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Early postoperative risk stratification in patients with pancreatic fistula after pancreaticoduodenectomy

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ABSTRACT

Background: Early stratification of postoperative pancreatic fistula according to severity and/or need for invasive intervention may improve outcomes after pancreaticoduodenectomy. This study aimed to identify the early postoperative variables that may predict postoperative pancreatic fistula severity.
Methods: All patients diagnosed with biochemical leak and clinically relevant-postoperative pancreatic fistula based on drain fluid amylase >300 U/L on the fifth postoperative day after pancreaticoduodenectomy were identified from a consecutive cohort from Birmingham, UK. Demographics, intraoperative parameters, and postoperative laboratory results on postoperative days 1 through 7 were retrospectively extracted. Independent predictors of clinically relevant-postoperative pancreatic fistula were identified using multivariable binary logistic regression and converted into a risk score, which was applied to an external cohort from Verona, Italy.
Results: The Birmingham cohort had 187 patients diagnosed with postoperative pancreatic fistula (biochemical leak: 99, clinically relevant: 88). In clinically relevant-postoperative pancreatic fistula patients, the leak became clinically relevant at a median of 9 days (interquartile range: 6–13) after pancreaticoduodenectomy. Male sex ($P = .002$), drain fluid amylase-postoperative day 3 ($P < .001$), c-reactive protein postoperative day 3 ($P < .001$), and albumin-postoperative day 3 ($P = .028$) were found to be significant predictors of clinically relevant-postoperative pancreatic fistula on multivariable analysis. The multivariable model was converted into a risk score with an area under the receiver operating characteristic curve of 0.78 (standard error: 0.038). This score significantly predicted the need for invasive intervention (postoperative pancreatic fistula grades B3 and C) in the Verona cohort (n = 121; area under the receiver operating characteristic curve: 0.68; standard error = 0.06; $P = .006$) but did not predict clinically relevant-postoperative pancreatic fistula when grades B1 and B2 were included (area under the receiver operating characteristic curve 0.52; standard error = 0.07; $P = .802$).
Conclusion: We developed a novel risk score based on early postoperative laboratory values that can accurately predict higher grades of clinically relevant-postoperative pancreatic fistula requiring invasive intervention. Early identification of severe postoperative pancreatic fistula may allow earlier intervention.

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Introduction

Postoperative pancreatic fistula (POPF) is a well-recognized complication after pancreaticoduodenectomy (PD), with a reported incidence between 11% to 28%,[1] and is responsible for significant perioperative morbidity, mortality, and prolonged hospitalization.[2,3] The introduction of standardized definitions by the International Study Group for Pancreatic Surgery (ISGPS) facilitated comparison between centers.[4] These were revised in 2016,[5] to distinguish between biochemical leak (BL) and clinically relevant (CR) -POPF. Patients with a BL remain clinically well, and the leak resolves rapidly without intervention. At the same time, a CR-POPF may lead to sepsis and/or secondary hemorrhage, necessitating intensive care support and/or invasive intervention, and is associated with increased morbidity and mortality. However, the distinction between BL- and CR-POPF can only be made retrospectively and, therefore, is of limited clinical value in guiding patient management in the early postoperative period.

Several risk scores are available which may predict POPF (or CR-POPF) based on preoperative and/or intraoperative parameters (eg, body mass index, pancreatic duct width, pancreatic texture, and intraoperative blood loss).[6–8] However, these scores were not designed to differentiate between BL- and CR-POPF. Recent studies have indicated a potential role for postoperative biochemical parameters, such as drain fluid amylase (DFA) and C-reactive protein (CRP), in predicting CR-POPF, but available data are limited by small sample sizes[9,10] or heterogeneous patient cohorts that have included distal pancreatectomies in addition to PD.[11]

Postoperatively, patients who undergo PD are routinely monitored for complications. In the vast majority of cases, the diagnosis of POPF is made by the third postoperative day (POD3), based on elevated DFA values.[12,13] From POD3 onwards, patients with a POPF will either remain as a BL or clinically deteriorate and become CR-POPF. Although the principles of treatment of CR-POPF (eg, optimized drainage, antibiotics, and nutrition) are well established, the optimal timing of intervention is less clear, but it may be expected that earlier intervention in patients with CR-POPF would lead to improved clinical outcomes. Thus, this study aimed to establish when POPFs become clinically relevant and to differentiate between BL- and CR-POPF in the early postoperative period using preoperative, intraoperative, and early postoperative factors.

Methods

Data collection

The primary cohort used in the analysis comprised patients treated at Queen Elizabeth Hospital, Birmingham, UK ("Birmingham cohort") and was used to assess differences between patients with BL- and CR-POPF. The resulting analysis was then used to produce a risk score, which was subsequently calculated for a second cohort from Verona University Hospital, Verona, Italy ("Verona cohort"). Further information about these 2 cohorts is detailed below.

This study was registered as a retrospective audit in both contributing centers (Birmingham and Verona), and ethical approval was waived by the local ethics committees due to the retrospective nature of the study.

Birmingham cohort

Consecutive patients who underwent PD between January 1, 2009 and March 31, 2019 and subsequently developed POPF (of any grade) were identified from a prospectively maintained database. Patients were classified into BL- and CR-POPF, as per ISGPS definitions. Data on baseline characteristics, comorbidities, and peri and postoperative outcomes were then extracted, including postoperative laboratory results up to POD7, where available. Of these, CRP and serum albumin were routinely recorded on each POD, whereas the DFA was only measured on POD1, 3, and 5, and white blood cell count (WBC) on POD1 and 3.

Verona cohort

Consecutive patients who developed POPF after PD between January 1, 2016 and April 30, 2021 were retrospectively identified. Details of the POPF grade were then extracted, along with data for the newly derived risk score components. Where laboratory values were unavailable on POD3, the value on the nearest POD was used to calculate the risk score. Measurements of DFA had an upper limit for reporting of 7,500 U/L; for levels greater than this, a value of 7,500 U/L was assumed.

Postoperative management

At both centers, the postoperative protocol was to remove drains from patients between POD3 to 5, if there was no evidence of POPF. For both cohorts, this was defined as a DFA level <3 times the upper limit of normal (ie, <300 U/L). However, in Verona, drains were additionally left in situ in selected patients with a normal DFA if they were considered to be "high risk" based on the alternative Fistula Risk Score (a-FRS),[7] had an external stent, or produced drain fluid with a "sinister" appearance. After POPF had been diagnosed, the treating surgeon made decisions around management.

Definitions of variables

The POPF was initially classified according to ISGPS 2016 definitions, and graded as BL, grade B, or grade C. The primary outcome was CR-POPF, which was defined as leaks of grade B or C. Because this study aimed to differentiate between CR-POPF and BL in patients diagnosed with a POPF by POD5 based on raised DFA values, patients with normal DFA POD3 to 5 values diagnosed with a POPF later in the postoperative course were excluded from the analysis.

Preliminary comparisons between the 2 cohorts found the proportion of CR-POPF (compared to BL) to be considerably higher in the Verona cohort (87.6%) compared with Birmingham (47.1%; see the Results section for further details). To allow for further investigation of this discrepancy, grade B POPF was further subdivided into grade B1 (prolonged drainage; >3 weeks), grade B2 (pharmacological treatment), and grade B3 (interventional treatment).[14] Additionally, a modified version of CR-POPF, designated *critical POPF*, was also assessed. Critical POPF was defined as POPF grades B3 or C only (ie, requiring interventional or surgical treatment), with BL and grades B1 to B2 treated as noncritical POPF.

Two existing risk scores were also calculated for all patients to assess whether these had any utility in differentiating between BL- and CR-POPF. The first was the Birmingham (B)-FRS, a preoperative score designed to predict POPF (versus no POPF). This was calculated using the formula proposed in the original study by Roberts et al,[15] with the absolute risks of POPF being updated using the underlying formula from the plot in the subsequent validation paper,[8] namely: $\exp[x] / (1 + \exp[x])$, where $x = -2.917 + 1.706 \log_{10}[100 \text{ B-FRS}]$. The a-FRS is an intraoperative score intended to

predict CR-POPF (versus BL- *OR* no POPF). This was calculated as described by Mungroop et al.[7]

Statistical methods

The primary analysis was performed on the Birmingham cohort, for which characteristics were compared between patients with BL- and CR-POPF using Mann-Whitney *U* tests for the continuous variables, with Fisher exact or χ^2 analysis used for nominal variables with $\geq$2 groups, respectively. Associations between postoperative laboratory parameters and POPF grade were assessed using receiver operating characteristic (ROC) curves, which were quantified using the area under (AU) the ROC curve and the associated standard error (SE). Continuous variables that were approximately normally distributed were summarized using arithmetic means and SDs. Skewed variables were either $\log_{10}$-transformed to normalize the distribution for analysis and summarized using geometric means with 95% CIs or reported as medians with IQRs.

A multivariable analysis was then performed to identify patient characteristics and postoperative laboratory parameters measured on POD3 that were independent predictors of CR-POPF (versus BL). To minimize the quantity of missing data for the postoperative laboratory parameters, where data were unavailable on POD3, measurements for the previous POD of data collection (ie, POD2 for CRP or serum albumin and POD1 for DFA or WBC) were used instead. A multivariable binary logistic regression model was then produced, using a forward stepwise approach to variable selection. Factors selected by the stepwise procedure were then entered into a new model to prevent the exclusion of cases caused by missing data on factors not included in the final model. The multivariable model was then used to produce a risk score. For continuous variables, the values associated with log odds of 1, 2, and 3 were identified and used to define cut-off values for which the associated number of points would be assigned. The predictive accuracy of the risk score was then quantified using the AUROC, on both the Birmingham and Verona cohorts, for both the outcomes of CR- and critical POPF. All analyses were performed using IBM SPSS 22 (IBM SPSS, Inc, Armonk, NY), with $P < .05$ indicative of statistical significance.

Results

Birmingham cohort characteristics

In the Birmingham cohort, for the 830 patients undergoing PD, the incidence of POPF was 24.7% ($n = 205$), consisting of 99 (11.9%) with BL, 81 (9.8%) grade B leaks, and 25 (3.0%) grade C leaks. Further breaking down the grade B POPFs, based on the criteria described by Maggino et al,[14] found grades B1, B2, and B3 POPFs to have developed in 7, 39, and 35 patients, respectively. Of these, all grade B1 leaks were treated with prolonged drainage. In contrast, grade B2 POPFs were defined either by the use of antibiotics ($n = 5$) or parenteral nutrition ($n = 34$), and grade B3 POPFs were defined either by angiographic intervention ($n = 3$) or radiological drainage ($n = 32$). Grade C POPFs were defined by organ failure in 18 patients, with the remaining 7 patients who did not require organ support either undergoing surgical intervention ($n = 6$) or dying before invasive interventions ($n = 1$).

Predictors of CR-POPF

Of those patients who developed POPF, $n = 18$ (8.8%) had normal DFA values between POD 3 to 5 but were diagnosed with CR-POPF at a later date. These patients were excluded from the analysis of early postoperative risk factors. The remaining $n = 187$ patients consisted of $n = 99$ (52.9%) with BLs and $n = 88$ (47.1%) with CR-POPF. For those in the developing CR-POPF group, the leak was classified as being clinically relevant a median of 9 days (IQR: 6–13) after surgery (Figure 1).

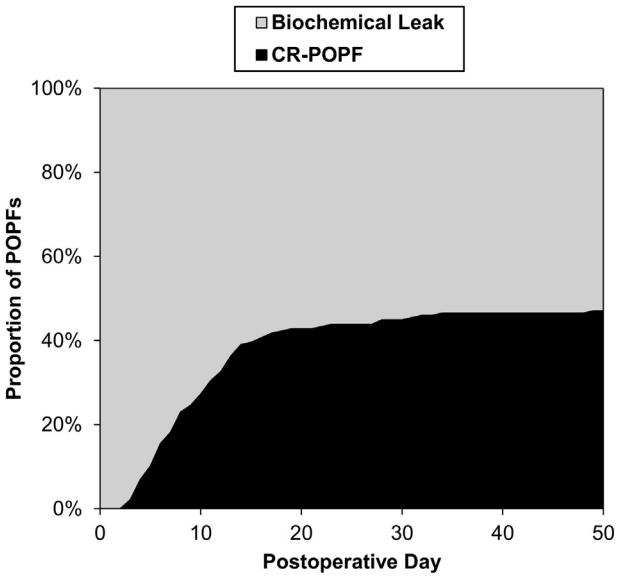

Figure 1. Timing of clinically relevant–postoperative pancreatic fistula (POPF) development. The plot initially classifies all POPFs as biochemical leaks on postoperative day 1. The black area represents the cumulative proportion of POPFs classified as clinically relevant–POPF as of each postoperative day. *CR-POPF*, clinically relevant-postoperative pancreatic fistula.

Comparisons between the patient demographics of the BL- and CR-POPF groups are reported in Table I. This comparison found patients with CR-POPF significantly more likely to be male (65% vs 43%; $P = .005$) than those with a BL-POPF. Clinically relevant–POPF was also associated with a significantly smaller PD width (median: 2 vs 3 mm; $P = .042$) and, consequently, a higher B-FRS (mean: 0.35 vs 0.31; $P = .015$). Patients with CR-POPF had a median length of hospital stay of 24 days (IQR: 17–38), which was significantly longer than the 10 days (IQR: 8–14) in those with BLs ($P < .001$). No significant difference in 90-day mortality rates was observed (6% vs 2%; $P = .257$), although the low event rate limited this comparison.

Associations between laboratory parameters and the grade of POPF are reported in Table II and Figure 2. For all variables considered, the discriminatory ability tended to increase over time. On POD1, only DFA was found to be significantly predictive of POPF grade, with a geometric mean of 1,397 U/L in those with BL-POPF, compared with 2,309 U/L in CR-POPF ($P = .011$). On POD3, significant discrimination was observed for DFA ($P < .001$), CRP ($P < .001$), and serum albumin ($P = .014$) but not WBC ($P = .714$). CRP and serum albumin then remained significantly discriminative on all subsequent days (up to POD7), whereas DFA was significant at the final measurement on POD5.

A multivariable analysis was then performed, to identify independent predictors of CR-POPF. This considered all patient characteristics from Table I for inclusion and the laboratory parameters measured on POD3 from Table II. The resulting model (Table III) found the male sex to be the only patient characteristic significantly associated with a higher risk of CR-POPF ($P = .002$). Of the postoperative laboratory parameters assessed, higher DFA ($P < .001$) or

Table I
Patient characteristics and outcomes by grade of POPF

Characteristics	*n*	Biochemical leak	CR-POPF	*P* value
Age (y)	187	67.9 (59.8–72.9)	66.8 (58.3–74.0)	.809
Sex (% male)	187	43 (43%)	57 (65%)	.005
BMI (kg/m^2)	187	26.2 ± 4.4	27.1 ± 5.0	.261
Smoking status	187			.326
Never		81 (82%)	64 (73%)	
Ex-		7 (7%)	10 (11%)	
Current		11 (11%)	14 (16%)	
Diagnosis	187			.753
Pancreatic cancer		23 (23%)	20 (23%)	
Periampullary cancer		32 (32%)	33 (38%)	
Cholangiocarcinoma		19 (19%)	11 (13%)	
Neuroendocrine tumor		9 (9%)	10 (11%)	
Others		16 (16%)	14 (16%)	
Charlson Comorbidity Index	187	4.9 ± 1.9	4.6 ± 1.5	.387
PMH asthma	187	8 (8%)	4 (5%)	.382
PMH cardiac	187	10 (10%)	18 (20%)	.064
PMH chronic lung disease	187	5 (5%)	9 (10%)	.266
PMH hypertension	187	36 (36%)	37 (42%)	.455
PMH diabetes mellitus	187	10 (10%)	11 (13%)	.648
PMH renal failure	187	6 (6%)	2 (2%)	.285
Preoperative biliary stent	187	41 (41%)	35 (40%)	.882
Pancreatic duct width (mm)[*]	186	3 (2–4)	2 (1–3)	.042
B-FRS	186	0.31 ± 0.09	0.35 ± 0.11	.015
Type of surgery (% PPPD)	187	89 (90%)	78 (89%)	.816
Vascular reconstruction	187	10 (10%)	7 (8%)	.800
R-status (% r1)[†]	164	13 (15%)	11 (14%)	1.000
Outcomes				
Length of stay (d)	187	10 (8–14)	24 (17–38)	< .001
90-day mortality	187	2 (2%)	5 (6%)	.257

Continuous variables are reported as median (IQR) or as arithmetic mean ± SD, as applicable, with *P* values from Mann-Whitney *U* tests. Nominal variables are reported as *n* (%), with *P* values from Fisher's exact tests for variables with 2 categories, or χ^2 analysis for those with >2 categories.
POPF, postoperative pancreatic fistula; *CR-POPF*, clinically relevant-POPF; *BMI*, body mass index; *PMH*, past medical history; *B-FRS*, Birmingham Fistula Risk Score; *PPPD*, pylorus-preserving pancreaticoduodenectomy.
[*] On preoperative computed tomography scan.
[†] Excludes patients with diagnoses for which the R-status was not applicable.

Table II
Association between postoperative laboratory parameters and grade of POPF

Parameter/	Biochemical leak		CR-POPF		AUROC (SE)	*P* value
POD	*n*	Average	*n*	Average		
DFA (U/L)						
POD1	82	1397 (1078–1810)	65	2309 (1511–3529)	0.62 (0.05)	.011
POD3	81	991 (808–1215)	65	2129 (1509–3003)	0.68 (0.05)	< .001
POD5	68	213 (145–314)	61	1443 (889–2345)	0.78 (0.04)	< .001
CRP (mg/L)						
POD1	76	74 (67–83)	68	87 (77–99)	0.58 (0.05)	.111
POD2	74	182 (163–203)	62	215 (191–241)	0.61 (0.05)	.030
POD3	66	193 (172–217)	56	257 (228–290)	0.70 (0.05)	< .001
POD4	66	147 (129–167)	61	210 (183–241)	0.69 (0.05)	< .001
POD5	64	103 (87–121)	59	165 (138–196)	0.72 (0.05)	< .001
POD6	66	87 (75–101)	70	137 (117–161)	0.68 (0.05)	< .001
POD7	64	69 (57–84)	61	125 (104–151)	0.71 (0.05)	< .001
Albumin (g/L)						
POD1	98	27.3 ± 4.8	87	27.0 ± 5.0	0.51 (0.04)	.788
POD2	89	27.1 ± 3.8	76	26.3 ± 4.2	0.57 (0.05)	.143
POD3	89	27.3 ± 3.6	77	25.9 ± 3.9	0.61 (0.04)	.014
POD4	86	28.0 ± 3.6	76	26.0 ± 6.7	0.67 (0.04)	< .001
POD5	81	28.7 ± 3.5	75	25.4 ± 4.8	0.71 (0.04)	< .001
POD6	86	29.2 ± 3.9	83	26.0 ± 4.8	0.69 (0.04)	< .001
POD7	80	29.9 ± 4.2	82	26.1 ± 4.7	0.74 (0.04)	< .001
WBC (x10^9/L)						
POD1	98	14.8 ± 5.2	88	14.8 ± 5.5	0.50 (0.04)	0.947
POD3	98	12.3 ± 3.5	88	12.6 ± 4.7	0.52 (0.04)	0.714

Average values are reported as arithmetic mean ± SD for normally distributed variables or as geometric mean (95% CI) for those with skewed distributions. *P* values are from Mann-Whitney *U* tests.
POPF, postoperative pancreatic fistula; *POD*, postoperative day; *CR-POPF*, clinically relevant-POPF; *AUROC*, area under the receiver operating characteristic curve; *SE*, standard error; *DFA*, drain fluid amylase; *CRP*, C-reactive protein; *WBC*, white blood cell count.

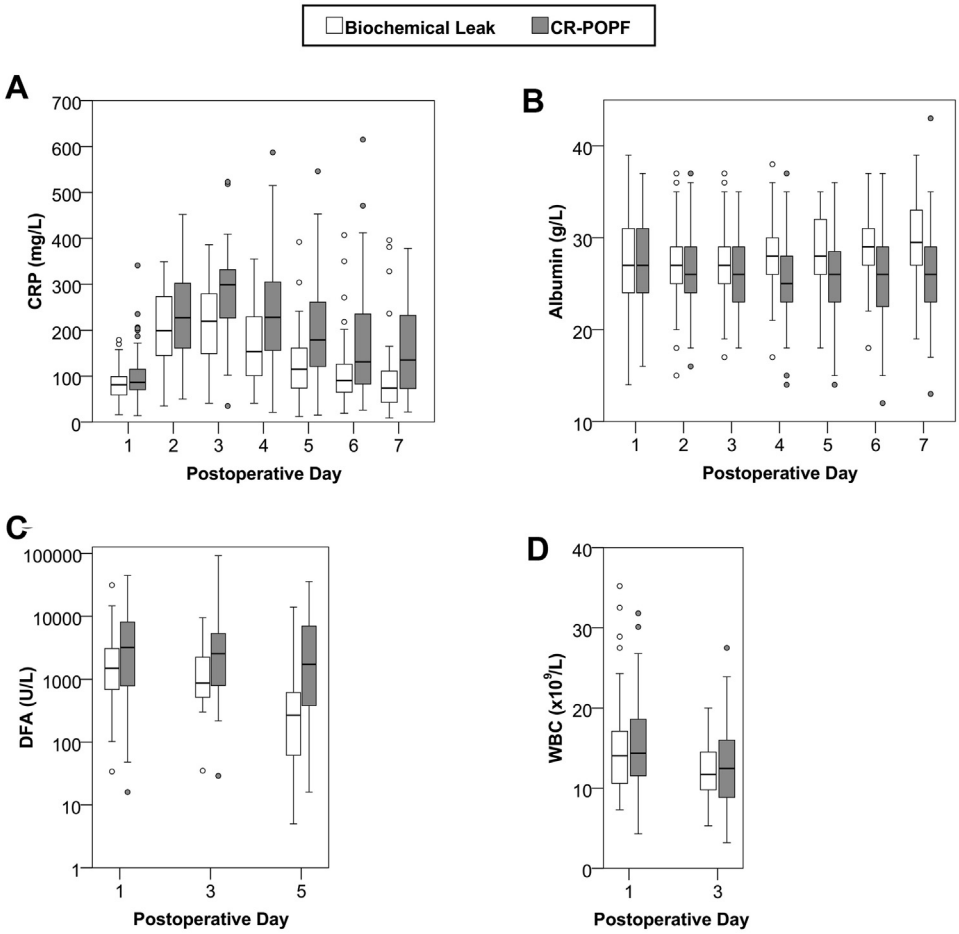

Figure 2. Box plots of postoperative laboratory parameters by grade of postoperative pancreatic fistula. The plot of drain fluid amylase uses a logarithmic scale on the y-axis to improve scaling. *CR-POPF*, clinically relevant-postoperative pancreatic fistula; *CRP*, C-reactive protein; *DFA*, drain fluid amylase; *WBC*, white blood cell count.

Table III
Multivariable analysis of predictors of CR-POPF (versus biochemical leak)

Characteristics	Odds ratio (95% CI)	*P* value
Sex (male)	3.66 (1.61–8.34)	.002
DFA on POD3 (per 1,000 U/L)	1.37 (1.14–1.65)	< .001
CRP on POD3 (per 100 mg/L)	2.13 (1.37–3.33)	< .001
Albumin on POD3 (per 1 g/L)	0.89 (0.79–0.99)	.028

Results are from a multivariable binary logistic regression model, with POPF grade (CR- versus biochemical leak) as the dependent variable. Variable selection used a forward stepwise approach, with all patient characteristic factors from Table I, along with the DFA, CRP, serum albumin, and white blood cell count measured on POD3, considered for inclusion. To minimize exclusions, where patients had missing data for a blood marker on POD3, data from the previous day (ie, day 2 for CRP or serum albumin and day 1 for DFA or white blood cell count) was used instead, where available. Factors selected by the stepwise procedure were then entered into a new model to prevent the exclusion of cases caused by missing data on factors not included in the final model. The final analysis was based on $n = 146$ cases ($n = 65$ with CR-POPF). For the laboratory parameters, odds ratios are reported per increase of the stated number of units to give values of a reasonable magnitude.
CR-POPF, clinically relevant-postoperative pancreatic fistula; *DFA*, drain fluid amylase; *POD*, postoperative day; *CRP*, C-reactive protein.

CRP ($P < .001$) and lower serum albumin ($P = .028$) on POD3 were all found to be significant independent predictors of CR-POPF. The relationships between these laboratory parameters and CR-POPF rates are visualized in Figure 3, *A* through *C*. The multivariable model returned an AUROC of 0.80 (SE: 0.036) for the differentiation between CR-POPF and BL-POPF.

The multivariable model was then converted to a risk score by assigning between 0 to 3 points to ranges of the included variables (Table IV). The resulting score generated values in the range 0 to 9, with a CR-POPF rate of 0% in the 8 patients scoring 0 to 1 and 100% in the 13 scoring 6 to 9 points (Figure 3, *D*), yielding an AUROC of 0.78 (SE: 0.038).

Application of the risk score to an external cohort

The risk score was then applied to the Verona cohort. This comprised a total of 211 patients with POPF; however, 90 (42.6%) of these were subsequently excluded because their DFA was either not raised (ie, <300 U/L) or not recorded between POD3 to 5. Of the remaining 121 cases, CR-POPF was diagnosed in 87.6% ($n = 106$), which was considerably higher than the 47.1% (88/187) in the Birmingham cohort ($P < .001$). To explain this discrepancy, the POPF grades were further broken down, with the grade B leaks subdivided into grades B1 to B3 (Figure 4, *A*). This found a large difference in the rates of grade B1 leaks between cohorts, comprising 45.5% vs 3.2% of the Verona versus Birmingham cohorts. However, combining the BL- and grade B1-POPF groups resulted in the distribution of POPF grades being similar in the 2 cohorts ($P = .978$).

The risk score was then calculated for each patient in the Verona cohort. Not all components of the score were routinely recorded on

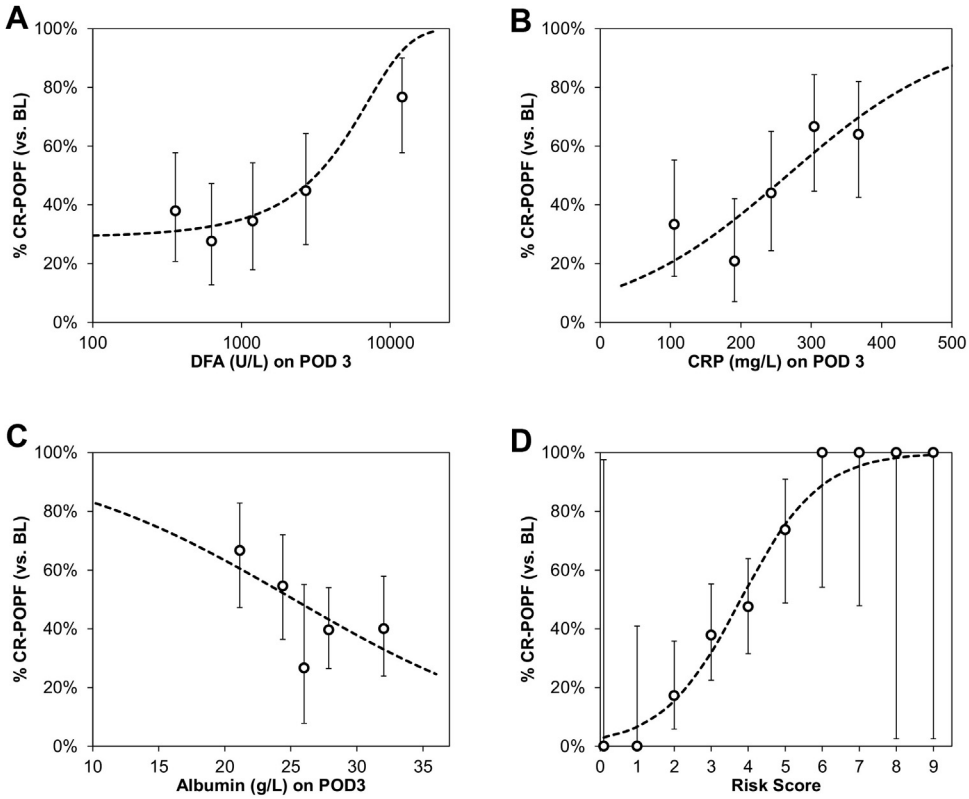

Figure 3. Associations between laboratory parameters on postoperative day 3 and grade of postoperative pancreatic fistula. For the postoperative laboratory parameters, points represent the observed rates within quintiles of the distribution and are plotted at the mean of the interval. For the risk score, points represent observed rates for each possible value of the score. The whiskers represent 95% CIs. The trend lines are from univariable binary logistic regression models on the patient-level data, with the laboratory parameter or risk score as a continuous covariate, and postoperative pancreatic fistula grade (clinically relevant− versus biochemical leak−) as the dependent variable. The plot of drain fluid amylase uses a logarithmic scale on the x-axis to improve scaling. *BL*, biochemical leak; *CR-POPF*, clinically relevant-postoperative pancreatic fistula; *CRP*, C-reactive protein; *DFA*, drain fluid amylase; *POD*, postoperative day.

Table IV
Risk score for CR-POPF (versus biochemical leak)

Factor	Points
Sex	
Female	0
Male	1
DFA on POD3 (U/L)	
<3,000	0
3,000–5,999	1
6,000–8,999	2
9,000+	3
CRP on POD3 (mg/L)	
<130	0
130–259	1
260–399	2
400+	3
Albumin on POD3 (g/L)	
<26	2
26–33	1
34+	0

To calculate the risk score, the value of each of the four factors should be looked up in the table, and the associated number of points added together to give a value in the range 0 to 9.
CR-POPF, clinically relevant-postoperative pancreatic fistula; *DFA*, drain fluid amylase; *POD*, postoperative day; *CRP*, C-reactive protein.

POD3, with data available in 114 (94.2%), 55 (45.5%), and 20 (16.5%) cases for CRP, DFA, and serum albumin, respectively. As such, the measurement between POD1 to 10 that was performed closest to POD3 was used to impute missing values, where available. As a result, all patients had measurements for CRP and DFA, with 106 having serum albumin levels recorded; hence, the risk score was calculable in 106 (87.6%) cases. Measurements of DFA were reported with an upper limit of 7,500 U/L; for patients with values above this limit ($n = 14$; 11.6%), a value of 7,500 U/L was assumed, resulting in a score of 2 points on the DFA component of the risk score.

The risk score was not found to have significant predictive accuracy for discriminating between CR-POPF and BL-POPF when applied to the Verona cohort, with an AUROC of 0.52 (SE = 0.07, $P = .802$, Figure 4, *B*). This was largely a result of the inflated CR-POPF rate in the Verona versus Birmingham cohorts, which was caused by the discrepancy in the numbers of grade B1 POPFs. As such, the analysis was additionally performed for the alternative outcome of critical POPF (versus noncritical POPF). The risk score was found to be significantly predictive of this outcome in the Verona cohort, with an AUROC of 0.68 (SE = 0.06; $P = .006$) and rates of critical POPF increasing from 9% (2/22) to 63% (5/8) in those scoring 0 to 2 and 6 to 9 points, respectively (Figure 4, *C*). Applying the score to the outcome of critical POPF in the Birmingham cohort returned similar results, with an AUROC of 0.70 (SE = 0.05; $P < .001$), and rates increasing from 8% (3/37) to 54% (7/13) for those scoring 0 to 2 and 6 to 9 points, respectively.

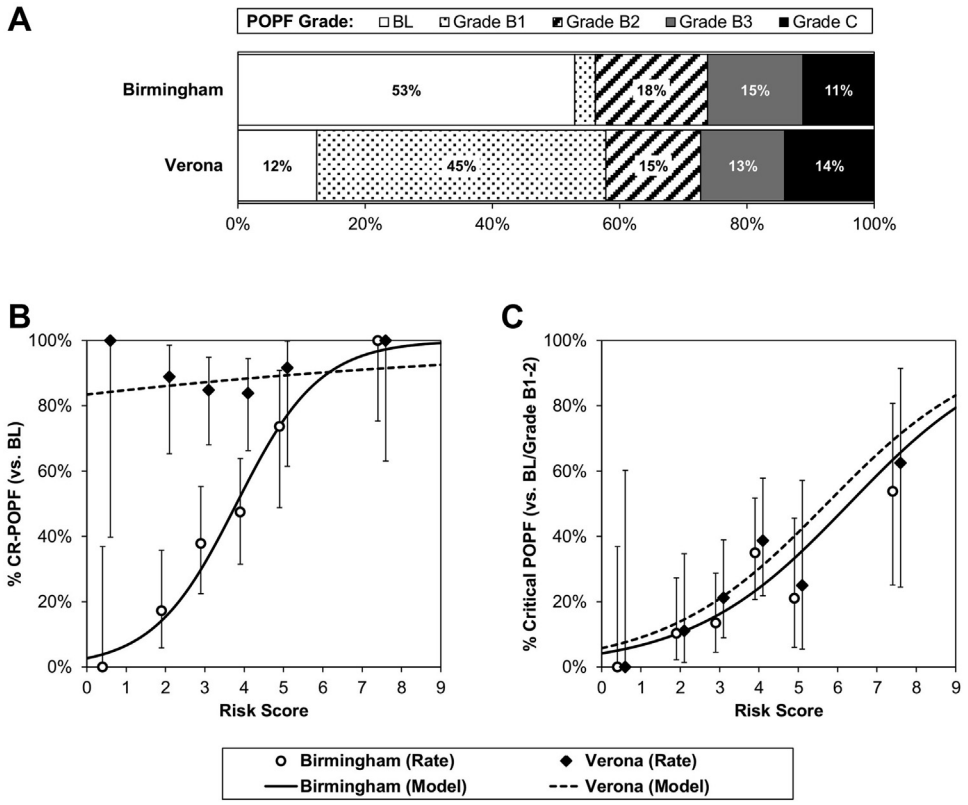

Figure 4. Postoperative pancreatic fistula (POPF) distribution and associations between the risk score and POPF rates by cohort. In *(A)*, the distribution of POPF grades was found to differ significantly between the 2 cohorts (Mann-Whitney *U* test: $P < .001$). However, after combining the biochemical leak− and grade B1-POPF groups, the distribution of leak grades was found to be similar in both cohorts ($P = .978$). In *(B)* and *(C)*, points represent the rates of clinically relevant− or critical−POPF in patients with each value of the risk score, with whiskers representing 95% CIs; scores of 0 to 1 and 6 to 9 were combined, caused by small numbers, and plotted at the midpoint of the range. Trend lines are from univariable binary logistic regression models on the patient-level data, with the risk score as a continuous covariate, and either clinically relevant− or critical-POPF as the dependent variable; separate models were produced for the Birmingham and Verona cohorts. Each graph depicts the relationship between individual laboratory parameters (graphs *A*–*C*) on the third postoperative day and the derived risk score (graph *D*) on the incidence of clinically relevant POPF: (*A*) Drain fluid amylase (*B*) C-reactive protein (*C*) Serum albumin (*D*) Risk score. *BL*, biochemical leak; CR-POPF, clinically relevant-postoperative pancreatic fistula.

Comparison to existing risk scores

The proposed risk score was compared to existing Fistula Risk Scores (a-FRS and B-FRS) that had been developed for predicting POPF (versus no POPF). An ROC analysis of the Birmingham cohort data was carried out and found that CR-POPF and BL-POPF could only be discriminated using the proposed risk score (AUROC 0.78; SE = 0.04; $P < .001$) and not by existing risk scores (a-FRS: AUROC 0.59; SE = 0.05; $P = .060$ and B-FRS: AUROC 0.57; SE = 0.05; $P = .175$).

Discussion

The main finding of this study was that it is possible to differentiate between BL- and a CR-POPF as early as POD3, based on sex and laboratory data (DFA, CRP, and serum albumin). The currently available risk scores are based on preoperative and/or intraoperative variables and were developed to predict POPF (versus no POPF), either pre- or intraoperatively. Consequently, we did not find these effective in differentiating between BL- and CR-POPF, as one might expect. However, a novel risk score based on early postoperative demographic and laboratory data showed promise in stratifying the risk of CR-POPF development.

In our cohort, approximately half of patients with POPF diagnosed by a raised DFA on POD3 were subsequently diagnosed with CR-POPF, a median of 9 days after surgery. Thus, there is a window of opportunity after POD3 in which patients with POPF remain clinically well but have the potential to progress to CR-POPF. Suppose it was possible to identify those at the highest risk of progression to CR-POPF. In that case, these patients could be targeted for early, pre-emptive intervention and/or recruited into clinical trials. The timing and type of early intervention before the onset of CR-POPF may be debated and should ideally be tested within the constraints of a randomized trial. For example, high-risk patients may benefit from avoiding/modifying fast-track policies, earlier initiation of antibiotics, supplemental nutrition, and/or earlier cross-sectional imaging.

The introduction of universally accepted definitions for POPF has been welcomed by the pancreatic surgery community and has facilitated the development of Fistula Risk Scores and comparisons of outcomes between centers.[4,5] However, although the ISGPS definitions of BL- and CR-POPF are relatively clear and straightforward, there are 3 main drawbacks to classifying POPF based on the extent of treatment. The first is that the severity of POPF can only be classified retrospectively and, therefore, cannot be used to guide patient management.

Secondly, the underlying assumption that more intensive management indicates more severe POPF can penalize proactive centers in treating POPF. This was observed in the current study, during which POPF cases in the Verona cohort were almost twice as likely to be classified as clinically relevant, compared to those in Birmingham, as a result of differences in the criteria for removing

surgical drains. Finally, these definitions do not necessarily mirror the "severity" or magnitude of a POPF from a pathophysiologic viewpoint. Pancreatic fistulae may encompass a spectrum of pathologic processes, from postoperative pancreatitis,[16,17] suture hole leaks or minor defects in the anastomosis, to partial or full anastomotic dehiscence. In addition to "technical failure," which presents as a POPF in the early postoperative period, there may also be a small subset of patients who develop a "late leak," the etiology of which is unclear but may include ischemia. Although BL- and CR-POPF may broadly reflect 2 ends of a spectrum of severity, a correlation between the pathophysiologic processes is imperfect with significant overlap. For example, a patient with a "minor" leak may be diagnosed with a CR-POPF simply caused by failure of a surgical drain.

The DFA values have been used to define POPF and guide drain management, and our data indicate a strong correlation between CR-POPF and DFA values in the early postoperative period. This would suggest that higher DFA values may be more likely to reflect a major anastomotic failure, whereas moderately raised DFA values may be more common in suture hole leaks or minor anastomotic leaks. Debate remains about the optimal cut-off value of DFA on POD1 below which it is deemed safe to remove surgical drains,[18–21] but higher threshold values are associated with a higher rate of false negatives, potentially converting some patients from BL- to CR-POPF.

In addition to DFA, other factors that differentiated between BL- and CR-POPF in our study were male sex and laboratory values of CRP and serum albumin on POD3. Male patients with POPF were around 1.5-times more likely to develop CR-POPF than female patients. Although this is unclear, it may reflect a higher incidence of visceral adiposity in men, which may be associated with pancreatic steatosis.[22,23] C-reactive protein is an inflammatory marker that increases after major surgery,[24] and peaks on POD3 or 4. Our study has shown that the CRP value diverges in patients with BL- and CR-POPF as early as POD2 and that this difference persists until at least POD7. This difference in CRP presumably reflects an increased local inflammatory response in the perianastomotic tissues and/or pancreatitis rather than infection, which may occur later. An association between CRP and CR-POPF has also been noted in other smaller studies.[25,26] Patients with CR-POPF are susceptible to secondary bacterial and/or fungal infections, although the timing of infection and its role in the pathogenesis of CR-POPF is not clear. It is feasible that secondary infection may also trigger the conversion of BL- into CR-POPF.[27] The role of antibiotic and/or antifungal prophylaxis warrants prospective study in a clearly defined population of high-risk patients. Postoperative hypoalbuminemia is a normal physiologic response after major surgery, but an excessive drop was associated with CR-POPF in our study. This is consistent with findings from other studies and may reflect hypoalbuminemia having a detrimental effect on tissue repair, potentially leading to delayed fistula closure.[28–30]

The primary limitations of the analysis related to the fact that data were not available for all laboratory results on each POD. When deriving the risk score in the Birmingham cohort, a last measure carried-forwards approach was used to maximize the number of cases included. However, the final model excluded 22% of cases for which data for the markers of interest were not available. This will have reduced the statistical power of the analysis and may have introduced selection bias if these cases were not missing at random. In the Verona cohort, the majority of cases did not have complete data for the risk score components on POD3, and so the measurement nearest to POD3 was used, where available. However, because the predictive accuracy of the laboratory results was shown to vary over the postoperative period, this may have impacted the predictive accuracy of the risk score when applied to the Verona cohort. In addition, the Verona cohort used an upper limit of 7,500 U/L for DFA, with values above this assumed to be in the interval 6,000 tp 8,999 U/L when calculating the risk score. However, if the value was actually $\geq$9,000 in some of these patients, then their risk score will have been underestimated by 1 point. To confirm the clinical utility of the proposed risk score, external validation in a prospective cohort would be required.

The second limitation stemmed from the discrepancies in the distributions of POPF grade between the Birmingham and Verona cohorts. The high rate of grade B1-POPF in the latter resulted in the analysis of the Verona cohort finding the risk score not to be significantly discriminative between CR-POPF and BL-POPF. Repeating the analysis on the alternative outcome of critical POPF did find performance of the risk score to be acceptable; hence, it was assumed that performance would have been similar for CR-POPF had the two cohorts used similar POPF treatment protocols. However, this highlighted the issue with using the extent of treatment to define the severity of POPF and implies that the accuracy of any risk score for identifying CR-POPF could vary dramatically between centers with disparate approaches to POPF management. In light of this, before any such risk score could be used in practice, it would need to be validated locally, potentially using retrospectively collected data, to ensure that it has adequate performance at the specific center at which it is implemented.

Finally, the analyses excluded the subgroup of patients who developed POPF but did not have raised DFA between POD3 to 5. As a result of these exclusions, the results of the study are only generalizable to those patients who are initially diagnosed with POPF before POD5 and may not be applicable to those developing "late" POPF.

In conclusion, we identified several factors that may permit differentiation between BL- and CR-POPF by the POD3. High-risk patients may benefit from earlier diagnostic imaging and/or interventions and could be targeted for prospective studies of therapeutic interventions for CR-POPF.

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Conflict of interest/Disclosure

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