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**EDITORIAL**

- 1261 Bridging the gap: Unveiling the crisis of physical inactivity in inflammatory bowel diseases  
*Stafie R, Singeap AM, Rotaru A, Stanciu C, Trifan A*
- 1266 Double role of depression in gastric cancer: As a causative factor and as consequence  
*Christodoulidis G, Konstantinos-Eleftherios K, Marina-Nektaria K*
- 1270 Capsule endoscopy and panendoscopy: A journey to the future of gastrointestinal endoscopy  
*Rosa B, Cotter J*
- 1280 Vonoprazan-amoxicillin dual regimen with *Saccharomyces boulardii* as a rescue therapy for *Helicobacter pylori*: Current perspectives and implications  
*Dirjayanto VJ, Audrey J, Simadibrata DM*
- 1287 Women health and microbiota: Different aspects of well-being  
*Nannini G, Amedei A*
- 1291 Nomograms and prognosis for superficial esophageal squamous cell carcinoma  
*Lin HT, Abdelbaki A, Krishna SG*

**REVIEW**

- 1295 Overview of the immunological mechanisms in hepatitis B virus reactivation: Implications for disease progression and management strategies  
*Ma H, Yan QZ, Ma JR, Li DF, Yang JL*
- 1313 Optimizing nutrition in hepatic cirrhosis: A comprehensive assessment and care approach  
*Mendez-Guerrero O, Carranza-Carrasco A, Chi-Cervera LA, Torre A, Navarro-Alvarez N*
- 1329 Optimizing prediction models for pancreatic fistula after pancreatectomy: Current status and future perspectives  
*Yang F, Windsor JA, Fu DL*

**ORIGINAL ARTICLE****Retrospective Cohort Study**

- 1346 Cumulative effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease in China  
*Chen JF, Wu ZQ, Liu HS, Yan S, Wang YX, Xing M, Song XQ, Ding SY*
- 1358 Time trends and outcomes of gastrostomy placement in a Swedish national cohort over two decades  
*Skogar ML, Sundbom M*

**Retrospective Study**

- 1368 Stage at diagnosis of colorectal cancer through diagnostic route: Who should be screened?  
*Agatsuma N, Utsumi T, Nishikawa Y, Horimatsu T, Seta T, Yamashita Y, Tanaka Y, Inoue T, Nakanishi Y, Shimizu T, Ohno M, Fukushima A, Nakayama T, Seno H*

**Observational Study**

- 1377 Differential diagnosis of Crohn's disease and intestinal tuberculosis based on ATR-FTIR spectroscopy combined with machine learning  
*Li YP, Lu TY, Huang FR, Zhang WM, Chen ZQ, Guang PW, Deng LY, Yang XH*

**Prospective Study**

- 1393 Establishment and validation of an adherence prediction system for lifestyle interventions in non-alcoholic fatty liver disease  
*Zeng MH, Shi QY, Xu L, Mi YQ*

**Basic Study**

- 1405 Alkaline sphingomyelinase deficiency impairs intestinal mucosal barrier integrity and reduces antioxidant capacity in dextran sulfate sodium-induced colitis  
*Tian Y, Li X, Wang X, Pei ST, Pan HX, Cheng YQ, Li YC, Cao WT, Petersen JDD, Zhang P*
- 1420 Preliminary exploration of animal models of congenital choledochal cysts  
*Zhang SH, Zhang YB, Cai DT, Pan T, Chen K, Jin Y, Luo WJ, Huang ZW, Chen QJ, Gao ZG*
- 1431 Serotonin receptor 2B induces visceral hyperalgesia in rat model and patients with diarrhea-predominant irritable bowel syndrome  
*Li ZY, Mao YQ, Hua Q, Sun YH, Wang HY, Ye XG, Hu JX, Wang YJ, Jiang M*

**META-ANALYSIS**

- 1450 Shear-wave elastography to predict hepatocellular carcinoma after hepatitis C virus eradication: A systematic review and meta-analysis  
*Esposito G, Santini P, Galasso L, Mignini I, Ainora ME, Gasbarrini A, Zocco MA*

**LETTER TO THE EDITOR**

- 1461 Current considerations on intraductal papillary neoplasms of the bile duct and pancreatic duct  
*Pavlidis ET, Galanis IN, Pavlidis TE*
- 1466 Are we ready to use new endoscopic scores for ulcerative colitis?  
*Quera R, Núñez F P*

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## Optimizing prediction models for pancreatic fistula after pancreatectomy: Current status and future perspectives

Feng Yang, John A Windsor, De-Liang Fu

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### Abstract

Postoperative pancreatic fistula (POPF) is a frequent complication after pancreatectomy, leading to increased morbidity and mortality. Optimizing prediction models for POPF has emerged as a critical focus in surgical research. Although over sixty models following pancreaticoduodenectomy, predominantly reliant on a variety of clinical, surgical, and radiological parameters, have been documented, their predictive accuracy remains suboptimal in external validation and across diverse populations. As models after distal pancreatectomy continue to be progressively reported, their external validation is eagerly anticipated. Conversely, POPF prediction after central pancreatectomy is in its nascent stage, warranting urgent need for further development and validation. The potential of machine learning and big data analytics offers promising prospects for enhancing the accuracy of prediction models by incorporating an extensive array of variables and optimizing algorithm performance. Moreover, there is potential for the development of personalized prediction models based on patient- or pancreas-specific factors and postoperative serum or drain fluid biomarkers to improve accuracy in identifying individuals at risk of POPF. In the future, prospective multicenter studies and the integration of novel imaging technologies, such as artificial intelligence-based radiomics, may further refine predictive models. Addressing these issues is anticipated to revolutionize risk stratification, clinical decision-making, and postoperative management in patients undergoing pancreatectomy.

**Key Words:** Pancreatic fistula; Pancreaticoduodenectomy; Distal pancreatectomy; Central pancreatectomy; Prediction model; Machine learning; Artificial intelligence

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**Core Tip:** Postoperative pancreatic fistula (POPF) is a common complication following pancreatectomy, associated with increased morbidity and mortality. Optimizing prediction models for POPF is a critical focus in surgical research. Although over sixty models following pancreaticoduodenectomy have been documented, their predictive accuracy remains suboptimal across diverse populations. The validation of models after distal pancreatectomy is anticipated, while POPF prediction after central pancreatectomy requires further development and validation. Machine learning and big data analytics offer promising prospects for enhancing prediction model accuracy. Personalized prediction models and novel imaging technologies, such as AI-based radiomics, may further refine predictive models.

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## INTRODUCTION

With the ongoing development of surgical techniques and technologies, the outcomes of pancreatectomy has significantly improved. Although the mortality rate after pancreatectomy has decreased to less than 5%, the occurrence of morbidity remains high, ranging from 15% to 65% [1,2]. One frequent complication that arises after pancreatectomy is postoperative pancreatic fistula (POPF), which varies in incidence depending on many factors including the definition of POPF and type of pancreatic anastomosis employed. The rate of POPF has not shown significant changes over time. Recent reports indicate that the incidence of POPF after pancreaticoduodenectomy (PD) is about 15%-20% [3], and after distal pancreatectomy (DP) 20%-30% [4]. Central pancreatectomy (CP) has the highest incidence of POPF, exceeding 30% [5]. The consequences of POPF include secondary complications of intra-abdominal abscess, sepsis, and life-threatening massive hemorrhage, which combine to further extend hospital stay and increase healthcare costs.

While accurate prediction of patients at high risk of POPF is a high priority, it remains a challenge. Predictive models serve as useful tools for risk stratification and resource allocation, with a focus on patients who stand to benefit the most. By efficiently identifying patients at a higher risk of POPF, these models allow healthcare providers to tailor their management approach based on an individual patient's risk profile. With the ability to pinpoint high-risk patients, predictive models empower providers to proactively implement preventive strategies, including appropriate anastomotic technique, octreotide administration, prophylactic drains, and Wirsung's duct stenting, while also initiating closer postoperative monitoring. Furthermore, predictive models offer valuable information for shared decision-making between healthcare providers and patients. This ensures that patients are well-informed about their risk of developing POPF, along with the potential benefits and risks associated with various prevention and management strategies. As a result, patients can actively participate in decisions regarding their treatment and care. These models utilize a range of risk factors, including clinical parameters, to determine the likelihood of POPF in individual patients, thereby improving surgical outcomes and reducing healthcare burden. Future iterations of these models hold the potential to further enhance their accuracy and effectiveness by incorporating valid risk factors and improving predictive algorithms. The aim of this paper is to provide a reference for surgeons to select suitable models in their clinical practice, and to propose strategies for optimizing these models.

## LITERATURE SEARCH

A comprehensive literature search was conducted in the PubMed database to identify relevant studies on prediction models for POPF after pancreatectomy. The search strategy included the terms "pancreatic fistula" AND "predictive model" or "score" AND "pancreaticoduodenectomy" or "pancreatic resection". Only studies published in English between January 2005 and October 2023 were included in the screening process.

## GRADING OF POPF

The definition (drain fluid amylase level from postoperative day 3 exceeds 3 times the serum amylase activity) and grading system of POPF was first published in 2005 [6] and later revised by the International Study Group of Pancreatic Surgery (ISGPS) in 2016 [7]. This system is now widely accepted and utilized, grading POPF on the basis of its severity. Grade A refers to a 'biochemical leak' that is characterized by an elevated drain fluid amylase level. However, it does not result in adverse clinical consequences and is no longer considered a true POPF. Grade B affects postoperative recovery and requires intervention, although it does not lead to severe consequences. This grade is clinically relevant as it can interfere with the management and impact clinical outcome. Within Grade B, there are three subtypes: B1, B2, and B3, each increasing in severity [8]. B1 is the least prevalent subtype and is characterized by persistent abdominal drainage for more than three weeks. Although it does not require specific treatment, it still requires monitoring. B2 is the most

common subtype and necessitates medical therapy, including antibiotics, enteral or parenteral nutrition, somatostatin and analogues, and transfusions, regardless of the need for extended catheter drainage. B3 is the most severe subtype, which demands interventional procedures under general anesthesia. Grade C is the most severe form of POPF and is associated with significant clinical implications, including organ failure and death. This grade requires immediate attention and intervention. Clinically relevant POPF (CR-POPF, B+C grades only) is accompanied by clinically relevant developments or conditions directly related to the POPF. By using this grading system, healthcare professionals can effectively grade and manage POPF based on its severity, helping to ensure appropriate treatment.

In recent study, it has been observed that patients who experienced postoperative pancreatitis (POAP) had an increased likelihood of developing CR-POPF[9]. Although the exact mechanism by which POAP leads to CR-POPF formation is yet to be determined, the association between them suggests a potential link. Postoperative hyperamylasemia, which is considered a biochemical marker of pancreatic tissue irritation, can be likened to a biochemical leak. Its significance in terms of clinical outcomes is not well understood. Additional research is required to clarify the clinical implications of postoperative hyperamylasemia and its relationship with the development of POPF[10].

## RISK FACTORS OF POPF

### **Risk factors in the models for PD**

Numerous risk factors have been identified in association with POPF (Table 1), leading to the development of several prediction models based on these factors. The risk factors can be described in three groups: preoperative, intraoperative, and postoperative factors[11]. It's important to note that the risk factors of POPF may vary depending on the type of pancreatic resection being performed[12].

Preoperative risk factors for POPF in patients undergoing PD include demographic characteristics such as gender, age, and body mass index (BMI)[13-15]. Comorbidities such as diabetes and pancreatitis, as well as imaging findings including pancreatic density, main pancreatic duct (MPD) diameter, visceral adipose tissue and radiomics score, are also risk factors [13,15-19]. Furthermore, biochemical markers like preoperative bilirubin and albumin levels, as well as preoperative biliary drainage and neoadjuvant chemotherapy, also contribute to the risk.

Intraoperative risk factors for POPF include pancreas-specific characteristics, such as soft pancreas and small MPD diameter. The surgical approach utilized (open, laparoscopic, and robotic) and type of anastomosis are also important. Other intraoperative risk factors include extended operating time, massive blood loss, combined venous resection, and extended lymphadenectomy[20-23].

Postoperative risk factors for POPF include high drain amylase levels, hyperamylasemia, hyperlipasemia, hypoalbuminemia, elevated C-reactive protein (CRP) level, and increased neutrophil count. Delayed gastric emptying is also a risk factor[24]. The pathology report may describe risk factors for POPF such as pancreatosteatosis and the absence of pancreatic fibrosis. Many prediction models for POPF after PD have been developed, and the reported predictors for these models are detailed in Table 1.

### **Risk factors in the models for DP**

Numerous studies have examined the risk factors associated with POPF following DP. However, compared with PD, there are fewer reported risk factors. These predictors can also be grouped as preoperative, intraoperative, and postoperative factors.

Preoperative risk factors for DP include young age, high BMI, the presence of preoperative comorbidities such as diabetes and coronary artery disease, hypoalbuminemia and certain pancreas-specific characteristics[25-27]. For instance, large MPD diameter and thick pancreas have been identified as potential risk factors.

Intraoperative risk factors include extended operating time, massive blood loss, soft pancreas, transection at pancreatic neck, and vascular resection.

Postoperative risk factors include surgical drain characteristics such as high amylase levels, elevated CRP, and the presence of high-risk pathology. Interestingly, there is a reversed predictive effect of MPD diameter between DP and PD. While a wider diameter is considered a risk factor for DP, it is reported as having a protective effect in PD[28]. Several models for predicting POPF following DP have been developed, with their reported predictors summarized in Table 2. Further research is needed to expand the understanding risk factors for POPF after DP, as well as to identify additional indicators that may contribute to more accurate prediction models. By considering a broader range of factors and conducting larger-scale studies, researchers can gain a more comprehensive understanding of POPF risk and develop effective strategies for its prevention and management.

### **Risk factors in the models for CP**

Only a limited number of risk factors for POPF after CP have been reported, and of potential value for establishing prediction models. These risk factors include sex, BMI, diabetes, MPD diameter, pancreatic thickness and texture, operating time, transection site, technique of pancreatic anastomosis, and pathology (Table 3). As research in this field progresses, it is expected that additional risk factors will be identified to enhance our understanding of POPF risk after CP.

**Table 1 Reported risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy**

Stage	Factors
Preoperative	(1) Sex, (2) age, (3) BMI, (4) weight, (5) weight loss, (6) smoking history, (7) hypertension, (8) diabetes mellitus, (9) history of acute pancreatitis, (10) history of abdominal surgery, (11) chronic steroid use, (12) ASA score, (13) preoperative biliary drainage, (14) preoperative chemotherapy, (15) albumin, (16) bilirubin, (17) alanine transaminase, (18) creatine, (19) tumor site, (20) MPD diameter, (21) MPD index <sup>1</sup> , (22) pancreatic thickness, (23) pancreatic density, (24) pancreatic texture, (25) relation with PV on CT, (26) pancreatic density index, (27) intra-abdominal fat thickness, (28) visceral adipose tissue, (29) total adipose tissue, (30) sarcopenic obesity, (31) L3 subcutaneous fat area, (32) pancreatic remnant volume, (33) stump area, (34) fat score, (35) atrophy score, (36) A/L ratio, (37) subcutaneous fat index, (38) radiomics score, (39) combined radiomics score, (40) liver density, (41) muscle attenuation, (42) PS Slratio, (43) PM Slratio, (44) fat mass at BIVA, (45) SWV value of pancreas, (46) MIPD experience, (47) preoperative diagnosis
Intraoperative	(A) MPD diameter, (B) pancreatic texture, (C) operating time, (D) estimated blood loss, (E) transfusion, (F) intraoperative colloid infusion, (G) surgical approach, (H) minimally invasive approach, (I) open conversion, (J) pancreatic anastomosis, (K) gastrojejunostomy, (L) extended lymphadenectomy, (M) venous resection, (N) nasojejunal feeding tube
Postoperative	(a) Postoperative DFA, (b) change of postoperative DFA, (c) WBC on POD1, (d) change of postoperative WBC, (e) neutrophil on POD3, (f) postoperative CRP, (g) temperature on POD3, (h) postoperative albumin, (i) albumin difference <sup>2</sup> , (j) postoperative CRP/albumin, (k) serum creatinine on POD1, (l) hyperamylasemia on POD1-2, (m) serum lipase on POD1, (n) DFL on POD1, (o) pathology, (p) PV invasion, (q) pancreatic fibrosis, (r) pancreatic steatosis, (s) deep surgical site infection, (t) DGE

<sup>1</sup>Main pancreatic duct index indicates the ratio of main pancreatic duct diameter to pancreatic thickness at the transection site.

<sup>2</sup>Albumin difference indicates the difference of albumin level between preoperative and postoperative day 1.

A/L ratio: Arterial/late phase pancreas computed tomography attenuation value ratio; ASA: American Society of Anesthesiologists; BIVA: Bioimpedance vector analysis; BMI: Body mass index; CRP: C-reactive protein; CT: Computed tomography; DFA: Drain fluid amylase; DFL: Drain fluid lipase; DGE: Delayed gastric emptying; L3: The third lumbar vertebra; MIPD: Minimally invasive pancreaticoduodenectomy; MPD: Main pancreatic duct; POD: Postoperative day; PV: Portal vein; SWV: Shear wave velocity; PM Slratio: Signal intensity ratio of pancreas to muscle; PS Slratio: Signal intensity ratio of pancreas to spleen; WBC: White blood cell.

**Table 2 Reported risk factors for postoperative pancreatic fistula after distal pancreatectomy**

Preoperative	Intraoperative	Postoperative
(1) Age	(A) Epidural use	(a) CRP on POD1
(2) BMI	(B) Operating time	(b) DFA on POD1
(3) Diabetes mellitus	(C) Estimated blood loss	(c) DFA on POD3
(4) Coronary artery disease	(D) Transfusion	(d) Change of postoperative DFA
(5) ASA score	(E) Pancreatic texture	(e) Pathology
(6) Albumin	(F) Transection site	
(7) MPD diameter	(G) Splenectomy	
(8) Pancreatic thickness	(H) Vascular resection	
(9) Pancreatic neck major diameter		
(10) Pancreatic neck minor diameter		
(11) Predicted pancreatic neck area		

ASA: American Society of Anesthesiologists; BMI: Body mass index; CRP: C-reactive protein; DFA: Drain fluid amylase; MPD: Main pancreatic duct; POD: Postoperative day.

## DEVELOPING PREDICTION MODELS

A range of statistical methods are used to develop POPF prediction models. These models can take the form of scores, calculation formulas, or nomograms, providing clinicians with a tool to assess individual patient risk. It is important to note that certain risk factor can be evaluated at different stages of the patient’s journey. For example, the MPD diameter can be measured preoperatively using enhanced CT/MRI scans or during the surgical procedure itself. Although both measurements may introduce some degree of error, MPD diameter measured through preoperative imaging is generally considered accurate[29]. Similarly, while pathology is typically assessed postoperative, a preoperative diagnosis by radiological imaging or biopsy serves as a reliable proxy. Furthermore, advancements in imaging technology have enabled evaluation of pancreatic texture not only during surgery but also with preoperative imaging by CT/MRI scans, and elastography[30]. This expanded imaging capability provides additional insights into the identification of risk factors such as pancreatic fibrosis or inflammation.

**Table 3** Reported risk factors for postoperative pancreatic fistula after central pancreatectomy

Preoperative	Intraoperative	Postoperative
(1) Sex	(A) Operating time	(a) Pathology
(2) BMI	(B) Pancreatic texture	
(3) Diabetes mellitus	(C) Transection site	
(4) Cephalic MPD diameter	(D) Pancreatic anastomosis	
(5) Distal MPD diameter		
(6) Pancreatic thickness		

BMI: Body mass index; MPD: Main pancreatic duct.

## PREDICTION MODELS FOR POPF AFTER PD

In the past decade, over sixty prediction models for POPF after PD have demonstrated potential value in clinical practice. Among these models, one of the earliest reported prediction scores, originating from a single-center prospective study conducted in 2010, categorized patients into four subgroups based on the presence of three risk factors: BMI, pancreatic steatosis and fibrosis[31]. This model shed light on the impact of pancreatic fat infiltration and fibrosis on the potential for POPF and showed high accuracy in predicting grade B and C POPF. However, the reliance on histological analysis for determining the scores of pancreatic steatosis and fibrosis is only available after surgery and cannot be used for surgical strategies, limiting the applicability of this model for instituting steps to prevent or reduce the risk of POPF. Subsequently, Wellner *et al*[13] and Yamamoto *et al*[14] proposed models that utilized preoperative indicators to predict the occurrence of POPF. However, these models did not gain widespread acceptance possibly due to the challenges associated with evaluating certain variables, including the MPD index and the distance from the portal vein. Furthermore, subsequent external validations revealed suboptimal performance of these models[32,33], further limiting their adoption into clinical practice.

Despite the limitations of early prediction models, continued research efforts have led to more models. These new models take into consideration a broader range of variables and aim to improve accuracy and clinical applicability. In 2013, a prospective study introduced the fistula risk score (FRS) to predict the risk of POPF[34]. The FRS is based on four variables: pancreatic texture, MPD diameter, intraoperative blood loss, and pathology. This scoring system was developed to address the limitations of preoperative assessments and has been validated by several studies, demonstrating its acceptable predictive performance with a c-statistic of over 0.7[35,36]. One of the areas of debated with this model is the relationship between blood loss and the occurrence of POPF[37]. It has been observed that minimally invasive surgery, which results in lower blood loss compared to open surgery, is not consistently associated with a reduced incidence of POPF. In light of this, Mungroop *et al*[37] proposed an alternative FRS (a-FRS), which removes the variables of intraoperative blood loss and pathological diagnosis. Instead, it includes the BMI as an additional variable. Subsequently, an updated alternative FRS (ua-FRS) was introduced, which incorporates the gender variable specifically for patients undergoing minimally invasive PD (MIPD)[38]. These modified scoring systems have shown improved convenience and enhanced predictive performance compared to the original FRS in subsequent external validations[39].

### Preoperative prediction

Preoperative prediction models may have the potential to help in enabling preventive measures and guiding surgical decision-making compared to intraoperative and postoperative prediction models. One such preoperative predictive score was developed by Roberts *et al*[15], utilizing only BMI and MPD diameter, and it showed a significant increase with increasing severity of POPF ( $P < 0.001$ ) in a subsequent multicenter study[40]. Building on this, Perri *et al*[41] established a more simplified risk-tree using the same two parameters. This risk-tree effectively categorized patients into three distinct risk groups with significantly different rates of POPF. However, it is worth noting that the area under the curve (AUC) for this risk-tree in the validation cohort was 0.65, indicating only moderate predictive accuracy. This would mean that 35% of patients are misclassified, which is not sufficiently accurate for application to individual patients.

With the advancements in medical imaging technology, imaging parameters have gained prominence in POPF prediction, and many preoperative prediction models now rely on these parameters (Table 4)[13-15,17,19,41-53]. However, certain imaging parameters require external software for preoperative evaluation, which poses challenges in terms of accessibility, standardization, and compatibility with different imaging systems, as well as external validation for these models. Additionally, the past three years have witnessed the development of over 10 POPF prediction models based on machine learning algorithms (Table 5)[22,48,54-64]. While these models are often considered superior to traditional regression models, it is important to highlight that a recent study revealed machine learning did not outperform logistic regression in predicting POPF after PD[22]. Furthermore, the predictive models developed using nationwide population data exhibited lower AUC values compared to models developed in single- and multicenter studies[22,60,62,63]. This discrepancy implies that the generalisability of the latter two models may be compromised in terms of their predictive value.

**Table 4 Preoperative prediction models of postoperative pancreatic fistula after pancreaticoduodenectomy**

Ref.	Year	Country	Center	Study period	Design cohort	CR-POPF (%)	Variables <sup>5</sup>	C-index/AUC (95%CI)	Validation
Wellner <i>et al</i> [13]	2010	Germany	Single	2006-2008	62	30.6 <sup>4</sup>	(2)(5)(6)(9)(47)		Internal
Yamamoto <i>et al</i> [14]	2011	Japan	Single	2004-2007	279	36.9	(1)(21)(25)(27)(47)	0.808 (0.757-0.860)	Internal
Roberts <i>et al</i> [15]	2014	United Kingdom	Single <sup>1</sup>	2007-2012	217	22.1 <sup>4</sup>	(3)(20)	0.832 (0.768-0.897)	Internal
Casadei <i>et al</i> [42]	2015	Italy	Single	2008-2012	208 <sup>2</sup>	20.2	(3)(20)(47)		
Zhang <i>et al</i> [43]	2018	China	Single		80	42.5 <sup>4</sup>	(38)	0.825 (0.736-0.913)	Internal
Shi <i>et al</i> [44]	2020	China	Multi	2009-2019	718	15.6	(20)(32)(33)(34)(35)	0.729 (0.678-0.775)	External
Yu <i>et al</i> [17]	2021	China	Single	2016-2018	124	25.8	(21)(23)	0.775 (0.687-0.862)	Internal
Lin <i>et al</i> [19]	2021	China	Single	2013-2019	175	21.1	(38) (39)	0.801 (0.719-0.884) 0.871 (0.816-0.926)	Internal
Tang <i>et al</i> [45]	2021	China	Single	2013-2019	239	19.7	(3)(20)(36)	0.823 (0.769-0.877)	
Lapshyn <i>et al</i> [46]	2021	Germany	Single <sup>1</sup>	2012-2018	120	19 <sup>3</sup>	(1)(20)(22)	0.808 (0.726-0.874)	Internal
Perri <i>et al</i> [41]	2021	Italy	Multi	2017-2019	566	20	(3)(20)	0.70 (0.63-0.77)	External
Savin <i>et al</i> [47]	2021	Romania	Single	2015-2020	78	28.2	(20)(23)(32) (20)(32)(40)	0.846 (0.694-0.941) 0.774 (0.599-0.850)	
Skawran <i>et al</i> [48]	2021	Switzerland	Single	2008-2018	62	27.4	(43)	0.75 (0.63-0.84)	
Box <i>et al</i> [49]	2021	United States	Single	2013-2018	220	15.9 <sup>4</sup>	(3)(20)(37) (3)(20)(26) (3)(20)(26)(37)	0.822 0.757 0.844	
Kolbinger <i>et al</i> [50]	2022	Germany	Single	2012-2021	195	28.7	(20)(24)(47) (20)(24)(32)(47)	0.82 0.83	Internal
Maqueda González <i>et al</i> [51]	2022	Spain	Single	2010-2019	103	30.1	(20)(29)	0.78 (0.68-0.87)	
Zou <i>et al</i> [52]	2023	China	Single	2015-2021	125	17.6	(20)(28)(42)	0.903	Internal
Tian <i>et al</i> [53]	2023	China	Single <sup>1</sup>	2020-2021	143 <sup>2</sup>	36	(20)(45)	0.866	Internal

<sup>1</sup>Indicates prospective studies, others are retrospective studies.

<sup>2</sup>Surgical procedures included pancreaticoduodenectomy and distal pancreatectomy.

<sup>3</sup>The data is the CR-POPF rate of total cohort.

<sup>4</sup>The data includes biochemical leak.

<sup>5</sup>From Table 1.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.

### Intraoperative prediction

The simplest intraoperative prediction model for POPF is known as the ISGPS risk classification. This classification categorizes patients into four risk groups based on intraoperative measurements of MPD diameter and pancreatic texture [65]. Interestingly, a nationwide validation study of this classification revealed no significant difference between the two intermediate risk categories, leading to the proposal of a simplified three-tier system [66]. The current literature indicates that a-FRS [37] and ua-FRS [38] have been validated by numerous external studies with acceptable accuracy and are two recommended models. However, the surgeon's determination of pancreatic texture by intraoperative palpation is subjective and prone to bias. Specific details regarding more intraoperative POPF prediction model are shown in Table 6 [16,18,21,22,37,38,50,61,65,67-71].

### Postoperative prediction

Recent studies have made significant advances in identifying early postoperative variables that are closely associated with POPF, including high drain fluid amylase (DFA), hyperamylasemia, and high-risk pathology, among others. These variables, combined with postoperative clinical data, biochemical indicators, and histopathological analysis, contribute to the development of dynamic POPF prediction models (Table 7) [20,23,24,31,34,72-88]. One particularly intriguing model is the "90-1000" score, which demonstrates superior performance in predicting POPF after PD compared to intraoperative

**Table 5** Machine learning prediction models of postoperative pancreatic fistula after pancreaticoduodenectomy

Ref.	Year	Country	Center	Study period	Design cohort	CR-POPF (%)	C-index/AUC (95%CI)	Validation
Mu <i>et al</i> [54]	2020	China	Multi	2006-2019	359	15.6	0.85 (0.80-0.90)	Internal-external
Han <i>et al</i> [55]	2020	Korea	Single	2007-2016	1769	12.5	0.74	
Skawran <i>et al</i> [48]	2021	Switzerland	Single	2008-2018	62	27.4	0.82 (0.74-0.89), 0.74 (0.63-0.89), 0.90 (0.84-0.95)	Internal
Giovinazzo <i>et al</i> [56]	2021	Multinational	Multi		1638	27	0.962 (0.940-0.984)	
Shen <i>et al</i> [57]	2022	China	Single	2010-2021	2421	17.5	0.79-0.81	Internal
Long <i>et al</i> [58]	2022	China	Multi	2012-2021	618	18.1	0.897 (0.370-1.424)	Internal
Capretti <i>et al</i> [59]	2022	Italy	Single <sup>1</sup>	2011-2019	100	20	0.807, 0.749	Internal
Chen <i>et al</i> [60]	2022	United States	Nationwide	2014-2019	13940	14.4	0.746 (0.733-0.760)	Internal-external
Zheng <i>et al</i> [61]	2023	China	Single	2013-2021	257 <sup>2</sup>	21.8	0.977	Internal
Ingwersen <i>et al</i> [22]	2023	Netherlands	Nationwide	2014-2020	4912	16.3	0.74 (0.73-0.74)	
Verma <i>et al</i> [62]	2023	United States	Nationwide	2014-2018	8597	11	0.74 (0.72-0.76)	Internal-external
Ashraf Ganjouei <i>et al</i> [63]	2023	United States	Nationwide	2014-2019	8666	13	0.67-0.72	Internal
Ingwersen <i>et al</i> [64]	2023	Multinational	Multi	2013-2018	118	42.4	0.9 (0.71-0.99), 0.86, 0.81, 0.8	Internal-external

<sup>1</sup>Indicates prospective studies, others are retrospective studies.

<sup>2</sup>Surgical procedures included open and laparoscopic pancreaticoduodenectomy.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.

pancreatic parenchymal features[79]. This model relies on the measurement of DFA and serum CRP levels on the first postoperative day. Its simplicity makes it particularly suitable for clinical practice; however, further validation is needed to establish its reliability, accuracy and applicability.

Many postoperative prediction models incorporate a combination of preoperative and intraoperative parameters. This approach holds the potential to enhance the clinical risk stratification of POPF and may offer a window of opportunity for pre-emptive interventions before the actual occurrence of POPF.

## PREDICTION MODELS FOR POPF AFTER DP

Compared to PD, there have been fewer studies of prediction models for POPF after DP. Efforts in developing reliable models after DP are relatively limited. Although DP involves fewer anastomoses, it appears to be associated with a higher incidence of POPF[2]. A retrospective study conducted on 2026 patients from 10 institutions identified several risk factors for CR-POPF after DP[25]. These risk factors included age below 60 years, obesity, low levels of albumin, absence of epidural use, high-risk pathology such as neuroendocrine and benign tumors, combined splenectomy, and vascular resection. However, the model constructed using these factors exhibited relatively poor accuracy in predicting POPF, with a c-statistic of 0.654 [95% confidence interval (CI): 0.620-0.688].

Recently, De Pastena *et al*[27] developed two DP fistula risk score (D-FRS) models. The preoperative model included two factors (pancreatic thickness and MPD diameter) and showed good predictive performance with an AUC of 0.83 (95%CI: 0.78-0.88) and 0.73 (95%CI: 0.70-0.76) for internal and external validation, respectively. In addition to pancreatic thickness and MPD diameter, the intraoperative D-FRS model included BMI, pancreatic texture, and operating time as factors and this achieved an AUC of 0.80 (95%CI: 0.74-0.85) without external validation. The DISPAIR model, developed by Bonsdorff *et al*[89] in the same year, incorporated three parameters: transection at pancreatic neck, pancreatic thickness, and diabetes. The model's internal and external validation resulted in notable AUC values of 0.904 (95%CI: 0.855-0.949) and 0.798 (95%CI: 0.748-0.848), respectively. While these models offer valuable insights, it is vital to consider their limitations, one of which is the need for external validation across diverse populations. To address this, Xu *et al*[28] conducted a validation study on the D-FRS and DISPAIR models using 653 Chinese patients who underwent DP. The study demonstrated acceptable discrimination for both models, with no significant differences between them. The AUC values were as follows: preoperative D-FRS 0.723 (95%CI: 0.687-0.757), intraoperative D-FRS 0.737 (95%CI: 0.701-0.770), and DISPAIR model 0.721 (95%CI: 0.685-0.755). The preoperative D-FRS is the most recommended model due to its

**Table 6** Intraoperative prediction models of postoperative pancreatic fistula after pancreaticoduodenectomy

Ref.	Year	Country	Center	Study period	Design cohort	CR-POPF (%)	Variables <sup>5</sup>	C-index/AUC (95%CI)	Validation
Kim <i>et al</i> [67]	2013	Korea	Single	2003-2008	100	41 <sup>4</sup>	(A)(B)(M)	0.728 (0.630-0.812)	Internal
Chen <i>et al</i> [68]	2015	China	Single	2008-2013	921	9.7	(3)(A)(B)(D)(E)	0.812 (0.766-0.858)	
Kantor <i>et al</i> [69]	2017	United States	Nationwide	2011-2012	1731	18.3	(1)(3)(16)(A)(B)	0.70 (0.65-0.74)	Internal-external
Li <i>et al</i> [70]	2019	China	Single	2011-2014	189	20.1	(15)(A)(B)(D)	0.821 (0.736-0.905)	Internal
Mungroop <i>et al</i> [37]	2019	Multinational	Multi	2007-2016	1924	12 <sup>4</sup>	(3)(20)(B)	0.75 (0.71-0.78)	Internal-external
Angrisani <i>et al</i> [21]	2020	Italy	Multi <sup>1</sup>	2016-2018	148	19.6	(44)(A)(B)(D) (44)(A)(B)	0.774 (0.683-0.866) 0.784 (0.680-0.888)	
Zhang <i>et al</i> [16]	2021	China	Single	2012-2020	232	7.8	(7)(8)(10)(B)(K)	0.916	
Mungroop <i>et al</i> [38]	2021	Multinational	Multi	2007-2017	952 <sup>2</sup>	21	(1)(3)(20)(B)	0.75 (0.71-0.79)	External
Kolbinger <i>et al</i> [50]	2022	Germany	Single	2012-2021	195	28.7	(47)(A)(B)	0.82	Internal
Lucassen <i>et al</i> [18]	2022	Netherlands	Single	2009-2018	329	16.7	(20)(41)(B) (20)(28)(B) (20)(28)(41)(B)	0.73 (0.68-0.79) 0.81 (0.75-0.86) 0.81 (0.75-0.86)	
Zheng <i>et al</i> [61]	2023	China	Single	2013-2021	257	21.8	(3)(20)(B)	0.743	Internal
Hayashi <i>et al</i> [71]	2023	Japan	Single	2010-2021	169	22.5	(30)(31)(B)	0.832	
Ingwersen <i>et al</i> [22]	2023	Netherlands	Nationwide	2014-2020	4912	16.3	(1)(3)(5)(13)(16)(19)(A)(B)(G)(J)(M)(N)	0.73	
Schuh <i>et al</i> [65]	2023	Multinational	Multi	2004-2019	5533 <sup>3</sup>	15.7	(A)(B)		External

<sup>1</sup>Indicates prospective studies, others are retrospective studies.

<sup>2</sup>The surgical procedure was minimally invasive pancreaticoduodenectomy.

<sup>3</sup>The cohort is for validation.

<sup>4</sup>The data includes biochemical leak.

<sup>5</sup>From Table 1.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.

practicality and ease of use, as it relies on easily measurable radiographic images to assess pancreatic thickness and MPD diameter for preoperative risk stratification. Despite these positive outcomes, there is still room for improvement in the performance of the predictive models. Standardizing classification thresholds may help to enhance their accuracy. There has been the emergence of additional prediction models for POPF after DP, and these are summarized in Table 8[26,79,90-92].

## PREDICTION MODELS FOR POPF AFTER CP

There is a trend toward offering CP more frequently in clinical practice because it allows for preservation of more pancreatic endocrine and exocrine function by resecting less normal pancreatic tissue. However, it appears to have a higher risk of POPF compared with PD and DP because of the presence of two pancreatic stumps[93]. While previous studies have primarily focused on the safety of CP and risk factors for POPF, the exploration of prediction models for POPF after CP has been relatively recent (Table 9). In a study by Ouyang *et al*[94], involving 194 CP patients, independent

**Table 7 Postoperative prediction models of postoperative pancreatic fistula after pancreaticoduodenectomy**

Ref.	Year	Country	Center	Study period	Design cohort	CR-POPF (%)	Variables <sup>6</sup>	C-index/AUC (95%CI)	Validation
Gaujoux <i>et al</i> [31]	2010	France	Single <sup>1</sup>	2004-2005	100	24	(3)(q)(r)	0.82	
Callery <i>et al</i> [34]	2013	United States	Single <sup>1</sup>	2002-2007	233	13	(A)(B)(D)(o)	0.942	Internal
Xia <i>et al</i> [23]	2018	China	Single	2009-2017	225	17.8	(A)(B)(L)(h)	0.813 (0.737-0.889)	Internal
Xingjun <i>et al</i> [72]	2019	China	Multi	2014-2017	457	12.6 <sup>5</sup>	(A)(q)(r)	0.868	External
You <i>et al</i> [73]	2019	Korea	Single	2007-2016	1771	12.5	(1)(3)(12)(15)(A)(o)	0.709	Internal
Guo <i>et al</i> [74]	2020	China	Single	2012-2016	220	22.7	(A)(B)(o)(p)	0.793 (0.731-0.855)	Internal
Li <i>et al</i> [75]	2021	China	Single	2018-2020	176	21.1	(a)(e)(f)(g)(k)	0.814 (0.736-0.892)	
Shen <i>et al</i> [76]	2021	China	Single	2016-2020	302	16.6	(3)(B)(a)(i)	0.87 (0.81-0.94)	Internal
Liu <i>et al</i> [77]	2021	China	Single	2016-2019	251 <sup>4</sup>	7.6	(15)(18)(a)(j)	0.866 (0.737-0.996)	
							(15)(18)(a)(j)	0.896 (0.814-0.978)	
							(15)(18)(a)(j)	0.888 (0.806-0.971)	
Huang <i>et al</i> [78]	2021	China	Multi	2010-2018	762	11.4	(3)(A)(a)	0.934 (0.914-0.950)	External
Guilbaud <i>et al</i> [79]	2021	France	Multi <sup>1</sup>	2017-2019	182 <sup>3</sup>	21.2	(a)(f)	0.834 (0.769-0.900)	
Honselmann <i>et al</i> [20]	2021	Germany	Single	2012-2017	182	16	(12)(A)(C)(c)(m)	0.903	Internal
							(12)(B)(c)(d)(m)	0.891	
Suzuki <i>et al</i> [80]	2021	Japan	Single	2007-2012	349	17.5	(20)(B)(b)(n)		
Al Abbas <i>et al</i> [81]	2021	United States	Nationwide	2014-2016	9867	13.9	(1)(2)(3)(7)(8)(A)(B)(o)	0.70 (0.69-0.71)	Internal
Yin <i>et al</i> [82]	2022	China	Single	2012-2016	662	16.3	(17)(A)(F)(M)(o)	0.667	Internal
							(A)(F)(a)(e)	0.809	
Gu <i>et al</i> [24]	2023	China	Nationwide	2014-2017	3609 <sup>2</sup>	16.7	(4)(20)(B)(o)(s)(t)	0.855 (0.702-0.853)	External
Bannone <i>et al</i> [83]	2023	Italy	Single <sup>1</sup>	2016-2021	905	20.2	(A)(B)(D)(a)(o)	0.85 (0.82-0.87)	
							(A)(B)(D)(a)(l)(o)	0.87 (0.84-0.89)	
							(A)(B)(D)(a)(f)(l)(o)	0.90 (0.87-0.91)	
Choi <i>et al</i> [84]	2023	Korea	Multi	2012-2020	429 <sup>4</sup>	12.4	(12)(20)(46)(B)(E)(H)(I)(o)	0.739 (0.668-0.800)	Internal
van Dongen <i>et al</i> [85]	2023	Netherlands	Nationwide	2014-2018	3271	14.6	(1)(3)(8)(20)(o)	0.73	External
Raza <i>et al</i> [86]	2023	United Kingdom	Multi	2009-2019	187	12.8	(1)(a)(f)(h)	0.78	External
Mohamed <i>et al</i> [87]	2023	United States	Nationwide	2015-2018	5975	17	(1)(3)(14)(A)(B)(o)	0.72 (0.704-0.737)	
Ahmad <i>et al</i> [88]	2023	United States	Nationwide	2014-2017	2417	12.6	(3)(11)(B)(C)(a)	0.720 (0.687-0.752)	Internal
							(3)(11)(B)(C)(a)(b)	0.758 (0.726-0.789)	

<sup>1</sup>Indicates prospective studies, others are retrospective studies.

<sup>2</sup>The study population was from the American College of Surgeons-National Surgical Quality Improvement Program database in the United States.

<sup>3</sup>Surgical procedures included pancreaticoduodenectomy and distal pancreatectomy.

<sup>4</sup>The surgical procedure was minimally invasive pancreaticoduodenectomy.

<sup>5</sup>The data is the clinically relevant postoperative pancreatic fistula rate of total cohort.

<sup>6</sup>From Table 1.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.

Table 8 Postoperative pancreatic fistula prediction models after distal pancreatectomy									
Ref.	Year	Country	Center	Design cohort	Study period	CR-POPF (%)	Variables <sup>3</sup>	AUC (95%CI)	Validation
Ecker <i>et al</i> [25]	2019	Multinational	Multi	2026	2001-2016	15.1	(1)(2)(6)(A)(G)(H)(e)	0.654 (0.620-0.688)	
Guilbaud <i>et al</i> [79]	2021	France	Multi <sup>1</sup>	92 <sup>2</sup>	2017-2019	21.2	(a)(b)	0.762 (0.640-0.885)	
Rollin <i>et al</i> [90]	2022	France	Single	103	2015-2019	32	(2)(8)(B)(c)	0.83 (0.75-0.92)	
Nassour <i>et al</i> [91]	2022	USA	Nationwide	692	2014-2018	15.9	(1)(B)(D)(b)	0.731 (0.685-0.796)	Internal
							(1)(B)(b)(d)	0.791 (0.742-0.836)	
Bonsdorff <i>et al</i> [89]	2022	Multinational	Multi	266	2013-2021	19.5	(3)(8)(F)	0.904 (0.855-0.949)	Internal-external
He <i>et al</i> [92]	2023	China	Single	115	2005-2020	33	(2)(6)(8)(E)	0.842 (0.762-0.921)	
Pecorelli <i>et al</i> [26]	2023	Italy	Single	220	2016-2019	33.6	(2)(3)(4)(5)	0.651 (0.58-0.73)	Internal
							(2)(9)(10)(C)	0.725 (0.66-0.79)	
							(5)(11)(C)	0.733 (0.64-0.80)	
De Pastena <i>et al</i> [27]	2023	Multinational	Multi <sup>1</sup>	339	2014-2016	23	(7)(8)	0.731 (0.70-0.76)	Internal-external
							(2)(7)(8)(B)(E)	0.851 (0.80-0.90)	

<sup>1</sup>Indicates prospective studies, others are retrospective studies.

<sup>2</sup>Including patients underwent pancreaticoduodenectomy.

<sup>3</sup>From Table 2.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.

risk factors for POPF were identified as obesity and pancreatic anastomosis technique. They constructed a nomogram based on these variables, which demonstrated a modest AUC of 0.678. However, this study overlooked certain pancreas-specific features such as pancreatic texture, MPD diameters on both sides of the transection, and pancreatic thickness, despite its large sample size.

In light of these omissions, Yang *et al*[95] conducted a study that identified additional risk factors for POPF after CP. They found that BMI, pancreatic thickness, and MPD diameters at both ends of the lesion were independent predictors. Building upon the probability (P) of the union of two events [formula:  $P(PD \cup DP) = P(PD) + P(DP) - P(PD \cap DP)$ ], they innovatively combined the existing FRS for PD and DP to develop specific FRS for CP (Figure 1). Consequently, they obtained a total of 12 central FRS (C-FRS) models. The predictive performance of these C-FRS models was generally acceptable, with AUC values ranging from 0.748 to 0.847. Particularly, the Preop-D-Roberts-FRS model emerged as a preoperative prediction model composed of four parameters: BMI, MPD diameters at both ends of the lesion, and pancreatic thickness. This model exhibited an AUC of 0.832 (95%CI, 0.751-0.895). Using this model, patients were categorized into three risk groups: low risk (< 25%), intermediate risk (25%-45%), and high risk (> 45%). The corresponding incidence of POPF in these risk groups was 0%, 30%, and 66.7%, respectively. Due to its ease of use and accurate preoperative prediction, the Preop-D-Roberts-FRS is recommended for clinical practice.

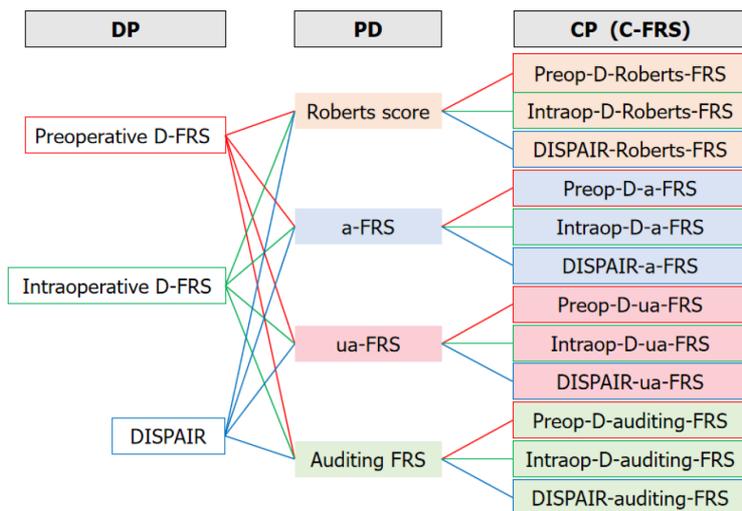
It is worth noting, however, that despite the promising predictive efficacy of these models, they were both derived from single-center retrospective studies in China and lacked valid external validation. Therefore, further prospective studies involving multiple centers and diverse populations are required for external validation and generalizability of the C-FRS models.

**Table 9 Postoperative pancreatic fistula prediction models after central pancreatectomy**

Ref.	Year	Design cohort	Study period	CR-POPF (%)	Variables <sup>1</sup>	AUC (95%CI)
Ouyang <i>et al</i> [94]	2022	194	2009-2020	45.9	(2)(D)	0.678
Yang <i>et al</i> [95]	2023	115	2010-2022	30.4	(2)(4)(5)(6)	0.832 (0.751-0.895)
					(2)(4)(5)(6)(B)	0.827 (0.745-0.891)
					(1)(2)(4)(5)(6)(B)	0.828 (0.746-0.892)
					(1)(2)(3)(4)(5)(6)(a)	0.826 (0.744-0.890)
					(2)(4)(5)(6)(A)(B)	0.845 (0.766-0.906)
					(2)(4)(5)(6)(A)(B)	0.847 (0.768-0.907)
					(1)(2)(4)(5)(6)(A)(B)	0.823 (0.741-0.888)
					(1)(2)(3)(4)(5)(6)(A)(B)(a)	0.840 (0.760-0.902)
					(2)(3)(5)(6)(C)	0.758 (0.669-0.833)
					(2)(3)(5)(6)(B)(C)	0.748 (0.659-0.824)
					(1)(2)(3)(5)(6)(B)(C)	0.784 (0.698-0.855)
(1)(2)(3)(5)(6)(C)(a)	0.750 (0.661-0.826)					

<sup>1</sup>From Table 3.

AUC: Area under the curve; CI: Confidence interval; CR-POPF: Clinically relevant postoperative pancreatic fistula.



**Figure 1 Central fistula risk score models for central pancreatectomy based on the fistula risk score for pancreaticoduodenectomy and distal pancreatectomy.** C-FRS: Central fistula risk score; CP: Central pancreatectomy; D-FRS: Distal fistula risk score; DP: Distal pancreatectomy; FRS: Fistula risk score; PD: Pancreaticoduodenectomy.

## CURRENT STATUS AND LIMITATIONS

Due to the influence of multiple risk factors (pre, intra and postoperative) and the inherent complexity of pancreatectomy, there is still room to improve the accuracy of predicting POPF. It is unlikely that a single model will be possible for all circumstances. The pathophysiological mechanisms relevant to POPF are not fully understood, and with time other factors might be identified. Moreover, the lack of consensus on diagnostic thresholds, judging criteria, non-blinded assessment of predictors, different statistical methods and potential interactions among various risk factors contribute to inferior performance of prediction models. A comprehensive review of 52 prediction models revealed that the average adherence rate to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines for POPF prediction models after PD was 65% [33]. Only 13 models surpassed this average TRIPOD adherence rate, indicating the importance of improving reporting standards and ensuring transparency in model development and evaluation.

Despite the development of many POPF prediction models, including some that are based on multicenter or nationwide cohort studies, over 80% of them lack external validation or demonstrate modest performance during subsequent validation[96], with AUCs ranging from 0.62 to 0.70[97]. One of the main reasons is their reliance on retrospective data, which may not encompass all the relevant factors contributing to POPF. Additionally, different models may incorporate varying variables and scoring systems, creating challenges when it comes to comparing and validating their performance. The lack of standardized and objective variables and scoring systems further hampers the universal applicability and reliability of these models. Another significant factor that has been overlooked in most models is the impact of individual surgeon experience and skill on the occurrence of POPF[98]. The surgical technique employed, decision-making process during operation, and proficiency of the surgeon can all have a substantial influence on the development of postoperative complications, including POPF. Ignoring these important aspects in the prediction models may contribute to their modest performance and decrease the translation of POPF prediction models into clinical practice.

Notably, while existing POPF prediction models show good performance in sample populations, their ability to predict and generalize may be limited when applied to ethnically diverse populations. Blunck *et al*[99] conducted an external validation study and found that although some models performed well for the overall population, their predictive value was limited for Black patients. Kang *et al*[100] validated three prediction models in a Korean population, yielding AUCs of 0.61-0.64, which were significantly lower than the original reports[15,34,37]. It is important to recognize that models developed in Western countries may not be directly applicable to Asian populations. In recent years, numerous prediction models have been developed in Asian countries such as China, Japan, and Korea. However, most of these models are from single-center retrospective studies and lack external validation. Consequently, there is a pressing need for large-scale prospective studies that integrate various factors to establish prediction models specifically suitable for respective populations.

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## FUTURE PERSPECTIVES

The risk of POPF following pancreatectomy remains high, highlighting the need for a thorough understanding of pathophysiology and risk factors in order to reduce the risk where possible and improve surgical outcomes. Continuous improvement and refinement of POPF prediction models is necessary for better clinical utility. This iterative process allows for development of personalized treatment strategies to optimize patient outcomes. To overcome the limitations and challenges faced by current models, future efforts should consider collecting comprehensive and standardized data. Ongoing research is directed towards developing robust models that account for the multifactorial nature of POPF. By predicting the risk of POPF based on preoperative factors, clinicians will be able to adequately prepare patients before surgery, choose appropriate surgical procedure, and make timely decisions regarding whether the patient should be transferred to a specialized surgical center for further treatment. In addition to static variables, efforts should also be focused on developing models that incorporate dynamic variables. Intraoperative findings and early postoperative markers, which can provide valuable real-time information, could be integrated into the prediction models. By including these factors, the models can better adapt to individual patient characteristics and enhance their predictive power. The dynamic monitoring models can guide surgeons in determining the best course of postoperative treatment for patients affected by POPF.

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## CONCLUSION

Prospective studies involving large cohorts and multiple centers are of utmost importance to establish reliable prediction models. Advancements in imaging techniques hold great promise in refining prediction models. High-resolution imaging modalities can provide detailed information about pancreatic and abdominal features and help identify important predictive factors. The integration of machine learning algorithms and artificial intelligence systems are likely to enhance the predictive capabilities of these models. By continuously learning from real-time data and adapting to new information, it is anticipated these systems will provide more accurate predictions of POPF. Nevertheless, it is crucial to validate the developed models externally to ensure their generalizability across different clinical settings and patient populations.

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## FOOTNOTES

**Author contributions:** Yang F collected the materials, discussed the topic, wrote the manuscript, and supervised this publication; Windsor JA and Fu DL discussed the topic and revised the manuscript.

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