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Original Article

Postoperative complications after pancreatoduodenectomy for malignancy: results from the Recurrence After Whipple's (RAW) study

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Abstract

Background: Pancreatoduodenectomy (PD) is associated with significant postoperative morbidity. Surgeons should have a sound understanding of the potential complications for consenting and benchmarking purposes. Furthermore, preoperative identification of high-risk patients can guide patient selection and potentially allow for targeted prehabilitation and/or individualized treatment regimens. Using a large multicentre cohort, this study aimed to calculate the incidence of all PD complications and identify risk factors.

Method: Data were extracted from the Recurrence After Whipple's (RAW) study, a retrospective cohort study of PD outcomes (29 centres from 8 countries, 2012–2015). The incidence and severity of all complications was recorded and potential risk factors for morbidity, major morbidity (Clavien–Dindo grade > IIIa), postoperative pancreatic fistula (POPF), post-pancreatectomy haemorrhage (PPH) and 90-day mortality were investigated.

Results: Among the 1348 included patients, overall morbidity, major morbidity, POPF, PPH and perioperative death affected 53 per cent ($n = 720$), 17 per cent ($n = 228$), 8 per cent ($n = 108$), 6 per cent ($n = 84$) and 4 per cent ($n = 53$), respectively. Following multivariable tests, a high BMI ($P = 0.007$), an ASA grade > II ($P < 0.0001$) and a classic Whipple approach ($P = 0.005$) were all associated with increased overall morbidity. In addition, ASA grade > II patients were at increased risk of major morbidity ($P < 0.0001$), and a raised BMI correlated with a greater risk of POPF ($P = 0.001$).

Conclusion: In this multicentre study of PD outcomes, an ASA grade > II was a risk factor for major morbidity and a high BMI was a risk factor for POPF. Patients who are preoperatively identified to be high risk may benefit from targeted prehabilitation or individualized treatment regimens.

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Introduction

Pancreatoduodenectomy (PD) remains the only curative-intent treatment option for fit patients with a resectable pancreatic head adenocarcinoma (PDAC), ampullary adenocarcinoma (AA) or distal cholangiocarcinoma (CC). It is a major operation that is associated with high morbidity[1] and mortality[2] rates. Cancer recurrence is common after PD, particularly in patients with PDAC, and only around one in five achieves 5-year survival[3,4].

Due to the complexities of the resection, several general and procedure-specific complications may occur after PD. Pancreatic surgeons must have a sound understanding of the incidence of these, as this will guide the consenting process and allow them to benchmark their own complication rates when auditing. The preoperative identification of high-risk patients allows for targeted prehabilitation and/or individualized treatment regimens, which may lead to subtle gains. For example, selected patients might benefit from an intensive preoperative diet and exercise plan[5], and others might benefit from neoadjuvant chemotherapy[6]. While the latter is not currently recommended in those with resectable disease, high-risk patients who may have their adjuvant treatment delayed or omitted as a result of a serious complication may stand to benefit from this approach[6].

Several studies[7,8] have recently reported on the procedure-specific outcomes of PD, but no large studies have compiled a robust complication profile. Using a large multicentre cohort, this study aimed to calculate the incidence and severity of all PD complications and identify risk factors for overall morbidity, major morbidity, postoperative pancreatic fistula (POPF), post-pancreatectomy haemorrhage (PPH) and 90-day mortality.

Methods

Data were extracted from the Recurrence After Whipple's (RAW) study (clinicaltrials.gov identifier: NCT04596865). This study was approved by North West–Greater Manchester South Research Ethics Committee (20/NW/0397) and adhered to the standards laid down in the Declaration of Helsinki (revised 2013). The RAW study included patients that underwent PD for histologically confirmed PDAC, AA or distal CC at one of 29 participating centres between 1 June 2012 and 31 May 2015. The study involved 19 centres from the UK, three from Spain, two from Italy, and one from Australia, Austria, Mexico, Pakistan and Sudan (see *Supplementary Material* for full details). The end date of 31 May 2015 was selected so that 5-year follow-up data were available for all included patients. However, the current study did not utilize the 5-year follow-up data as it focussed on perioperative outcomes.

Each participating unit collected data from physical and electronic patient records and uploaded this onto a purpose-built electronic REDCap database (v11.0.3, Nashville, TN, USA). Details of the following were collected: patient demographics, co-morbidities, preoperative imaging and staging, neoadjuvant therapy, preoperative blood results, type of PD, postoperative management and complications, histology results, and adjuvant treatment. Specific data were collected on the following complications: postoperative pancreatic fistula (POPF), bile leak, gastro-jejunal (G-J) anastomotic leak, PPH, delayed gastric emptying (DGE), acute kidney injury, cardiac arrhythmia, chest infection, cholangitis, chyle leak, *Clostridium difficile* infection, ileus, intra-abdominal collection, liver abscess, myocardial infarction, pancreatic necrosis, pancreatitis, portal vein/superior mesenteric vein thrombosis, sepsis of unknown origin, splenic vein thrombosis, surgical site infection (SSI), urinary tract infection, deep vein thrombosis and pulmonary embolism (*Supplementary Material*).

G-J leak was categorized as grade A (no change to patient management), grade B (requiring active therapeutic intervention other than surgery) or grade C (requiring reoperation). Postoperative pancreatitis was diagnosed on imaging only; serum amylase/lipase levels were not used for this purpose. All other complications were diagnosed based on predefined clinical and/or radiological criteria. An unplanned return to theatre was defined as any emergency reoperation within the index admission. An unplanned readmission was defined as any emergency presentation within 30 days of discharge that included at least one overnight stay.

The patients were compared according to binary groupings: complications *versus* no complications, major morbidity (at least one Clavien–Dindo grade ≥ IIIa complication) *versus* no major morbidity, POPF *versus* no POPF, PPH *versus* no PPH, 90-day mortality *versus* no 90-day mortality.

Statistical methods

Categorical data are presented as frequency counts and associated percentages, and continuous data are presented as mean (s.d.) or median with interquartile range (i.q.r.). Means were compared using Student's *t*-test, distributions using the Mann–Whitney *U* test, and percentages using Pearson's χ^2 test or Fisher's exact test. Following the univariable tests, each of the outcomes in turn was fitted using logistic regression to all the key demographic variables (age, sex), baseline co-morbidities (diabetes, cardiovascular disease, respiratory disease), key risk groups (ASA grade, preoperative nodes on CT) and salient procedural features (classic Whipple *versus* pylorus-preserving approach, anastomosis type). $P < 0.05$ was considered significant. Analyses were performed using Microsoft Excel (v2103, Redmond, WA, USA) and GraphPad Prism (v9.3.1, San Diego, CA, USA).

Results

A total of 3705 patient records were assessed for eligibility and 2212 were excluded as they did not meet the inclusion criteria (*Fig. 1*). Nine records were removed as they were incomplete and 136 records were removed as they did not include data on complications. The final analysis included 1348 patients. *Table 1* displays the demographics, preoperative, intraoperative and postoperative details of those included. The mean patient age was 66 years (s.d.: 9.8 years), and 42 per cent ($n = 587$) were female. The mean BMI was 25.5 kg/m^2 (s.d.: 4.4 kg/m^2) and the ASA grade was > II in 34 per cent ($n = 467$) of cases. A classic Whipple was performed in 49 per cent ($n = 660$) of patients and 51 per cent ($n = 685$) underwent a pylorus-preserving (PPPD) approach. A pancreato-jejunostomy (P-J) was fashioned in 81 per cent ($n = 1064$) of patients and 19 per cent ($n = 246$) received a pancreato-gastrostomy (P-G). The median length of stay was 13 days (i.q.r.: 10–20 days) and 6 per cent ($n = 74$) of patients had an unplanned urgent reintervention. The 30-day readmission rate was 10 per cent ($n = 134$) and the 90-day mortality rate was 4 per cent ($n = 51$). Regarding postoperative histology, 792 (59 per cent), 363 (27 per cent) and 192 (14 per cent) patients had PDAC, AA and CC, respectively.

A total of 1340 complications were reported; 72 per cent ($n = 968$) were Clavien–Dindo grade I–II, 18 per cent ($n = 240$) were

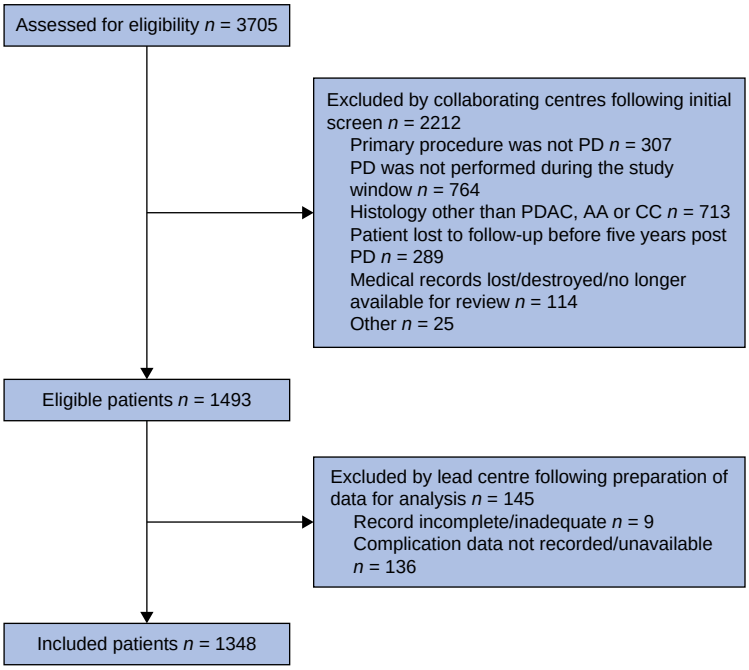

Fig. 1 Cohort flow diagram. AA, ampullary carcinoma; CC, cholangiocarcinoma; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma

Table 1 Demographic, preoperative, operative and postoperative details

Total no. of patients included	1348	
Age (years), mean (s.d.)	66.0 (9.8)	
Female gender	587 (42.4)	
BMI (kg/m^2), mean (s.d.)	25.5 (4.4)	Unknown/not recorded: 561 (40.5)
Preoperative co-morbidities		
Diabetes	277 (20.6)	Unknown/not recorded: 38*
Cardiovascular	590 (42.6)	
Respiratory	142 (10.5)	
Preoperative biliary stent	875 (63.3)	Unknown/not recorded: 2*
Neoadjuvant chemotherapy received	61 (4.6)	
Preoperative blood tests, median (i.q.r.)		
Bilirubin (μmol/l)	42 (10-52)	Unknown/not recorded: 2 (0.1)
Albumin (g/l)	10 (32-42)	Unknown/not recorded: 100 (7.4)
Neutrophils (×10^9/l)	2.8 (3.7-6.5)	Unknown/not recorded: 28 (2.1)
Lymphocytes (×10^9/l)	1.2 (1.3-2.5)	Unknown/not recorded: 28 (2.1)
ASA grade > II	467 (33.7)	Unknown/not recorded: 116*
Positive nodes on preoperative CT	324 (27.7)	Unknown/not recorded: 177*
Type of PD performed	Classic Whipple: 660 (49.1) Pylorus-preserving PD: 685 (50.9)	Unknown/not recorded: 3*
Pancreatic anastomosis	P-J: 1064 (81.2) P-G: 246 (18.8)	Unknown/not recorded: 38*
Concomitant venous resection	205 (15.5)	Unknown/not recorded: 28*
Concomitant arterial resection	25 (1.9)	Unknown/not recorded: 29*
Intraoperative blood transfusion	164 (18.1)	Unknown/not recorded: 442*
Unplanned return to theatre	74 (5.5)	
Length of stay (days), median (i.q.r.)	10 (10-20)	Unknown/not recorded: 70 (5.2)
30-day unplanned readmission	134 (10.0)	Unknown/not recorded: 5 (0.4)
90-day mortality	51 (4.0)	
Postoperative histology		
PDAC	792 (58.8)	
AA	364 (27.0)	
CC	192 (14.2)	

Values are *n* (%) unless otherwise indicated. AA, ampullary adenocarcinoma; CC, cholangiocarcinoma; CT, computed tomography; HDU, high dependency unit; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma; P-G, pancreato-gastrostomy; P-J, pancreato-jejunostomy. *Not included in percentages.

grade III, 7 per cent ($n = 79$) were grade IV, and 4 per cent ($n = 53$) were grade V (*Table 2*). Postoperative pancreatic fistula (excluding biochemical leaks), PPH, chyle leak, bile leak and G-J leak affected 8 per cent ($n = 108$), 6 per cent ($n = 84$), 4 per cent ($n = 47$), 3 per cent ($n = 44$) and 2 per cent ($n = 20$), respectively. Other notable complications included intra-abdominal collection (160; 12 per cent), SSI (115; 9 per cent) and chest infection (96; 7 per cent). In total, 720 patients (53 per cent) experienced at least one

Table 2 The postoperative complications recorded classified by their Clavien–Dindo grade

Postoperative complications *n* (%)	Incidence by Clavien–Dindo grade						
	I	II	IIIa	IIIb	IVa	IVb	V
Postoperative pancreatic fistula: 108 (15.6) Biochemical leak: 102 (7.6) Grade B and grade C POPF: 108 (8.0) Grade B: 85 Grade C: 23	68	91	22	14	5	5	5
Bile leak: 44 (3.3) Grade A: 13 Grade B: 18 Grade C: 13	12	9	8	7	3	2	3
Gastrojejunal leak: 20 (1.5) Grade A: 6 Grade B: 8 Grade C: 6	2	8	2	5	1	0	2
Postpancreatectomy haemorrhage: 84 (6.2) Grade A: 17 Grade B: 40 Grade C: 27	11	21	14	17	7	3	11
Delayed gastric emptying: 167 (12.4) Grade A: 73 Grade B: 59 Grade C: 35	50	97	8	9	0	2	1
Acute kidney injury: 33 (2.4)	10	9	0	0	8	2	4
Cardiac arrhythmia: 32 (2.4)	8	19	0	1	3	0	1
Chest infection: 96 (7.1)	10	70	3	0	11	1	1
Cholangitis: 6 (0.4)	0	5	0	0	1	0	0
Chyle leak: 47 (3.5)	24	17	6	0	0	0	0
Clostridium difficile infection: 9 (0.7)	0	9	0	0	0	0	0
Ileus: 37 (2.7)	15	20	0	2	0	0	0
Intra-abdominal collection: 160 (11.9)	21	64	52	16	2	1	4
Liver abscess: 13 (1.0)	1	6	6	0	0	0	0
Myocardial infarction: 3 (0.2)	0	2	0	0	1	0	0
Pancreatic necrosis: 2 (0.1)	1	0	0	0	1	0	0
Pancreatitis: 5 (0.4)	2	2	0	0	1	0	0
PV/SMV thrombosis: 16 (1.2)	1	6	1	3	1	0	4
Sepsis of unknown origin: 19 (1.4)	1	13	0	0	4	0	1
Splenic vein thrombosis: 3 (0.2)	0	2	0	0	0	0	1
Surgical site infection: 115 (8.5)	52	57	4	1	1	0	0
Urinary tract infection: 20 (1.5)	1	19	0	0	0	0	0
Deep vein thrombosis: 6 (0.4)	0	5	0	1	0	0	0
Pulmonary embolism: 15 (1.1)	4	10	0	0	0	0	1
Other complication: 177 (13.1)	34	79	16	21	9	4	14
Sum of complications ($n = 1340$) by Clavien–Dindo grade	328 (24.5%)	640 (47.8%)	142 (10.6%)	98 (7.3%)	59 (4.4%)	20 (1.5%)	53 (4.0%)

PV, portal vein; SMV, superior mesenteric vein.

complication. When patients who experienced a complication were compared to those who did not (*Table 3*), the mean BMI was higher in the former (25.9 *versus* 25.0 kg/m^2, $P = 0.003$), as was the number of patients with preoperative cardiovascular disease (47 per cent *versus* 40 per cent, $P = 0.006$) or an ASA grade > II (32 per cent *versus* 24 per cent, $P = 0.002$). The median preoperative serum albumin was lower in those who experienced morbidity (38 *versus* 39 g/l, $P = 0.004$). A higher proportion of patients who experienced complications had undergone a classic Whipple (*versus* PPPD, 53 per cent *versus* 44 per cent, $P < 0.0001$) or a P-G (*versus* P-J, 21 per cent *versus* 15 per cent, $P < 0.0001$). The histological diagnosis was similar between the groups that developed complications and the groups that did not; PDAC (54 per cent *versus* 59 per cent, $P = 0.06$), AA (29 per cent *versus* 27 per cent, $P = 0.2$) and CC (16 per cent *versus* 14 per cent, $P = 0.3$).

A total of 228 patients (17 per cent) experienced a Clavien–Dindo grade ≥ IIIa complication. This group were more often ASA grade > II (45 per cent *versus* 36 per cent, $P = 0.0006$). Patients with POPF were more often male (68 per cent *versus* 55 per cent, $P = 0.003$) or ASA grade > II (38 per cent *versus* 27 per cent, $P = 0.02$) and had a higher mean BMI (27.1 *versus* 25.3 kg/m^2, $P = 0.0002$). Those who experienced PPH had a higher median preoperative serum bilirubin (34 *versus* 20 µmol/l, $P = 0.02$), were more often ASA grade > II (44 per cent *versus* 26 per cent, $P = 0.002$) and were more likely to have received a P-G (29 per cent *versus* 18 per cent, $P = 0.02$). Patients who died within 90 days were significantly older (mean difference: 3.1 years, $P = 0.02$) but no other risk factors were identified. Among the major morbidity group, the numbers of patients with AA (33 per cent *versus* 27 per cent, $P = 0.07$) and CC (18 per cent *versus* 14 per cent, $P = 0.1$) were like that of the entire cohort. PDAC was less common among those who developed serious complications (49 per cent *versus* 59 per cent, $P = 0.04$).

Results from the multivariable analyses are displayed in *Table 4*. Factors associated with higher complication rate were increasing BMI (OR: 1.1, $P = 0.007$), ASA grade > II (OR: 2.2, $P < 0.0001$) and a classic Whipple procedure (OR: 1.2, $P = 0.01$). Only ASA grade > II correlated with major morbidity (OR: 2.2, $P < 0.0001$) and only increasing BMI (OR: 1.1, $P = 0.001$) correlated with POPF. ASA grade > II (OR: 2.5, $P = 0.002$) and positive nodes

Table 3 Univariable analysis: comparing patients by selected outcomes

Variable	Any complication ($n = 720$)	No complication ($n = 628$)	P
Age (years), mean (s.d.)	66.4 (9.6)	65.5 (10.1)	0.103
Age ≥80 years	46 (6.4)	36 (5.7)	0.649
Female sex	301 (41.8)	286 (45.5)	0.169
BMI (kg/m^2), mean (s.d.)	25.9 (4.5)	25.0 (4.2)	0.0028*
BMI ≥30 kg/m^2	82 (17.7)	40 (11.1)	0.010*
Preoperative co-morbidities			
Diabetes	144 (20.0)	133 (21.2)	0.593
Cardiovascular	340 (47.2)	250 (39.8)	0.006*
Respiratory	86 (11.9)	56 (8.9)	0.071
Preoperative biliary stent	471 (65.4)	404 (64.3)	0.700
Preoperative blood tests, median (i.q.r.)			
Bilirubin, μmol/l	20 (44)	21 (41)	0.800
Albumin, g/l	38 (12)	39 (9)	0.004*
Neutrophils ×10^9/l	4.9 (2.7)	4.9 (3.0)	0.649
Lymphocytes ×10^9/l	1.8 (1.2)	1.8 (1.1)	0.298
ASA grade > II	214 (32.3)	138 (24.2)	0.002*
Positive nodes on preoperative CT	176 (27.5)	148 (27.8)	0.948
Classic Whipple *versus* PPPD	382 (53.1)	278 (44.3)	0.0015*
P-J anastomosis *versus* P-G	553 (76.2)	511 (81.4)	0.004*
Variable	**Major morbidity ($n = 228$)**	**No major morbidity ($n = 1120$)**	**P**
Age (years), mean (s.d.)	66.0 (9.6)	66.0 (9.9)	0.905
Age ≥80 years	13 (5.7)	69 (6.2)	0.880
Female sex	96 (42.1)	491 (43.8)	0.660
BMI (kg/m^2), mean (s.d.)	25.5 (3.9)	25.5 (4.9)	0.990
BMI ≥30 kg/m^2	21 (13.8)	100 (14.9)	0.801
Preoperative co-morbidities			
Diabetes	46 (20.2)	231 (20.6)	0.929
Cardiovascular	101 (44.3)	489 (43.7)	0.884
Respiratory	21 (9.2)	121 (10.8)	0.554
Preoperative biliary stent	141 (61.8)	734 (65.5)	0.288
Preoperative blood tests, median (i.q.r.)			
Bilirubin, μmol/l	19 (52)	21 (41)	0.573
Albumin, g/l	37 (13)	38 (10)	0.456
Neutrophils ×10^9/l	5.0 (2.7)	4.9 (2.9)	0.650
Lymphocytes ×10^9/l	1.8 (1.4)	1.8 (1.1)	0.463
ASA grade > II	81 (39.3)	271 (26.4)	0.0003*
Positive nodes on preoperative CT	56 (27.9)	268 (27.6)	0.931
Classic Whipple *versus* PPPD	123 (54.0)	537 (47.9)	0.110
P-J anastomosis *versus* P-G	176 (77.2)	888 (79.3)	0.477
Variable	**Grade B/C POPF ($n = 142$)**	**No grade B/C POPF ($n = 1206$)**	**P**
Age (years), mean (s.d.)	65.6 (10.5)	66.0 (9.8)	0.595
Age ≥80 years	11 (7.7)	71 (5.9)	0.355
Female sex	45 (31.7)	542 (44.9)	0.003*
BMI (kg/m^2), mean (s.d.)	27.1 (4.5)	25.3 (4.3)	0.0002*
BMI ≥30 kg/m^2	21 (20.1)	100 (13.8)	0.070
Preoperative co-morbidities			
Diabetes	23 (16.2)	254 (21.1)	0.119
Cardiovascular	71 (50.0)	519 (43.0)	0.128
Respiratory	21 (14.8)	121 (10.0)	0.084
Preoperative biliary stent	95 (66.9)	780 (64.7)	0.643
Preoperative blood tests, median (i.q.r.)			
Bilirubin (μmol/l)	19 (54)	21 (42)	0.992
Albumin (g/l)	37 (11)	38 (10)	0.828
Neutrophils (×10^9/l)	4.9 (3.1)	4.9 (2.7)	0.831
Lymphocytes (×10^9/l)	1.9 (1.35)	1.8 (1.35)	0.195
ASA grade >II	51 (37.8)	301 (27.4)	0.0152*
Positive nodes on preoperative CT	35 (27.3)	289 (27.7)	1.00
Classic Whipple *versus* PPPD	76 (53.5)	584 (48.5)	0.287
P-J anastomosis *versus* P-G	111 (78.7)	953 (81.5)	0.425
Variable	**PPH ($n = 84$)**	**No PPH ($n = 1264$)**	**P**
Age (years), mean (s.d.)	65.0 (10.0)	66.0 (9.8)	0.330
Age ≥80 years	3 (3.6)	79 (6.3)	0.477
Female sex	36 (42.9)	551 (43.6)	0.910
BMI (kg/m^2), mean (s.d.)	25.5 (3.9)	25.5 (4.4)	0.898
BMI ≥30 kg/m^2	9 (14.5)	112 (14.7)	1.00

(continued)

Table 3 (continued)

Variable	PPH ($n = 84$)	No PPH ($n = 1264$)	P
Preoperative co-morbidities			
Diabetes	11 (13.1)	266 (21.1)	0.094
Cardiovascular	30 (35.7)	560 (44.3)	0.140
Respiratory	6 (7.1)	136 (10.8)	0.361
Preoperative biliary stent	48 (57.1)	827 (65.5)	0.125
Preoperative blood tests, median (i.q.r.)			
Bilirubin (μmol/l)	33.5 (122.5)	20 (40)	0.0219*
Albumin (g/l)	36 (11.5)	38 (10)	0.474
Neutrophils ($\times 10^9$/l)	5.0 (2.7)	4.9 (2.8)	0.707
Lymphocytes ($\times 10^9$/l)	1.8 (1.4)	1.8 (1.1)	0.985
ASA grade > II	35 (44.3)	317 (27.5)	0.002*
Positive nodes on preoperative CT	30 (37.5)	294 (26.9)	0.0515
Classic Whipple *versus* PPPD	48 (57.8)	612 (48.5)	0.113
P-J anastomosis *versus* P-G	60 (71.4)	1004 (81.9)	0.0211*
Variable	**90-day mortality ($n = 51$)**	**Alive at 90 days ($n = 1297$)**	**P**
Age (years), mean (s.d.)	69.0 (10.6)	65.8 (9.8)	0.0219*
Age ≥80 years	6 (11.8)	76 (5.9)	0.122
Female sex	22 (43.1)	565 (43.6)	1.00
BMI (kg/m^2), mean (s.d.)	25.5 (5.0)	25.5 (4.4)	0.929
BMI ≥30 kg/m^2	6 (11.8)	115 (14.5)	0.452
Preoperative co-morbidities			
Diabetes	15 (29.4)	262 (20.2)	0.114
Cardiovascular	26 (51.0)	564 (43.5)	0.315
Respiratory	2 (3.9)	140 (10.8)	0.160
Preoperative biliary stent	31 (60.8)	844 (65.2)	0.551
Preoperative blood tests, median (i.q.r.)			
Bilirubin (μmol/l)	17 (39)	21 (43)	0.287
Albumin (g/l)	35 (11)	38 (10)	0.233
Neutrophils ($\times 10^9$/l)	5.1 (3.5)	4.9 (2.7)	0.706
Lymphocytes ($\times 10^9$/l)	1.8 (0.8)	1.8 (1.2)	0.896
ASA grade > II	18 (40.0)	334 (28.2)	0.093
Positive nodes on preoperative CT	16 (35.6)	308 (27.4)	0.236
Classic Whipple *versus* PPPD	25 (49.0)	635 (49.1)	1.00
P-J anastomosis *versus* P-G	43 (89.6)	1021 (80.9)	0.185

Values are *n* (%) unless otherwise indicated. Major morbidity includes any Clavien–Dindo grade ≥ IIIa complication. Statistical methods: Student's *t*-test: age, BMI, Fisher's exact test: sex, co-morbidities, preoperative biliary stent, ASA grade, positive nodes on preoperative CT, classic Whipple *versus* PPPD, P-J *versus* P-G, Mann–Whitney *U* test: blood tests. Where data were missing (*Table 1*), patients were excluded from the relevant subanalysis. CR-POPF, clinically relevant postoperative pancreatic fistula; PD, pancreatoduodenectomy; P-G, pancreato-gastrostomy; PPH, post-pancreatectomy haemorrhage; P-J, pancreato-jejunostomy; PP, pylorus preserving. *Denotes statistical significance.

on preoperative imaging (OR: 2.1, $P = 0.01$) were associated with an increased risk of PPH. Preoperative diabetes (OR: 0.4, $P = 0.045$) and a P-J anastomosis (OR: 0.5, $P = 0.03$) were associated with a decreased risk of PPH. Interestingly, none of the studied variables had a significant relationship with 90-day mortality.

Discussion

This study described the complications experienced by a large cohort of patients who underwent PD for PDAC, AA or distal CC. While prior multicentre studies have been carried out with similar patient numbers, few have used strict diagnostic criteria and few have included only patients with a histologically confirmed cancer[9]. The patient demographics and postoperative outcomes of the present study were comparable to that of the current literature[10–12].

The incidence of POPF in the current study was 8 per cent, lower than the 10–35 per cent observed in most series[10,11,13,14]. The lower observed incidence among the RAW cohort could reflect the fact that only patients with a histologically confirmed cancer were included and that most of them had PDAC (59 per cent). Indeed, PDAC patients tend to have a firmer pancreas compared to those with AA or CC[15,16]. Similar to Lovasik *et al.*, this study observed that patients with a high BMI more often experienced POPF[17]. This may be because patients with a high BMI had a higher parenchymal fat content. This study did not observe a relationship between POPF and a P-J anastomosis, preoperative biliary drainage or preoperative diabetes, while Williamsson *et al.* found that a P-J was a risk factor and that both preoperative biliary drainage and preoperative diabetes were protective for POPF[18].

PPH is one of the most common causes of reoperation and death after PD[2]. The reported incidence is between 4 and 14 per cent[9,11], comparable to the current study (6 per cent). PPH was the leading cause of perioperative death among the RAW cohort, and, as previously described[19], preoperative diabetes was a protective factor for PPH.

Similar to other published series[20], the RAW patients who experienced morbidity had a significantly higher BMI than those who did not. Patients with a high BMI are likely to have a worse baseline fitness level; are often challenging to ventilate, which can increase the risk of respiratory and anaesthetic complications; and present technical challenges from a surgical point of view. In a recent meta-analysis by You *et al.*, patients with a BMI ≥ 25 kg/m^2 were compared to those with a BMI < 25 kg/m^2. The former were found to have longer operation times, increased intraoperative blood loss, higher rates of POPF, DGE and SSI, and a longer hospital stay[21].

The ASA impact on outcomes after pancreatic surgery is well documented[22,23]. The present study found that ASA grade > II

Table 4 Multivariable analysis: comparing patients by selected outcomes

Variable	Any complication OR (s.d.)	P
Age	1.009 (0.008)	0.261
Female sex (*versus* male)	0.918 (0.146)	0.589
BMI	1.054 (0.020)	0.007*
Preoperative diabetes	0.772 (0.157)	0.203
Preoperative cardiovascular disease	1.017 (0.170)	0.918
Preoperative respiratory disease	1.596 (0.449)	0.097
ASA grade > II	2.208 (0.404)	<0.00001*
Positive nodes on preoperative CT	0.835 (0.149)	0.313
Classic Whipple (*versus* PPPD)	1.589 (0.259)	0.005*
P-J anastomosis (*versus* P-G)	0.742 (0.154)	0.150
Variable	**Major morbidity OR (s.d.)**	**P**
Age	0.991 (0.010)	0.385
Female sex (*versus* male)	1.036 (0.202)	0.856
BMI	1.005 (0.023)	0.826
Preoperative diabetes	0.972 (0.238)	0.907
Preoperative cardiovascular disease	0.839 (0.180)	0.412
Preoperative respiratory disease	0.544 (0.188)	0.079
ASA grade > II	2.159 (0.429)	<0.00001*
Positive nodes on preoperative CT	1.220 (0.269)	0.365
Classic Whipple (*versus* PPPD)	1.245 (0.258)	0.290
P-J anastomosis (*versus* P-G)	1.155 (0.280)	0.552
Variable	**Grade B/C POPF OR (s.d.)**	**P**
Age	1.005 (0.013)	0.671
Female sex (*versus* male)	0.763 (0.181)	0.255
BMI	1.093 (0.028)	0.001*
Preoperative diabetes	0.611 (0.189)	0.111
Preoperative cardiovascular disease	1.087 (0.274)	0.739
Preoperative respiratory disease	1.269 (0.428)	0.480
ASA grade > II	1.096 (0.273)	0.712
Positive nodes on preoperative CT	1.600 (0.401)	0.061
Classic Whipple (*versus* PPPD)	0.819 (0.201)	0.414
P-J anastomosis (*versus* P-G)	1.072 (0.315)	0.813
Variable	**PPH OR (s.d.)**	**P**
Age	0.983 (0.014)	0.224
Female sex (*versus* male)	1.032 (0.291)	0.911
BMI	1.002 (0.032)	0.954
Preoperative diabetes	0.397 (0.183)	0.045*
Preoperative cardiovascular disease	0.638 (0.203)	0.158
Preoperative respiratory disease	0.392 (0.242)	0.129
ASA grade > II	2.470 (0.709)	0.002*
Positive nodes on preoperative CT	2.065 (0.603)	0.013*
Classic Whipple (*versus* PPPD)	1.718 (0.511)	0.069
P-J anastomosis (*versus* P-G)	0.510 (0.155)	0.027*
Variable	**90-day mortality OR (s.d.)**	**P**
Age	1.029 (0.025)	0.242
Female sex (*versus* male)	1.436 (0.608)	0.393
BMI	1.007 (0.049)	0.889
Preoperative diabetes	1.307 (0.636)	0.583
Preoperative cardiovascular disease	1.140 (0.519)	0.774
Preoperative respiratory disease	0.317 (0.329)	0.268
ASA grade > II	1.043 (0.470)	0.925
Positive nodes on preoperative CT	1.969 (0.863)	0.122
Classic Whipple (*versus* PPPD)	1.193 (0.523)	0.687
P-J anastomosis (*versus* P-G)	2.488 (1.626)	0.163

Major morbidity includes any Clavien-Dindo grade ≥ IIIa complication. Where data were missing (*Table 1*), patients were excluded from the relevant subanalysis. CR-POPF, clinically relevant postoperative pancreatic fistula; PD, pancreatoduodenectomy; P-G, pancreato-gastrostomy; PPH, post-pancreatectomy haemorrhage; P-J, pancreato-jejunostomy; PP, pylorus preserving. *Denotes statistical significance.

patients were more than twice as likely to develop complications, major morbidity or PPH. As such, one should consider the additional risks when offering PD to patients in this group, especially if they are elderly or have a high BMI.

A classic PD was found to be more common among those who experienced complications. Data in the literature are conflicting and several studies have shown that the operative approach does not significantly affect perioperative outcomes[24,25].

A P-G anastomosis was associated with higher rates of overall morbidity and PPH, as described in many studies in the literature[26,27]. Several other studies have found no advantage of one type of reconstruction compared to the other[28,29].

The preoperative identification of patients who are at high-risk for adverse perioperative outcomes is important for their management. 'Prehabilitation' is the concept of enhancing general health and well-being in high-risk patients prior to surgery[30]. Interventions could be multimodal and could include activities such as a structured exercise programme or a patient-centred dietary plan[5]. Prehabilitation programmes aim to help patients 'weather the storm' of an operation and reduce the morbidity associated with major surgery. Although evidence of their effectiveness in improving PD outcomes is limited, recent studies have highlighted the potential benefits that prehabilitation programmes can provide[5]. A recent survey of UK pancreatic surgeons suggested that around half of British centres offer a prehabilitation programme to PD patients, but there was little consistency in what was offered[31]. As further evidence emerges, it is likely that consensus guidelines will be formulated that will advise what should be offered and to whom. The preoperative identification of high-risk patients may help identify those who have the most to gain from prehabilitation.

Patients who are preoperatively deemed to be high risk may wish to reconsider the treatment to be received, as serious complications can affect suitability for adjuvant treatment[6]. While neoadjuvant treatment is not routinely offered to patients with resectable disease in many centres, a subset of patients (for example, those with a high BMI or ASA > II) might benefit from a tailored treatment approach. In high-risk individuals, a course of neoadjuvant therapy would ensure that a course of systemic therapy is delivered (regardless of the postoperative course).

This study had several weaknesses and biases due to its retrospective nature, and practice has evolved since the study inclusion period. While a robust data set has been produced, this was not complete. As is inevitable with large multicentre studies, the larger high-volume centres provided more cases than the smaller low-volume centres. Data for the intraoperative period, such as main pancreatic duct diameter and parenchyma texture, which are known for their association with POPF, were not collected and it was not possible to compare the cases from the different collaborating centres as the data set was fully anonymized.

In this multicentre study of patients who underwent PD for malignancy, the major morbidity rate was 17 per cent and the perioperative mortality rate was 4 per cent. A high BMI and an ASA grade > II were associated with POPF and major morbidity, respectively. Patients who fall into these subgroups should be made aware of the additional risks they face. The preoperative identification of high-risk patients is important as this group may benefit from a tailored treatment approach—for example, targeted prehabilitation or neoadjuvant chemotherapy.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

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