



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 morbidity¹ and mortality² 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 plan⁵, and others might benefit from neoadjuvant chemotherapy⁶. 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 approach⁶.

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 \geq 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/m² (s.d.: 4.4 kg/m²) 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 reoperation. 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

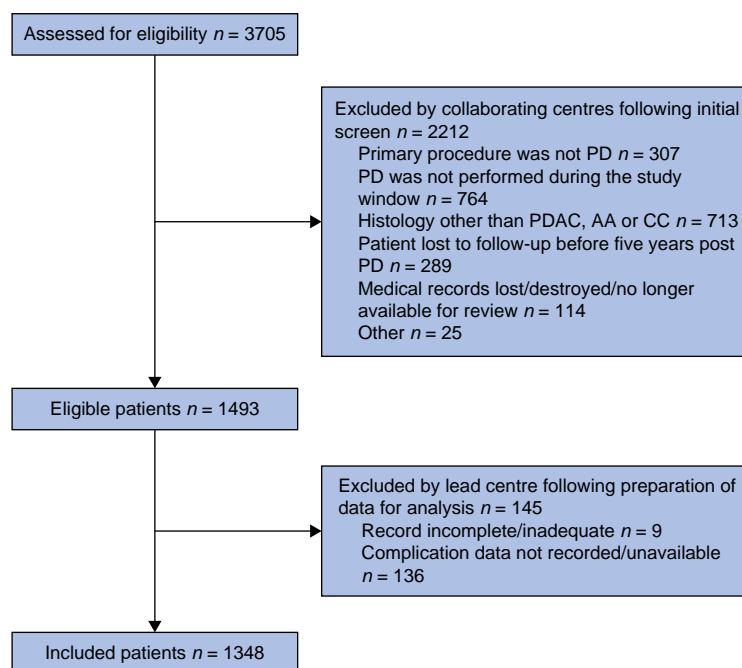


Fig. 1 Cohort flow diagram. AA, ampullary carcinoma; CC, cholangiocarcinoma; PD, pancreatoduodenectomy; PDAC, pancreatic ductal adenocarcinoma

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) | 68 | 91 | 22 | 14 | 5 | 5 | 5 |
| Biochemical leak: 102 (7.6) | | | | | | | |
| Grade B and grade C POPF: 108 (8.0) | | | | | | | |
| Grade B: 85 | | | | | | | |
| Grade C: 23 | | | | | | | |
| Bile leak: 44 (3.3) | 12 | 9 | 8 | 7 | 3 | 2 | 3 |
| Grade A: 13 | | | | | | | |
| Grade B: 18 | | | | | | | |
| Grade C: 13 | | | | | | | |
| Gastrojejunal leak: 20 (1.5) | 2 | 8 | 2 | 5 | 1 | 0 | 2 |
| Grade A: 6 | | | | | | | |
| Grade B: 8 | | | | | | | |
| Grade C: 6 | | | | | | | |
| Postpancreatectomy haemorrhage: 84 (6.2) | 11 | 21 | 14 | 17 | 7 | 3 | 11 |
| Grade A: 17 | | | | | | | |
| Grade B: 40 | | | | | | | |
| Grade C: 27 | | | | | | | |
| Delayed gastric emptying: 167 (12.4) | 50 | 97 | 8 | 9 | 0 | 2 | 1 |
| Grade A: 73 | | | | | | | |
| Grade B: 59 | | | | | | | |
| Grade C: 35 | | | | | | | |
| 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/m², $P=0.003$), 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 \geq 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/m², $P=0.0002$). Those who experienced PPH had a higher median preoperative serum bilirubin (34 versus 20 μ mol/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 ($\mu\text{mol/l}$) | 33.5 (122.5) | 20 (40) | 0.0219* |
| Albumin (g/l) | 36 (11.5) | 38 (10) | 0.474 |
| Neutrophils ($\times 10^9/\text{l}$) | 5.0 (2.7) | 4.9 (2.8) | 0.707 |
| Lymphocytes ($\times 10^9/\text{l}$) | 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 ($\mu\text{mol/l}$) | 17 (39) | 21 (43) | 0.287 |
| Albumin (g/l) | 35 (11) | 38 (10) | 0.233 |
| Neutrophils ($\times 10^9/\text{l}$) | 5.1 (3.5) | 4.9 (2.7) | 0.706 |
| Lymphocytes ($\times 10^9/\text{l}$) | 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 \geq 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 cancer⁹. 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 POPF¹⁷. 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 POPF¹⁸.

PPH is one of the most common causes of reoperation and death after PD². 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 described¹⁹, preoperative diabetes was a protective factor for PPH.

Similar to other published series²⁰, 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 stay²¹.

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 (<i>versus</i> 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 (<i>versus</i> PPPD) | 1.589 (0.259) | 0.005* |
| P-J anastomosis (<i>versus</i> P-G) | 0.742 (0.154) | 0.150 |
| Variable | Major morbidity OR (s.d.) | P |
| Age | 0.991 (0.010) | 0.385 |
| Female sex (<i>versus</i> 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 (<i>versus</i> PPPD) | 1.245 (0.258) | 0.290 |
| P-J anastomosis (<i>versus</i> 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 (<i>versus</i> 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 (<i>versus</i> PPPD) | 0.819 (0.201) | 0.414 |
| P-J anastomosis (<i>versus</i> P-G) | 1.072 (0.315) | 0.813 |
| Variable | PPH OR (s.d.) | P |
| Age | 0.983 (0.014) | 0.224 |
| Female sex (<i>versus</i> 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 (<i>versus</i> PPPD) | 1.718 (0.511) | 0.069 |
| P-J anastomosis (<i>versus</i> 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 (<i>versus</i> 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 (<i>versus</i> PPPD) | 1.193 (0.523) | 0.687 |
| P-J anastomosis (<i>versus</i> P-G) | 2.488 (1.626) | 0.163 |

Major morbidity includes any Clavien-Dindo grade \geq 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 surgery³⁰. Interventions could be multimodal and could include activities such as a structured exercise programme or a patient-centred dietary plan⁵. 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 provide⁵. 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 offered³¹. 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 treatment⁶. 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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