 (3,200–5,400)	4,000 (3,200–5,000)	4,400 (3,100–6,037)	0.047	2.407 (1.330–4.358) (>5,850 mL)	0.004
Total fluid output, mL	1,300 (1,000–1,900)	1,300 (995–1,850)	1,350 (1,050–2,055)	0.090		
Fluid balance, mL	2,700 (1,950–3,700)	2,620 (1,955–3,385)	2,705 (1,900–4,193)	0.192		
Surgical procedure						
Minimally invasive surgery	96	58	38	0.277		
Laparotomy	243	131	112			
Pancreas texture						
Soft	149	75	74	0.075		
Hard	190	114	76			
Tumor size, cm	3.50 (2.17–5.00)	3.50 (2.15–4.55)	3.50 (2.10–5.00)	0.481		
Total resected lymph node	10.00 (5.00–17.00)	10.00 (5.00–18.00)	10.00 (5.00–16.00)	0.305		
Pathology						
Pancreatic cancer and chronic pancreatitis	182	94	88	0.101		
Other	157	95	62			
Tumor location						
Pancreatic head	193	107	86	0.894		
Pancreatic body and tail	146	82	64			
AD, g/L	11.18±4.59	9.66±4.07	13.08±4.51	<0.001	3.824 (2.584–6.438) (>11.50 g/L)	<0.001

CI, confidence interval; OR, odds ratio; PNI, prognostic nutritional index; AD, albumin difference; OPCs, overall postoperative complications.

Table 2. Clinicopathological correlations of patients classified by AD

Variables	Overall (*n* = 339)	AD		Univariate analysis	Multivariate analysis	
		≤11.50 g/L (*n* = 192)	>11.50 g/L (*n* = 147)	*p* value	OR (95% CI)	*p* value
Age, years	54.42±12.53	54.89±12.06	53.80±13.13	0.429		
BMI, kg/m^2	22.53±3.29	22.37±3.47	22.74±3.05	0.300		
Sex						
Female	157	84	73	0.280		
Male	182	108	74			
Smoking						
Yes	95	54	41	0.962		
No	244	138	106			
Drinking						
Yes	69	39	30	0.983		
No	270	153	117			
Diabetes mellitus						
Yes	43	20	23	0.152		
No	296	172	124			
Hypertension						
Yes	83	47	36	0.998		
No	256	145	111			
Epigastric operation history						
Yes	67	42	25	0.265		
No	272	150	122			
Preoperative glucose, mmol/L	5.28 (4.70–6.30)	5.23 (4.70–6.30)	5.43 (4.68–6.50)	0.394		
Preoperative jaundice						
Yes	113	66	47	0.642		
No	226	126	100			
Preoperative biliary drainage						
Yes	14	10	4	0.254		
No	325	182	143			
Preoperative albumin, g/L	38.99±5.20	38.04±5.23	40.24±4.90	<0.001	1.101 (1.049–1.156)	<0.001
Operative time, min	294.01±94.12	287.10±89.44	303.04±99.49	0.122		
Pancreas duct size, mm	3.51±2.31	3.47±2.15	3.55±2.51	0.758		
Intraoperative red cell transfusion						
Yes	96	50	46	0.331		
No	243	142	101			
Fresh frozen plasma infusion						
Yes	75	39	36	0.360		
No	264	153	111			
Intraoperative blood loss (>695 mL)						
Yes	77	32	45	0.002	1.905 (1.060–3.423)	0.031
No	262	160	102			
Intraoperative urine output, mL	800.00 (600.00–1250.00)	800.00 (600.00–1300.00)	800.00 (600.00–1200.00)	0.703		
Total fluid input (> 6,100 mL)						
Yes	56	21	35	0.002		
No	283	171	112			
Total fluid output (> 1,175 mL)						
Yes	206	109	97	0.085		
No	133	83	50			
Fluid balance (> 4,225 mL)						
Yes	53	22	31	0.016		
No	286	170	116			
Surgical procedure						
Minimally invasive surgery	96	59	37	0.260		
Laparotomy	243	133	110			
Pancreas texture						
Soft	149	83	66	0.759		
Hard	190	109	81			
Tumor size	3.50 (2.17–5.00)	3.20 (2.00–4.50)	3.50 (2.50–5.00)	0.119		
Total resected lymph node	10.00 (5.00–17.00)	9.00 (4.00–18.00)	10.00 (5.00–17.00)	0.690		
Pathology						
Pancreatic cancer and chronic pancreatitis	182	104	78	0.840		
Other	157	88	69			
Tumor location						
Pancreatic head	193	111	82	0.741		
Pancreatic body and tail	146	81	65			

AD, albumin difference.

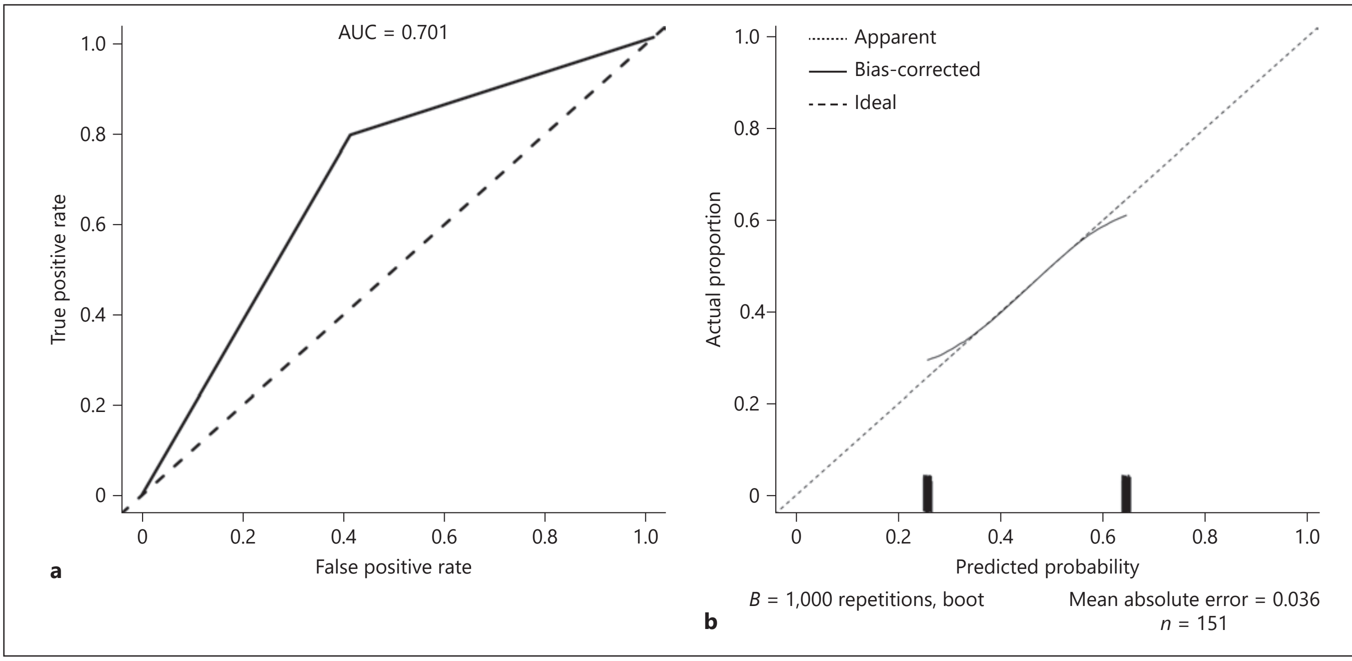


Fig. 1. The ROC curve and calibration curve of the AD. **a** The AUC under the ROC curve was 0.70. **b** The calibration curve of the DA showed accurate predictive ability. AD, albumin difference.

Results

A total of 512 patients were identified, and 22 patients were excluded: 7 for chronic renal insufficiency, 2 for chronic cardiac insufficiency, 9 for a pancreatectomy history, 2 for total pancreatectomy, and 2 due to age younger than 18 years. Finally, 490 patients were included in the final analysis; 339 patients were assigned to the training group and 151 were assigned to the validation group.

In the training group, a total of 150 (44.25%) patients experienced OPCs, among which 26 (7.67%), 68 (20.06%), 37 (10.91%), 16 (4.72%), and 3 (0.89%) patients presented CDC I, II, III, IV, and V complications, respectively. Three deaths were observed after surgery, 2 for POPF-related complications, and one for acute bleeding.

Clinicopathologic Characteristics of Patients in the Training Group

Among the 339 patients, 182 were male and 157 were female with an average age of 54.42 ± 12.53 years and a BMI of 22.53 ± 3.29 kg/m^2. The most common comorbidity was hypertension (24.48%). A total of 19.76% of the patients had a history of epigastric operation. A total of 193 (56.93%) patients underwent PD and 146 (43.07%) patients underwent DP. The median tumor size was 3.50 cm. The mean level of DA was 11.18 ± 4.59 g/L. Clinicopathologic characteristics are shown in Table 1.

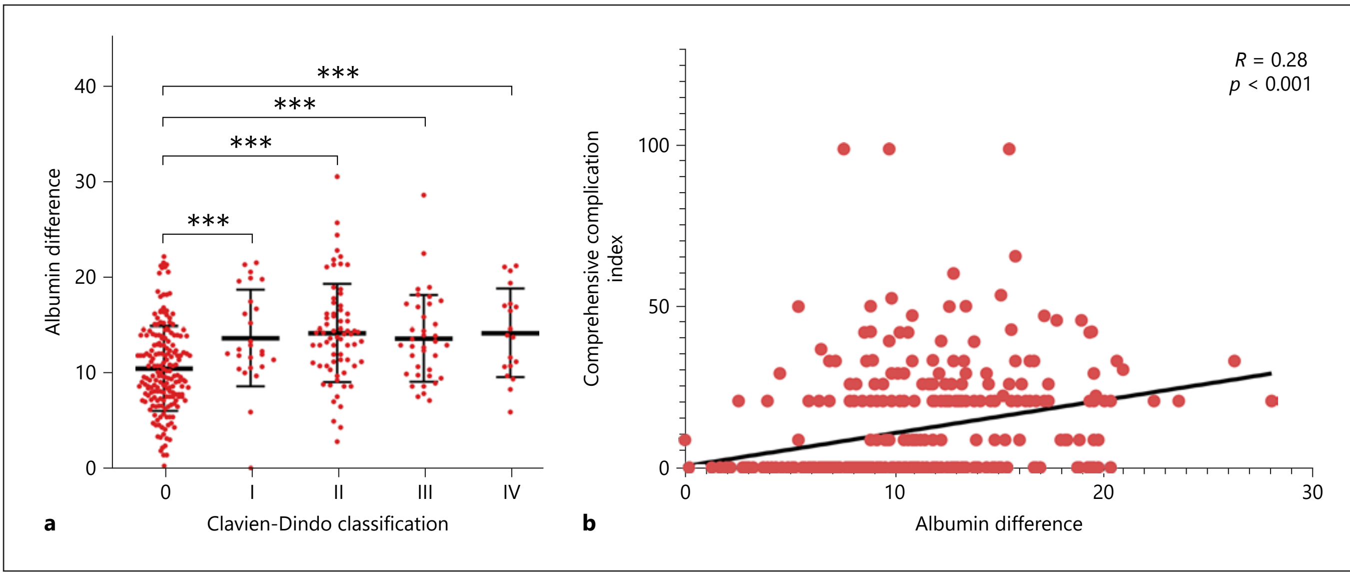
Univariate and Multivariate Regression Analysis of Predictive Factors

Variables suggested previously or thought to be clinically important were included in this analysis. As shown in Table 1, PNI ($p = 0.018$), intraoperative red cell transfusion ($p = 0.046$), fresh frozen plasma infusion ($p = 0.015$), total fluid input ($p = 0.047$), and AD ($p < 0.001$) may be associated with OPCs according to the univariate analysis.

The optimal cutoff value of the AD and total fluid input for predicting OPCs were 11.50 g/L and 5,850 mL. Those variables were entered into the logistic regression analysis using a stepwise backward method. Finally, total fluid inputs (>5,850 mL, OR = 2.407, 95% CI: 1.330–4.358, $p = 0.004$) and AD (>11.50 g/L, OR = 3.824, 95% CI: 2.584–6,438, $p < 0.001$) were independently correlated with OPCs. The C statistic was 0.73, and a moderate predictive ability was shown.

Associations between AD and Clinicopathological Variables

To clarify which clinicopathological variables are related to DA, the relationship between them was assessed.



Color version available online

Fig. 2. AD and complication severity. **a** The associations between AD and CDC grade (***$p < 0.001$). **b** The relationship between AD and CCI. CDC, Clavien-Dindo classification; AD, albumin difference; CCI, comprehensive complication index.

Of all 339 patients, 147 patients (43.36%) had AD > 11.50 g/L. The results suggested that preoperative albumin ($p <$ 0.001), intraoperative blood loss ($p = 0.002$), total fluid input ($p = 0.002$), and fluid balance ($p = 0.016$) may be associated with higher AD. The details are shown in Table 2. The logistic regression showed that blood loss (> 695 mL, OR = 1.905, 95% CI: 1.060–3.423, $p = 0.031$) and preoperative albumin (OR = 1.101, 95% CI: 1.049–1.156, $p < 0.001$) were independently associated with AD.

Internal Validation of the Cutoff Value of AD

The performance of the cutoff value of AD was further validated in our validation dataset (Fig. 1). Patients were divided into 2 groups based on the cutoff value of 11.50 g/L of AD. The AUC was 0.70, showing good discrimination ability (Fig. 1a). The calibration curves displayed good concordance between the prediction and actual observations (Fig. 1b). The result indicated that the cutoff value of AD may be used to predict the occurrence of OPCs.

Subgroup Analysis of Complications

Delayed gastric emptying (19.47%), POPF (17.40%), intra-abdominal infection (16.22%), and intra-abdominal hemorrhage (9.14%) were the most common OPCs. The relationship between the AD and the main OPCs was analyzed to further understand whether the AD is related to specific OPCs. Analysis revealed that delayed gastric emptying, pancreatic fistula, intra-abdominal hemorrhage, intra-abdominal infection, and re-intervention occurred more frequently when the AD value was >11.50 g/L ($p < 0.05$) (Table 3).

AD and Complication Severity

We further evaluated the correlation between AD and complication severity. The CDC and CCI, which are used to evaluate postoperative complication severity, were included in this study. Patients with any CDC grade complication were more inclined to present a higher AD (patients with grade V complications were not included due to their limited size) (shown in Fig. 2a). A small but significant positive correlation between the AD and the CCI was found ($R = 0.28$, $p < 0.001$, shown in Fig. 2b).

Discussion

Pancreatectomy remains a challenging procedure with substantial potential for OPCs. The incidence of OPCs was 44.25% in this study; delayed gastric emptying occurred most frequently (19.47%), followed by POPF (17.40%), intra-abdominal infection (16.22%), and intra-abdominal hemorrhage (9.14%). The PNI, an effective prognostic factor in several cancers [12] was not a predictor of OPCs. AD

Table 3. Relationship between AD and postoperative complications

Complications	Incidence, %	AD ≤11.5 (*n* = 192)	AD >11.5 (*n* = 147)	*p* value
Pancreatic fistula				
Yes	17.40	15	44	<0.001
No	82.60	177	103	
Intra-abdominal hemorrhage				
Yes	9.14	11	20	0.014
No	90.16	181	127	
Intra-abdominal infection				
Yes	16.22	22	33	0.007
No	83.78	170	114	
Delayed gastric emptying				
No	80.53	162	111	0.038
A	12.68	19	24	
B	5.02	6	11	
C	1.77	5	1	
Pneumonia				
Yes	5.31	7	11	0.118
No	94.69	185	136	
Re-intervention				
Yes	8.55	10	19	0.012
No	91.45	182	128	
Reoperation				
Yes	4.13	6	8	0.288
No	95.87	186	139	
Readmission				
Yes	5.60	7	12	0.073
No	94.40	185	135	
Clavien-Dindo classification				
0	55.75	133	56	<0.001
I	7.67	13	13	
II	20.06	23	45	
IIIa	8.85	12	18	
IIIb	2.06	3	4	
IVa	2.36	4	4	
IVb	2.36	2	6	
V	0.89	2	1	

AD, albumin difference.

was evaluated as a potential predictive factor for OPCs in patients after pancreatic surgery and is positively correlated with the severity of OPCs. Subgroup analysis revealed that AD was associated with delayed gastric emptying, pancreatic fistula, intra-abdominal hemorrhage, intra-abdominal infection, and re-intervention ($p < 0.05$).

Many studies have been conducted to reduce the incidence of postoperative complications. Some studies emphasized the importance of high-volume centers [6], some studies focused on the intraoperative supply cost [5], and some paid attention to the management of pancreatic anastomosis or the pancreatic stump [14, 15]. Risk stratification can play an important role in medical decisions, as doctors can make optimal strategies to prevent OPCs and improve patient care [16]. In regard to OPCs after pancreatic surgery, many doctors tend to first think of POPF. There is no doubt that POPF has attracted the attention of scholars, and numerous predictors of mitigation measures for POPF have been suggested [7, 16]. Other OPCs, such as delayed gastric emptying, intra-abdominal infection, and intra-abdominal hemorrhage, can also have serious effects on patients. Attention has previously been centered on either a single complication or single operation type [16], and few studies have focused on the overall OPCs of pancreatic surgery [16]. A recent study indicated that the level of C-reactive protein on POD 3 and POD 5 was a predictor of OPCs after PD. However, it cannot predict the occurrence of OPCs in the first 3 days after surgery [17]. Perianastomotic fluid collection after PD was suggested to be a risk factor for OPCs, but it may also be a result of OPCs [18]. In this study, the predictors may help physicians screen high-risk patients on POD 1. Intraoperative fluid transfusion and AD were identified as independent predictors of OPC risk.

Liquid therapy plays an important role in medical practice; however, excessive intraoperative fluid transfusion is associated with undesirable outcomes after various surgeries [19]. Our study is in line with previous studies. Reduced short-term complications following elective surgery were observed in patients treated with restrictive fluid management [19]. A retrospective study of 211 patients with DP demonstrated that excessive intraoperative fluid infusion was correlated with POPF [7]. Excessive fluid infusion also reported to have significant effects on outcomes following PD [20]. A higher frequency of cardiopulmonary complications in patients treated with excessive fluid was also reported [21]. Fluid transfusion is associated with cellular swelling, which impairs the cellular immunological function [22] and tissue healing [21]. A relationship was found between fluid overload and the blood coagulation state, and excessive intraoperative fluid may promote bleeding due to dilution of anticoagulants [19]. Other side effects of excessive intraoperative fluid transfusion include volume overload, tissue edema, tissue anoxia, and acidosis [7].

The results suggested that AD is an accessible and useful predictor of short-term outcomes in patients who undergo pancreatectomy. Patients with higher AD were more likely to experience uneventful postoperative course. In our validation dataset, AD with a cutoff value of 11.5 g/L showed a good discrimination and calibration ability. Preoperative hypoalbuminemia was suggested to be a risk factor for OPCs [9]. However, no difference in preoperative albumin was found between the 2 groups in our study. The mean level of AD in this study was 11.18 ± 4.59 g/L, which is consistent with the previously reported 10–15 g/L [9]. Previous studies have demonstrated that a higher AD was associated with POPF [7]. As the most abundant protein in blood, albumin plays an important role in the prevention of abnormal fluid distribution, which has been confirmed as a risk factor for complications after pancreatic surgery [24]. As albumin exists in the blood, it is easy to understand why blood loss was associated with AD. In this study, patients with higher preoperative albumin level tends more to experience higher AD, and the specific reason is still unidentified [9]. Maybe the body's compensation mechanism will not work until the serum albumin drops to a certain level. A higher AD may not be simply attributed to hemodilution. Although the total fluid input and fluid balance was correlated with AD in univariate analysis, they were not independent predictors of AD in the multivariate regression analysis ($p > 0.05$). As a negative acute-phase protein, the half-life of albumin shortens and the levels of plasma albumin decreases during the acute disease phase [23]. A higher AD may also be attributed to increased catabolism, decreased synthesis, an increased trans-capillary escape rate, and abnormal distribution [9, 23]. Unlike the majority of the predictors that reflect the physiological state at a certain moment, AD reflects the physiological dynamic changes brought by the operation, and this change may be a manifestation of the body's reserve function.

The CDC is a widely used tool for the assessment of disease severity. In this study, patients with OPCs tended to have a higher AD than patients without OPCs. However, no significant differences in AD were found among grade I-IV OPCs. As it is known, the CDC considers only the most serious complication, and other minor OPCs were ignored [11]. However, in clinical practice, patients with multiple OPCs after surgery are very common. The CCI, a continuous scale, focuses on all OPCs in individual patients [11]. In this study, a small but significant positive linear relationship between the CCI and the AD was found ($R = 0.28$, $p < 0.001$), which suggests that the AD is correlated with the severity of OPCs.

There are some limitations in this study. First, some bias, such as potential bias in the selection of information and patients, cannot be eliminated, as it was a retrospective study conducted at a single institution. Second, only the 2 most commonly used surgical procedures, PDs and DPs, were included in the study, which may limit its application value in other surgical methods, such as tumor enucleation and central pancreatectomy. Third, the sample size was limited, and further studies are needed. In addition, some data not included in the study may be important factors for OPCs.

Conclusions

Although pancreatectomy can be performed with a low rate of mortality, OPCs remain common. AD and total fluid input were independent risk factors for OPCs in patients who underwent pancreatectomy. AD as a new predictor of OPCs was associated with delayed gastric emptying, pancreatic fistula, intra-abdominal hemorrhage, intra-abdominal infection, and re-intervention, and was positively correlated with complication severity. Patients with higher AD should be regarded as a high risk group for OPCs and appropriate interventions should be taken. Intraoperative blood loss and preoperative albumin were independent predictors of AD. Due to the limitations of the study, further study should be carried out.

Statement of Ethics

Written informed consent from patients was obtained before participation. This study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (2019-S1193), and complied with the Helsinki Declaration.

Conflicts of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

The authors did not receive any funding.

Author Contributions

Study conception: H.S.W. and X.J.; study design: F.G. and J.S.; data acquisition: J.S. and Y.S.Z.; statistical analysis: J.S., J.Y.Z., and J.H.; manuscript preparation: J.S. and Y.S.; manuscript revision: D.Y.R. and X.J. J.S. and F.G contributed equally to this work.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2020;66(1):7–30.
2 Ramanathan R, Al Abbas AI, Mason T, Wolfe LG, Kaplan BJ. Age-related risks of complications after distal pancreatectomy for neuroendocrine and cystic neoplasms. HPB. 2019; 21(7):810–7.
3 El NA, Askar W, Atef E, Hanafy EE, Sultan AM, Salah T, et al. Trends and outcomes of pancreaticoduodenectomy for periampullary tumors: a 25-year single-center study of 1000 consecutive cases. World J Gastroenterol. 2017;23(38):7025–36.
4 Tung S, Davis LE, Hallet J, Mavros MN, Mahar AL, Bubis LD, et al. Population-level symptom assessment following pancreaticoduodenectomy for adenocarcinoma. JAMA Surg. 2019;154(11):e193348.
5 Brauer DG, Ohman KA, Jaques DP, Woolsey CA, Wu N, Liu J, et al. Surgeon variation in intraoperative supply cost for pancreaticoduodenectomy: is intraoperative supply cost associated with outcomes? J Am Coll Surg. 2018;226(1):37–e1.
6 Ahola R, Sand J, Laukkarinen J. Pancreatic resections are not only safest but also most cost-effective when performed in a high-volume centre: a Finnish register study. Pancreatology. 2019;19(5):769–74.
7 Shen J, Zhang Y, Hu J, Wei R, Wu H. Albumin difference as a new predictor of pancreatic fistula following distal pancreatectomy: a retrospective study of 211 consecutive patients. Langenbecks Arch Surg. 2020;405(1):55–62.
8 Watanabe N, Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, et al. The impact of stump closure techniques on pancreatic fistula stratified by the thickness of the pancreas in distal pancreatectomy. Dig Surg. 2020; 37(4):340–7.
9 Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. Intern Emerg Med. 2012;7(S3): 193–9.
10 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2):205–13.
11 de la Plaza LR, Ramia AJ, Bellon JM, Arteaga PV, Garcia AC, Lopez MA, et al. Clinical validation of the comprehensive complication index as a measure of postoperative morbidity at a surgical department: a prospective study. Ann Surg. 2018;268(5):838–44.
12 Tokunaga R, Sakamoto Y, Nakagawa S, Miyamoto Y, Yoshida N, Oki E, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. Dis Colon Rectum. 2015;58(11):1048–57.
13 Budczies J, Klauschen F, Sinn BV, Győrffy B, Schmitt WD, Darb-Esfahani S, et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One. 2012;7(12): e51862.
14 Deng Y, He S, Cheng Y, Cheng N, Gong J, Gong J, et al. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. Cochrane Database Syst Rev. 2020;3:CD009621.
15 Watanabe N, Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, et al. The impact of stump closure techniques on pancreatic fistula stratified by the thickness of the pancreas in distal pancreatectomy. Dig Surg. 2020; 37(4):340–7.
16 Mungroop TH, van Rijssen LB, van Klaveren D, Smits FJ, van Woerden V, Linnemann RJ, et al. Alternative fistula risk score for pancreatoduodenectomy (a-FRS). Ann Surg. 2019; 269(5):937–43.
17 van Dongen JC, Smits FJ, van Santvoort HC, Molenaar IQ, Busch OR, Besselink MG, et al. C-reactive protein is superior to white blood cell count for early detection of complications after pancreatoduodenectomy: a retrospective multicenter cohort study. Oxford: HPB; 2020.
18 Maehira H, Iida H, Matsunaga T, Yasukawa D, Mori H, Miyake T, et al. The location of perianastomotic fluid collection predicts postoperative complications after pancreaticoduodenectomy. Langenbecks Arch Surg. 2020 May;405:325–36.
19 Schol PB, Terink IM, Lancé MD, Scheepers HC. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. J Clin Anesth. 2016;35:26–39.
20 Sandini M, Fernández-Del Castillo C, Ferrone CR, Ruscic KJ, Eikermann M, Warshaw AL, et al. Intraoperative fluid administration and surgical outcomes following pancreaticoduodenectomy: external validation at a tertiary referral center. World J Surg. 2019;43(3): 929–36.
21 Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003;238(5):641–8.
22 Gao T, Li N, Zhang JJ, Xi FC, Chen QY, Zhu WM, et al. Restricted intravenous fluid regimen reduces the rate of postoperative complications and alters immunological activity of elderly patients operated for abdominal cancer: a randomized prospective clinical trail. World J Surg. 2012;36(5):993–1002.
23 Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. JPEN J Parenter Enteral Nutr. 2019; 43(2):181–93.
24 Sandini M, Paiella S, Cereda M, Angrisani M, Capretti G, Casciani F, et al. Perioperative interstitial fluid expansion predicts major morbidity following pancreatic surgery: appraisal by bioimpedance vector analysis. Ann Surg. 2019;270(5):923–9.