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Original Article

Establishment and external validation of neutrophil-to-lymphocyte ratio in excluding postoperative pancreatic fistula after pancreatoduodenectomy

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Abstract

Background: Factors excluding postoperative pancreatic fistula (POPF), facilitating early drain removal and hospital discharge represent a novel approach in patients undergoing enhanced recovery after pancreatic surgery. This study aimed to establish the relevance of neutrophil-to-lymphocyte ratio (NLR) in excluding POPF after pancreatoduodenectomy (PD).

Methods: A prospectively maintained database of patients who underwent PD at two high-volume centres was used. Patients were divided into three cohorts (training, internal, and external validation). The primary endpoints of this study were accuracy, optimal timing, and cutoff values of NLR for excluding POPF after PD.

Results: From 2012 to 2020, in a 2:1 ratio, 451 consecutive patients were randomly sampled as training ($n = 301$) and validation ($n = 150$) cohorts. Additionally, the external validation cohort included 197 patients between 2018 and 2020. POPF was diagnosed in 135 (20.8 per cent) patients. The 90-day mortality rate was 4.1 per cent. NLR less than 8.5 on postoperative day 3 (OR, 95 per cent c.i.) was significantly associated with the absence of POPF in the training (2.41, 1.19 to 4.88; $P = 0.015$), internal validation (5.59, 2.02 to 15.43; $P = 0.001$), and external validation (5.13, 1.67 to 15.76; $P = 0.004$) cohorts when adjusted for relevant clinical factors. Postoperative outcomes significantly differed using this threshold.

Conclusion: NLR less than 8.5 on postoperative day 3 may be a simple, independent, cost-effective, and easy-to-use criterion for excluding POPF.

Introduction

Postoperative pancreatic fistula (POPF) is the main cause of adverse clinical outcomes, prolonged hospital stay, increased medical costs, and life-threatening complications after pancreatoduodenectomy (PD)[1,2]. Pancreatic fistula was redefined in 2016 by the International Study Group of Pancreatic Surgery (ISGPS) as a clinically relevant condition related directly to a pancreatic leak, and the B/C grading system was confirmed but defined more strictly[3]. During the last decade, efforts have focused on the early prediction of POPF, and several related risk factors have been identified, such as clinical characteristics (age[4], sex[5], BMI[6], and sarcopenia[7,8]), pancreas-specific features[4–6,9–11], and intraoperative blood loss[9–11]. Some factors are influenced by subjectivity, whereas biochemical markers, such as drain fluid amylase[12,13] and C-reactive protein[14,15], are not. To date, these factors have been reported with variable results, and no final consensus has been reached in this regard.

The neutrophil-to-lymphocyte ratio (NLR) has recently emerged as an attractive alternative to other biological ratios associated with monocytes or platelets for characterizing the body's inflammatory status[16]. Based on the relationship between the inflammatory response and postoperative complications, some publications have focused on the NLR and demonstrated it to be a valuable predictor of postoperative complications after various surgeries[17,18].

As the enhanced recovery after pancreatic surgery is becoming increasingly adopted[19], factors that allow clinicians to exclude POPF and facilitate safe early drain removal and early hospital discharge may represent a novel approach to the management of this complication.

This study aimed to establish the relevance of NLR in excluding POPF after PD.

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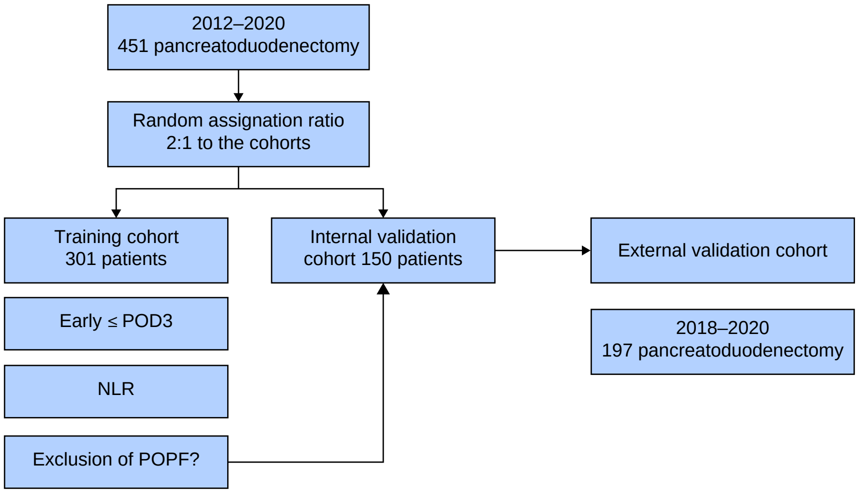

Fig. 1 Flow diagram of the patient distribution in the enrolled cohorts of the study

POD, postoperative day; NLR, neutrophil-to-lymphocyte ratio; POPF, clinically relevant postoperative pancreatic fistula.

Methods

Study population

The cohort for model development included consecutive patients who underwent PD between January 2012 and January 2020 at a comprehensive cancer centre (Paoli-Calmettes Institute, Marseille, France). The patients were randomly divided, in a ratio of 2:1, into training and internal validation cohorts. The external validation cohort included consecutive patients who underwent PD at another academic centre (Pontchaillou Hospital, Rennes, France) between January 2018 and December 2020.

Data were prospectively entered into a clinical database, approved by the Institutional Review Board of each facility, and labelled by the National Institute for Data Protection (Commission Nationale de l'Informatique et des Libertés; number: Sy50955016U). All participants provided written informed consent for their data to be included in the prospective institutional database (Clinical Trials.gov NCT02871336). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. The study was registered on ClinicalTrials.gov (NCT04724551).

Data regarding leucocyte, neutrophil, and lymphocyte count, along with the NLR, were available for all patients; however, drain fluid amylase (DFA) and C-reactive protein levels were not routinely recorded before 2017 for the internal cohorts at the Paoli-Calmettes Institute. This prospective investigation was conducted based on the 2015 Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement[20].

Table 1 Baseline characteristics of the study population

Characteristic	Non-POPF ($n = 513$)	POPF ($n = 135$)	P*
Female	267	55	0.019
Male	246	80	
Sex ratio F:M	1.085	0.687	
Age (years), median (range)	69 (15–90)	67 (20–85)	0.193
ASA PS ≥3	105 (20.6)	21 (15.6)	0.193
BMI, median (range)	23 (15.0–40.5)	24 (16.0–37.0)	0.001
>25 kg/m^2	167 (32.6)	56 (41.5)	0.052
Histological type			<0.001
Pancreatic adenocarcinoma	262 (51.0)	31 (23.0)	
Ampullary	59 (11.5)	34 (25.1)	
Cholangiocarcinoma	53 (10.3)	20 (14.8)	
Intraductal papillary mucinous neoplasm	43 (8.3)	10 (7.4)	
Duodenal adenocarcinoma	12 (2.3)	7 (5.2)	
Neuroendocrine tumour	27 (5.4)	10 (7.4)	
Benign tumour	20 (4.0)	8 (6.0)	
Other	37 (7.2)	15 (11.1)	
Borderline or locally advanced	137 (26.7)	15 (11.1)	<0.001

Values are *n* (%) unless otherwise indicated. *Data are based on the chi-squared test, Fisher's exact test, or the Wilcoxon P. ASA PS, ASA physical status; POPF, clinically relevant postoperative pancreatic fistula; F, female; M, male.

Surgical technique and postoperative management

Duct-to-mucosa pancreaticojejunostomy or double purse-string telescoped pancreaticogastrostomy was performed, based on the surgeon's preference and the pancreatic texture. An externalized pancreatic duct stent was routinely inserted in patients with a soft pancreatic texture, or according to the surgeon's judgement. Non-aspiration drainage was routinely placed in contact with the pancreatic anastomosis. Since 2014, an enhanced recovery after pancreatic surgery protocol has been followed. Briefly, the nasogastric tube was routinely removed at the end of surgery, a liquid diet was usually started on postoperative day (POD) 1, and a solid diet was started between POD2 and POD3. No perioperative hydrocortisone or octreotide was used during the study interval. Drain management was mostly influenced by the pancreatic texture, patient's clinical status, and drain output, and removal was based on the surgeon's judgement. The biological markers were not solely considered for clinical management until the end of this study. Early postoperative course was defined as POD of 3 or earlier.

Study parameters

Demographics, clinical characteristics, operation data, and postoperative outcomes were extracted from the prospectively maintained databases. The variables evaluated included age, sex, ASA physical status, BMI, biliary stenting, neoadjuvant therapy, pancreatic texture, and pathological findings. Morbidity and mortality (after surgery, and up to 90 days) were graded using the Clavien–Dindo classification[21]. All re-interventions, if any, were also recorded. All patients had an estimated POPF risk, based on the updated alternative fistula risk score

Table 2 Surgical and perioperative characteristics of the study population

Characteristic	All (*n* = 648)	Non-POPF (*n* = 513)	POPF (*n* = 135)	*P**
Neoadjuvant therapy	172 (26.5)	154 (30.0)	18 (13.3)	<0.001
Biliary stenting	386 (59.6)	309 (60.2)	77 (57.0)	0.520
Vascular resection				
Lateral venous resection	26 (4.0)	24 (4.7)	2 (1.5)	0.092
Segmental venous resection	127 (19.6)	111 (21.6)	16 (11.8)	0.018
Arterial resection	13 (2.0)	10 (2.0)	3 (2.2)	0.739
Pancreatic anastomosis				
Pancreaticogastrostomy	50 (7.7)	29 (5.6)	21 (15.6)	<0.001
Pancreaticojejunostomy	598 (92.2)	484 (94.4)	114 (84.4)	<0.001
Soft pancreatic texture	313 (48.3)	221 (43.1)	92 (68.2)	<0.001
Pancreatic duct diameter	4 (1–15)	4 (1–15)	3 (1–10)	
Duct size <3 mm	149 (23.8)	91 (18.5)	58 (43.3)	<0.001
Pancreatic duct stenting	436 (67.3)	318 (62.0)	118 (87.4)	<0.001
Biliary leakage	32 (4.9)	14 (2.7)	18 (13.3)	<0.001
Haemorrhage	57 (8.8)	20 (3.9)	37 (27.4)	<0.001
Re-intervention	59 (9.1)	23 (4.5)	36 (26.7)	<0.001
Clavien–Dindo V	19 (2.9)	9 (1.7)	10 (7.4)	0.002
Leukocytes POD1, median (range)	12.4 (4.7–48.0)	12.3 (4.7–48.0)	13.1 (5.3–29.6)	0.003
Leukocytes POD3, median (range)	10.7 (2.2–46.0)	10.2 (2.2–46.0)	12.6 (2.9–35.2)	<0.001
Neutrophils POD1, median (range)	10.4 (3.8–31.0)	10.1 (3.8–26.6)	11.6 (4.0–31.0)	<0.001
Neutrophils POD3, median (range)	8.5 (0.4–33.5)	8 (0.4–33.0)	11.2 (2.4–33.5)	<0.001
Lymphocytes POD1, median (range)	1 (0.1–4.2)	1 (0.1–4.2)	1 (0.2–2.5)	0.161
Lymphocytes POD3, median (range)	1 (0.1–15.5)	1 (0.1–15.5)	1 (0.2–2.4)	0.004
NLR POD1, median (range)	10.2 (1.8–112.3)	9.7 (1.8–112.3)	12 (3.6–96.9)	<0.001
NLR POD3, median (range)	8 (0.6–68.6)	7.3 (0.6–68.6)	10.9 (2.9–46.3)	<0.001

Values are *n* (%) unless otherwise indicated.*Data are presented based on the chi-squared test, Fisher's exact test, or Wilcoxon *P*. POPF, clinically relevant postoperative pancreatic fistula; POD, postoperative day; NLR, neutrophil-to-lymphocyte ratio.

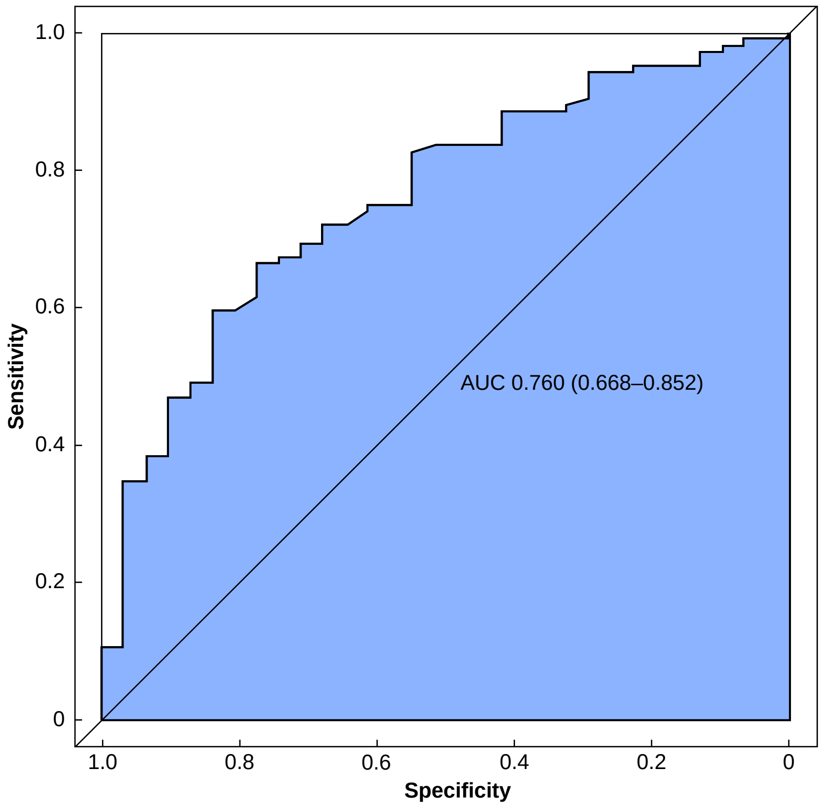

Fig. 2 Receiver operating characteristic (ROC) curve of neutrophil-to-lymphocyte ratio (NLR) on postoperative day 3 (POD3) in the external validation cohort (*n* = 197)

AUC, area under the receiver operating characteristic curve.

(ua-FRS)[22], which was calculated retrospectively for this study. Patients were divided into the following two groups: a control group (non-POPF) and a POPF group (grade B or C).

The primary endpoint of the study was to determine and validate the accuracy, optimal timing, and cutoff values of NLR in excluding POPF after PD.

Statistical analyses

Statistical analyses were conducted at a significance level of α = 0.05 and using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Data are summarized as counts (frequencies) for categorical variables and as medians (range) for quantitative variables. The characteristics of the populations, in addition to the training and internal validation/external validation cohorts, were compared using Fisher's exact test or the chi-squared test for qualitative variables, and the Wilcoxon test for quantitative variables. All tests were two-sided.

The optimal NLR cutoff value was determined by and corresponded to the value closest to the point of ideal sensitivity and specificity (0.1) on the receiver operating characteristic (ROC) curve to exclude the occurrence of POPF in the training sample. The area under the ROC curve (AUC) was estimated on the training sample using a bootstrap cross-validation resampling method (B = 100 replications).

The diagnostic impact of the classifiers determined using these optimal cutoff values was assessed in the training and internal/external validation samples using univariable logistic regression models. Additionally, multivariable logistic regression models that included the four classical clinical factors used in the ua-FRS[25]—sex, BMI, soft pancreatic texture, and pancreatic duct size—were utilized for the other covariates. ORs and bilateral Wald's confidence intervals were also estimated.

Diagnostic performance (accuracy, sensitivity, specificity, and positive and negative predictive values) was identified in the validation samples. Bilateral confidence intervals were computed using the exact binomial method. The AUC for quantitative NLR on POD3 in the validation samples was estimated together with the bilateral bootstrap cross-validation confidence interval. These diagnostic analyses were performed using the epiR version 0.9-99 and pROC version 1.9.1 packages from R (R Foundation for Statistical Computing).

To compare the diagnostic performance of the different predictors in the internal and external validation samples, DeLong's test for the ROC AUC, McNemar's test for sensitivity and specificity, and Leisering's test for positive and negative predictive values were used. The latter analyses were conducted using the DTComPair version 1.03 and epiR version 0.9-99 packages from R (R Foundation for Statistical Computing).

Table 3 Univariable and multivariable analyses of predictive factors for excluding postoperative pancreatic fistula in the internal validation cohort (*n* = 150)

	Univariable analysis		Multivariable analysis	
	OR (95% c.i.)	P	OR (95% c.i.)	P
Male sex	0.53 (0.24–1.16)	0.110	0.68 (0.26–1.79)	0.433
BMI	0.92 (0.83–1.00)	0.063	0.93 (0.83–1.04)	0.214
Soft pancreatic texture	0.64 (0.30–1.38)	0.258	0.66 (0.25–1.76)	0.407
Pancreatic duct diameter >3 mm	2.89 (1.21–6.90)	0.017*	2.12 (0.73–6.20)	0.168
Neutrophil-to-lymphocyte ratio <8.5 POD3	5.87 (2.30–14.99)	<0.001*	5.59 (2.02–15.43)	0.001*

*indicates a significant difference. POD, postoperative day.

Results

Patients' characteristics and postoperative outcomes

Altogether 451 consecutive patients were randomly sampled as training (*n* = 301) and validation (*n* = 150) cohorts, while the external validation cohort included 197 consecutive patients (*Fig. 1*). The characteristics of the study participants (*n* = 648) and their surgical and postoperative outcomes are summarized in *Tables 1* and *2* respectively. POPF was diagnosed in 135 (20.8 per cent) patients, including 95 (14.7 per cent) patients with grade B POPF, and 40 (4.6 per cent) patients with grade C POPF. Delayed gastric emptying occurred in 239 (37 per cent) patients, whereas postoperative haemorrhage occurred in 57 (8.8 per cent) patients. The in-hospital and 90-day mortality rates were 2.9 per cent (*n* = 19) and 4.1 per cent (*n* = 26) respectively. The mortality rate was higher in the POPF group than in the control group (7.4 per cent *versus* 1.7 per cent respectively; *P* = 0.002).

NLR cutoff determination for excluding POPF

In the training cohort (*n* = 301), POPF was diagnosed in 85 (18.9 per cent) patients. In the univariable analysis, NLR on POD1 and POD3 was associated with POPF. The optimal cutoff was identified at the threshold value of 8.5 on POD3, which was significantly associated with the exclusion of POPF (OR 2.61, 1.35 to 5.04; *P* = 0.004) (*Table S1*). In the multivariable analysis, NLR less than 8.5 on POD3 was significantly associated with the absence of POPF (OR 2.41, 1.19 to 4.88; *P* = 0.015), adjusted for sex, BMI, soft pancreatic texture, and pancreatic duct size.

Validation of the NLR cutoff on POD3

Preoperative characteristics, postoperative morbidity and mortality, and the incidence of POPF in the training and the two validation cohorts were comparable. NLR less than 8.5 on POD3 was the only classifier that remained significant in the multivariable analysis of the internal (*n* = 150) (OR 5.59, 2.02 to 15.43; *P* = 0.001; *Fig. S1*) and external (*n* = 197; OR 5.13, 1.67 to 15.76; *P* = 0.004) validation cohorts (*Fig. 2*, *Table S2* and *Table 3*). The NLR had similar characteristics as ua-FRS in excluding POPF (*Table 4* and *Table S3*). The outcomes, based on a threshold value

Table 4 Diagnostic performance in excluding clinically relevant postoperative pancreatic fistula cases in the external validation cohort (*n* = 197)

Parameter	Cut-off value	AUC	Sensitivity	Specificity	PPV	NPV
Neutrophil-to-lymphocyte ratio	<8.5	0.76	0.60	0.84	0.93	0.38
Soft pancreatic parenchyma	Yes/no	0.72	0.38	0.18	0.57	0.09
Pancreatic duct diameter, mm	<3	0.65	0.79	0.50	0.82	0.44
C-reactive protein, mg/l, POD3	185	0.70	0.74	0.66	0.86	0.47
Updated alternative fistula risk score	20	0.73	0.60	0.86	0.93	0.42

AUC, area under the receiver operating characteristic curve; NPV, negative predictive value; POD, postoperative day; PPV, positive predictive value.

of 8.5 for the entire cohort, were significantly different in terms of pancreatic fistula (9.6 per cent *versus* 30.7 per cent; $P < 0.001$), haemorrhage (3.4 per cent *versus* 14.4 per cent; $P < 0.001$) and in-hospital mortality (1.0 per cent *versus* 5.4 per cent; $P < 0.003$) (*Table S4*).

Discussion

This study explored and confirmed the NLR value of less than 8.5 at POD3 for excluding POPF. Such a simple postoperative surrogate marker could be utilized in PD patients and integrated with any other preoperative and intraoperative risk assessments (for example ua-FRS) and mitigation strategies (for example variability between institutions), independently of the surgeon's subjectivity (for example pancreatic parenchymal texture) or inadequate drainage (for example DFA).

After PD, not draining the pancreatic anastomosis may not be recommended in all cases[23]. Once drains are placed, questions regarding the implications of early drain removal with safe home discharge remain open for discussion[24]. During the past decade, several postoperative biochemical factors were studied to inform the pancreatic surgeon's decision. The first and most studied marker is the DFA, which is mandatory for confirming a POPF, but alone is unable to grade its severity. Additionally, it requires adequate pancreatic anastomosis/stump drainage. Furthermore, the appropriate timing (POD1, POD3, or later) or optimal cutoff value (less than 500[14], 1000[25], or 5000 UI/l[24]) varies widely based on the risk of fistula and type of anastomosis[26], and these have not yet been determined specifically, with a wide range of AUC, from 0.574[26] to 0.911[12]. Moreover, everyday practice[27] may sometimes be far different from theory, as recent studies have highlighted that only a few surgeons (13–27 per cent) follow the recommendation for drain removal on POD3 in Korea[28] and the United States[29], regardless of the ua-FRS[30] or DFA. One hypothesis for the low acceptance rate is the large discrepancy between guidelines and traditional experience-based management. Intuitively, DFA after PD does not fully consider the healing or inflammatory response of the body, requiring some complementary postoperative predictive factors[31], regardless of the mitigation strategy chosen, as the dice are not cast as soon as the surgery is completed. Consequently, inflammatory markers as early predictors of postoperative complications after pancreatic surgery[32] have also been investigated. C-reactive protein is one of the most studied factors with regard to POPF[25] or postoperative pancreatitis (PPAP)[33,34] (in combination with DFA or serum amylase respectively). In this series, NLR specificity (84 per cent *versus* 66 per cent) and positive predictive value (93 per cent *versus* 86 per cent) were superior to those of C-reactive protein level, in being considered for exclusion of POPF on POD3. Even though a recent study[35] has highlighted the role of lymphocytes in POPF, the specific mechanisms underlying the associations between systemic inflammation and postoperative complications remain unknown.

In patients with high ua-FRS a longer recovery time is expected[36]. Consequently, the decision for drain management usually occurs later in the clinical course, making POD3 more advisable than POD1 in terms of clinical implementation. To date, no consensus has been reached on the timing (POD1, POD3, or later) and a postoperative biochemical test (or combination of tests) greatly aids in the decision for a safe, early drain removal. For this reason, exploring a new test, which can be integrated into a combination of several tests, is of great interest. NLR lower than 8.5 on POD3 may be an objective tool to engage a risk-stratified approach[37] for early drain removal and mitigation of the surgeon's concerns. In the present study, it has been externally validated as an independent predictor of outcome. Moreover, NLR could be expanded to those pancreatectomies performed without drainage that are consequently not eligible for DFA testing.

Of course, as with every surrogate marker, NLR cannot guarantee 100 per cent exclusion criteria for a POPF and it may be contradictory to the ua-FRS. Therefore, when a controversial case of high ua-FRS and low NLR or DFA on POD3 is encountered, the surgeon's decision still requires a more robust predictive tool.

In this large series, ua-FRS and NLR had equal standing for predicting the exclusion of a POPF. A novel combination may be evaluated in future studies as these two tests include the major predictive factors of POPF. Thus, we have started a prospective evaluation of drain management based on ua-FRS and NLR, with the drainage being removed systematically at POD3 once ua-FRS is 20 per cent or lower and NLR less than 8.5. At the same time, this prospective evaluation will investigate the efficiency of both NLR and DFA in excluding POPF, as this comparison is lacking in this current retrospective series.

To date, this is the first multicentre large-scale study that illustrates the relevance of the NLR in excluding POPF; however, this study is not without limitations. First, the specificity does not equate to 100 per cent. Additionally, in cases of NLR more than 8.5, no conclusion was drawn for this high-risk zone. Hence, it should not supersede a surgeon's clinical judgement. Second, C-reactive protein, serum amylase, and DFA levels could not be investigated in the development phase. Thus, these variables were excluded from the analysis to avoid bias; however, undiagnosed postoperative pancreatitis could also serve as a source of bias in this study. Third, variability in the drains used may have led to bias. Last, the observational nature of the study makes it impossible to exclude residual confounding factors.

Nonetheless, the large sample size, robust statistical methodology (use of a training cohort and two validation cohorts designed to exclude POPF), multivariable analysis (including classic diagnostic clinical variables used in the ua-FRS), and prospective validation in an external cohort mitigate some of the disclosed limitations.

In conclusion, NLR less than 8.5 on POD3 may be a simple, independent, cost-effective, and easy-to-use postoperative criterion for excluding POPF. Combination with the robust ua-FRS (including pre- and intraoperative factors) could be of interest and is currently under prospective evaluation at our centre.

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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 sets generated and/or analysed during the present study are not publicly available due to patient privacy concerns, but are available from the corresponding author upon reasonable request.

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